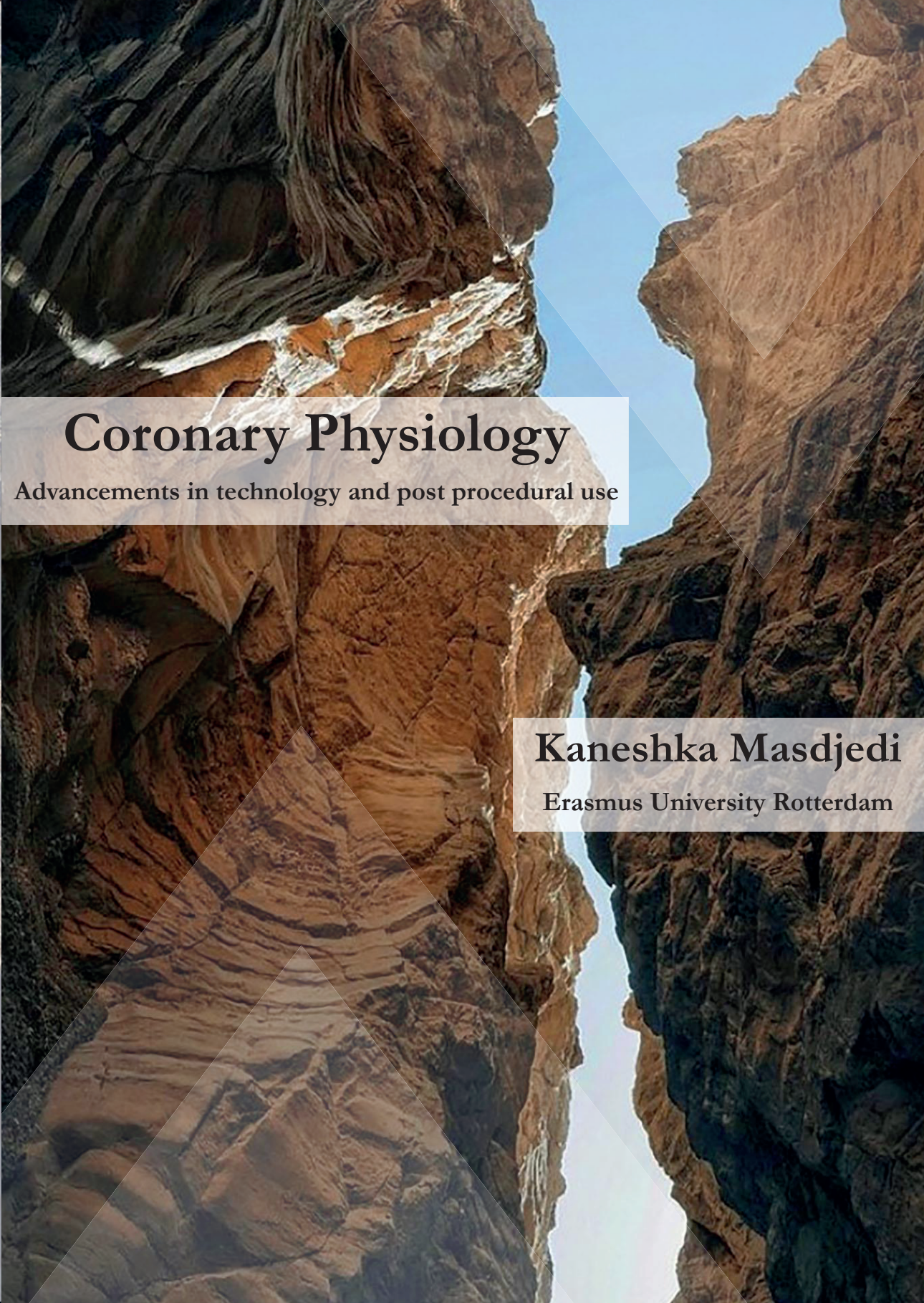


# Coronary Physiology

## Advancements in technology and post procedural use

Kaneshka Masdjedi

Erasmus University Rotterdam

# CORONARY PHYSIOLOGY

**Advancements in technology and post procedural use**

**KANESHKA MASDJEDI ( KEN )**

**Erasmus University Medical Center**

Financial support by: ACIST EUROPE B.V., Bayer B.V., Pie Medical Imaging and Servier Nederland Farma B.V.

ISBN/EAN: 978-94-6361-583-9
Cover photo by Khyber Khan
Layout and printed by Optima Grafische Communicatie, Rotterdam, the Netherlands

# CORONARY PHYSIOLOGY

**Advancements in technology and post procedural use**

**Coronaire Fysiologie**

Vooruitgang van de technologie en het post-procedureel gebruik ervan

Thesis

to obtain the degree of Doctor from the

Erasmus University Rotterdam

by command of the

rector magnificus

Prof. dr. A.L. Bredenoord

and in accordance with the decision of the Doctorate Board.

The public defence shall be held on

October 5th 2021 at 10:30 AM

by

**Kaneshka Masdjedi**

born in Charikar, Afghanistan.

**Erasmus University Rotterdam**

**Doctoral Committee:**

| | |
|---|---|
| **Promotor** | Prof. dr. N.M. Van Mieghem |
| **Other members** | Prof. dr. N. van Royen |
| | Prof. dr. N.M.S. de Groot |
| | Prof. dr. D.J.G.M. Duncker |
| **Co-promotor** | Dr. J. Daemen |

**Erasmus University Rotterdam**

**For Mashal,**
who flies like a bird & smiles like a flower,
with his heart

# TABLE OF CONTENTS

## ABBREVIATIONS

| | |
|---|---|
| 2D-QCA | Two-dimensional quantitative coronary angiography |
| ACS | Acute coronary syndrome |
| ARC | Academic research consortium |
| AUC | Area under the curve |
| BMI | Body Mass Index |
| CABG | Coronary artery bypass graft |
| CAD | Coronary artery disease |
| CFD | Computational fluid dynamics |
| CTO | Chronic total occlusion |
| CVD | Cardiovascular disease |
| dPR | Diastolic pressure ratio |
| DS | Diameter stenosis |
| FFR | Fractional flow reserve |
| Hb | Haemoglobin |
| iFR | Instantaneous wave free ratio |
| IQR | Interquartile range |
| IVUS | Intravascular ultrasound |
| MACE | Major adverse cardiac events |
| MI | Myocardial Infarction |
| MLA | Minimal Lumen Area |
| MLD | Minimum lumen diameter |
| MVD | Multivessel disease |
| MV-FFR | Multivessel FFR |
| NC | Non-compliant |
| NHPR | Non-hyperemic pressure ratios |
| NHPR | Non-hyperemic pressure ratio |
| NSTEMI | Non ST-elevation myocardial infarction |
| PCI | Percutaneous coronary intervention |
| Pd/Pa | Ratio of resting distal to aortic coronary pressure |
| Post-PCI FFR | Post percutaneous coronary interventions fractional flow reserve |
| PW-FFR | Conventional pressure-wire based fractional flow reserve |

# PART I
## PROLOGUE

"There are no incurable diseases, only the lack of will.
There are no worthless herbs, only the lack of knowledge"
—Avicenna

# Chapter

# 1

# General Introduction

Cardiovascular disease and more specifically coronary artery disease (CAD) is one of the leading causes of morbidity and mortality globally. (1) CAD is caused by atherosclerosis of the coronary artery wall, resulting in vessel lumen narrowing, limiting the ability to increase blood flow and supply of oxygen to the myocardium at instances of increased demand. Coronary angiography has traditionally served as the cornerstone for the assessment of coronary stenosis. However, coronary angiography frequently fails to identify the accurate hemodynamic significance of coronary stenoses, particularly in intermediate coronary lesions (vessels with diameter stenosis between 30% and 90%). (2, 3) To overcome these limitation, fractional flow reserve (FFR) has emerged as the mainstay of functional assessment of intermediate coronary artery lesions. FFR is defined as the ratio of maximal achievable blood flow in a coronary artery in the presence of a stenosis to the hypothetical maximal achievable blood flow in the same epicardial artery in the absence of the stenosis. The normal value of the ratio is expected to be 1.0. For example, an FFR of 75% or 0.75 means that the maximum blood flow in the myocardial distribution of the epicardial vessel is 75% of what it would be if the vessel would be completely normal. FFR is calculated by dividing the distal coronary pressure of the stenosis by the aortic pressure during maximal hyperemia using a 0.014-inch wire with a pressure sensor or a dedicated microcatheter along with the administration of a hyperemic agent. (4-7) Maximal hyperemia is achieved by dilatation of both the epicardial and microvascular arteries. Figure 1 illustrates the concept of FFR.

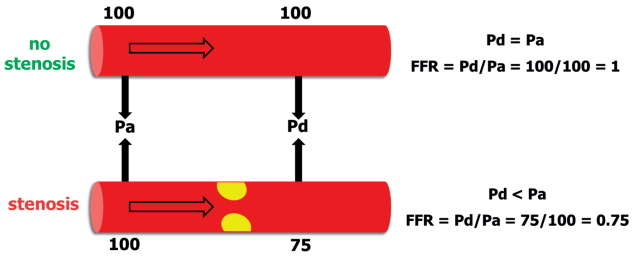



**Figure 1.** Concept of FFR: In case of no epicardial stenosis (above), the pressure loss across the coronary artery is negligible, and proximal aortic pressure (Pa) and distal coronary pressure (Pd) are equivalent, leading to an FFR of 1. In the presence of a stenosis (below), pressure loss across the stenosis will occur, and Pd will be lower than Pa, leading to an lower FFR. In this example, the stenosis leads to a pressure gradient across the stenosis of 25 mm Hg, leading to an FFR of 0.75.

Previous studies have shown that two-thirds of the coronaries with a diameter stenosis >50% were not functionally significant while for the left main coronary artery lesions, approximately one-fifth of the lesions with a diameter stenosis <50% were ischemia producing, defined as FFR≤0.80. (8)

Today, 25 years after the introduction of FFR, despite indisputable evidence supporting the benefit of FFR to guide clinical decision making, the adoption of FFR into daily practice has been

limited. The latter has been hypothesized to be due to the need for costly pressure wires or microcatheters, the perceived additional cost and time to perform FFR and hyperemic agents with known adverse events as dyspnea and arrhythmias. (9)

In recent years, non-hyperemic pressure ratios (NHPR), such as the instantaneous wave-free ratio (iFR), resting distal coronary artery pressure/aortic pressure (Pd/Pa) and resting full-cycle ratio (RFR) were introduced as alternative invasive indices to assess the severity of coronary artery stenosis. (10, 11) While Pd/Pa presents the ratio from the mean resting distal pressure to aortic coronary pressure during the whole cardiac cycle, iFR is based on the same ratio measured during the so-called "wave-free period", a period during diastole in which the microvascular resistance is low and constant. RFR represents the lowest Pd/Pa, independent of the ECG, landmark identification and timing within the cardiac cycle. (Figure 2).

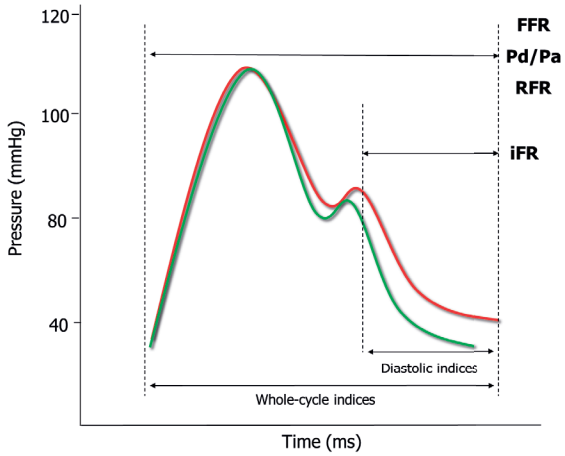



**Figure 2.** Whole-cycle and diastolic indices. FFR= fractional flow reserve; RFR= resting full-cycle ratio; iFR= instantaneous wave-free ratio

While Pd/Pa can be calculated from any type of pressure wire or microcatheter, the algorithm of iFR belongs to the iFR core laboratory (Imperial College, London, United Kingdom) and its use is restricted to the proprietary software of a single vendor hampering the widespread adoption of NHPR. We demonstrated the feasibility of a fast, simple and reproducible method of measuring a novel resting index called diastolic pressure ratio (dPR). dPR calculation was based on non-hyperemic DICOM pressure waveforms derived from either PW or microcatheter devices which could open up the field for a more widespread use of diastolic pressure gradients in real world clinical practice (Figure 3). By using a simple software tool to automatically detect the flat period in the dP/dt curve that indicates the so called "wave-free" period we were able to find an almost perfect correlation between iFR and dPR.

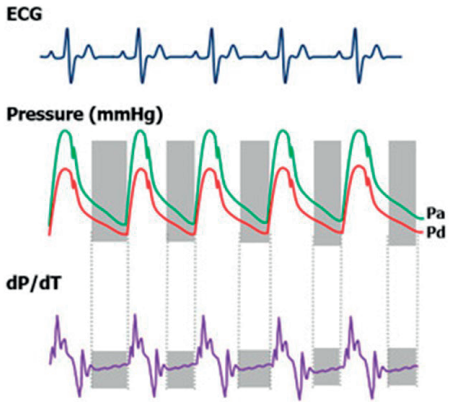



**Figure 3.** Identifying the diastolic period to calculate dPR by automatically indicating the "flat" period of the dP/Dt signal.

Although NHPR's have emerged as adenosine-free faster and easier methods to achieve physiologic assessment, the need for a costly pressure wire remains a fact. The latter stimulated to search towards novel technologies that are less costly, faster and more patient-friendly with the aim to assess the hemodynamic severity of intermediate coronary stenoses. Therefore we assessed the diagnostic performance and accuracy of three-dimensional quantitative coronary angiography (3D-QCA) based vessel FFR (vFFR) and validated the software in different patient settings.

At the same time, the use of post PCI physiological assessment is gaining attention. The significance of physiologic indices immediately after stenting to assess the impact of the treatment on coronary flow and the possible residual stenosis has been poorly investigated and data on this specific coronary physiology application are sparse. In brief the aims of this thesis were:

1. to validate a novel generic non-hyperemic diastolic index (dPR).
2. to validate a wireless non hyperemic angiography based FFR technology (vessel FFR, vFFR) and
3. to assess the distribution of post stenting physiologic indices (FFR, dPR and vFFR) and their association with clinical outcome.

## REFERENCES:

1. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation. 2012;125(1):e2-e220.
2. Nallamothu BK, Spertus JA, Lansky AJ, Cohen DJ, Jones PG, Kureshi F, et al. Comparison of clinical interpretation with visual assessment and quantitative coronary angiography in patients undergoing percutaneous coronary intervention in contemporary practice: the Assessing Angiography (A2) project. Circulation. 2013;127(17):1793-800.
3. Christou MA, Siontis GC, Katritsis DG, Ioannidis JP. Meta-analysis of fractional flow reserve versus quantitative coronary angiography and noninvasive imaging for evaluation of myocardial ischemia. Am J Cardiol. 2007;99(4):450-6.
4. Authors/Task Force m, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35(37):2541-619.
5. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367(11):991-1001.
6. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007;49(21):2105-11.
7. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.
8. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol. 2010;55(25):2816-21.
9. Toth GG, Toth B, Johnson NP, De Vroey F, Di Serafino L, Pyxaras S, et al. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. Circ Cardiovasc Interv. 2014;7(6):751-9.
10. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med. 2017;376(19):1824-34.
11. Svanerud J, Ahn JM, Jeremias A, van 't Veer M, Gore A, Maehara A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. EuroIntervention. 2018.

# Chapter

# 2

Outline of the thesis

Following the general introduction in **PART I**, **PART II** is focusing on distribution of post PCI FFR values using a novel monorail microcatheter FFR system that allows rapid and reliable post PCI FFR assessment without the risk of losing coronary artery access. We focus on predictors of suboptimal post PCI FFR value and the association of post PCI FFR with clinical outcome. **Chapter 3** aims to assess whether the theoretical advantages of the Navvus technology would result in overall reductions in contrast volume, radiation and costs as compared to conventional wire based FFR.

In **Chapter 4 and Chapter 5** we present the results of the The FFR-SEARCH study (Fractional Flow Reserve Stent Evaluated at Rotterdam Cardiology Hospital) which was a large prospective, open label, all comers study evaluating the impact of post stenting FFR at 30-days and 2 years. In Chapter 7 we elaborate on the rationale for low post PCI FFR by using high-definition intravascular ultrasound (HD-IVUS). We were able to identify a number of factors causing a post-PCI pressure drop across a treated vessel including residual disease in the proximal or distal segment, a geographically misplaced stent, stent underexpansion, malapposition, plaque protrusion, edge dissection and plaque shift (**Chapter 6**). **Chapter 7** describes the impact of the respective IVUS findings in patients with a low post PCI FFR on long-term clinical outcome. The objective of the study in **Chapter 8** was to assess specific patient and procedural predictors of post PCI FFR. **Chapter 9** is the rationale and design of the currently ongoing FFR REACT trial in which we aim to assess if FFR guided PCI optimization directed by HD-IVUS in patients with an increased risk for MACE (post-PCI FFR <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.

**PART III** describes the validation of a novel generic non-hyperemic diastolic pressure ratio (dPR) and its association with clinical outcome. **Chapter 10** is the validation study of dPR, a resting index calculated using novel software applicable to any type of pressure wire or microcatheter. The study aimed to assess the correlation of dPR with Instantaneous wave free ratio (iFR) as a reference. In addition, we assessed the diagnostic accuracy of dPR as compared to FFR and resting Pd/Pa. **Chapter 11** is the largest study on the distribution and predictive value of post PCI dPR to date and the first to assess the correlation between post PCI dPR and 2-year clinical outcome.

**PART IV** covers the validation of a wireless angiography based FFR technology (vFFR) based on simplified computational fluid dynamics (CFD). **Chapter 12** summarizes the advancements in physiological lesion assessment over the years. **Chapter 13** is the first (pre) clinical validation study of vFFR. We validated the vFFR algorithm in phantom models and subsequently correlated this index with pressure wire derived FFR in a consecutive series of patients and studied inter-observer variability. **Chapter 14** extends the findings reported in Chapter 12 towards a larger population in order to assess the performance of the technology in several angiographic subgroups. **Chapter 15** is a validation of the same software in a post PCI setting. We subsequently validated the software prospectively in an international multicenter study with the use of a blinded corelab **Chapter 16.**

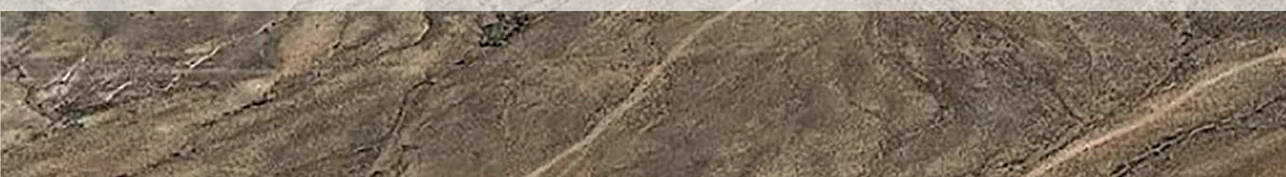
**Chapter 17** aimed to evaluate the feasibility of using vFFR for left main disease and to correlate vFFR values with IVUS measurements for evaluation of intermediate to severe LMCA stenosis. Distribution of post PCI vFFR and its association with clinical outcome at follow up has been described in **Chapter 18.** Finally, **Chapter 19** includes a case report demonstrating the pros and cons of different physiological indices alongside with intravascular imaging in a cardiac transplant patient.

# PART II

## FFR AND ITS POST STENTING VALUE

"When I want to understand what is happening today or try to decide what will happen tomorrow, I look back"

—O. Khayyam



# Chapter

# 3

# Navvus FFR to reduce CONTRAst, Cost and radiaTion (CONTRACT); insights from a single-centre clinical and economical evaluation with the RXi Rapid-Exchange FFR device

**Kaneshka Masdjedi, MD;** Nicolas M. Van Mieghem, MD, PhD; Roberto Diletti, MD, PhD; Robert-Jan van Geuns, MD, PhD; Peter de Jaegere, MD, PhD; Evelyn Regar, MD, PhD; Felix Zijlstra, Ron T. van Domburg, PhD; Joost Daemen, MD, PhD.

**Department of Cardiology, Thoraxcenter, Erasmus Medical Center, The Netherlands**

**Journal:** International Journal of Cardiology 233 (2017) 80–84

## ABSTRACT

**Objectives:** To assess whether the RXi Navvus system compared to the use of standard Fractional Flow Reserve (FFR) wires reduces total contrast volume, radiation and overall study cost in a real world patient population referred for coronary angiography or percutaneous coronary intervention.

**Background:** FFR is the mainstay of functional hemodynamic assessment of coronary artery lesions. The RXi Navvus system (ACIST Medical Systems, Eden Prairie, MN) is a monorail microcatheter with FFR-measurement capability through optical pressure sensor technology.

**Methods:** This is an investigator-initiated, prospective, single-center, observational cohort study. A total of 238 patients were enrolled, 97 patients with Navvus and 141 with conventional pressure-wire based FFR (PWFFR). Final analyses were performed on the cohort in which only 1 device was used (82 Navvus procedures vs. 136 PW-FFR procedures).

**Results:** No significant differences were found in the total amount of contrast used (150 ± 77 vs 147 ± 79 ml; p = 0.81), radiation use (6200 ± 4601 vs. 5076 ± 4655 centiG ∗ cm2; p = 0.09) or costs (€1994,- vs. €1930,-; p = 0.32) in the Navvus vs. PW-FFR groups respectively.

**Conclusions:** No significant differences were found in the amount of contrast used, total procedural costs or radiation when the Navvus system was used as compared to conventional FFR wires.

**Keywords:** Fractional flow reserve, Navvus, Cost-effectiveness, Pressure Wire.

## INTRODUCTION

Fractional Flow Reserve (FFR) is the mainstay of functional hemodynamic assessment of coronary artery lesions. (1) While visual assessment of the severity of coronary artery lesions correlates poorly with the functional severity of these lesions, FFR showed to overcome this major limitation. An FFR-value ≤ 0.80 under maximal hyperemia indicates a significant stenosis justifying treatment. (2,3) Several studies demonstrated the superiority of FFR-guided revascularization in reducing major adverse cardiac events as compared to anatomical coronary angiography- guided revascularization only. (4-6) FFR is now formally recommended by society guidelines to evaluate intermediate coronary artery lesions when non-invasive evidence of myocardial ischemia is unavailable. (1,7)

At present, several pressure wire systems are available and approved for FFR-measurements. The RXi Navvus system (ACIST Medical Systems, Eden Prairie, MN) is a novel monorail microcatheter with a lesion entry profile of 0.022" and an optical pressure sensor located close to the distal tip for FFR measurement. The rapid exchange catheter is compatible with any 0.014" coronary guidewire (8). This microcatheter technology allows to wire a lesion of interest with a guidewire of first choice which may facilitate negotiating complex anatomies and allows for multiple pullback measurements while maintaining guidewire position and thus preclude the need for repetitive wiring of lesions at risk for complications like embolization, dissection or perforation. Small validation studies confirmed a good correlation between Navvus and conventional wire-based FFR measurements.(9) The aim of this study was to assess whether the theoretical advantages of the Navvus technology would result in overall reductions in contrast volume, radiation and costs in comparison with conventional wire based FFR.

## METHODS

### 2.1 Study design and population

CONTRACT is an exploratory, investigator-initiated, prospective, single-center, observational cohort study. All consecutive patients referred for coronary angiography with or without percutaneous coronary intervention (PCI) and an indication to perform FFR (at the discretion of the operator) referred to Erasmus Medical Centre between September 1st, 2014 and February 28th 2015 were included. The design of our study is displayed in Figure 1.

Allocation to either the RXi Navvus system or the use of a conventional FFR device was based on the day of the month. On odd dates (1, 3, 5,…) conventional wire based FFR technology was used and on even dates (2, 4, 6,…) the RXi Navvus system was used. Systems used in the PW-FFR group were Radi Medical System/Certus™ /Aeris™ St. Jude Medical, St. Paul, MN, USA; Primewire

Prestige® and ComboWire® XT Volcano Corp, San Diego, CA, USA. All procedures were performed according to standard local practice with the decision to perform FFR in specific lesions, either pre- or post-stenting, at the discretion of the operator. Hyperemia was obtained with intravenous adenosine at a rate of 140 µg/kg/min.

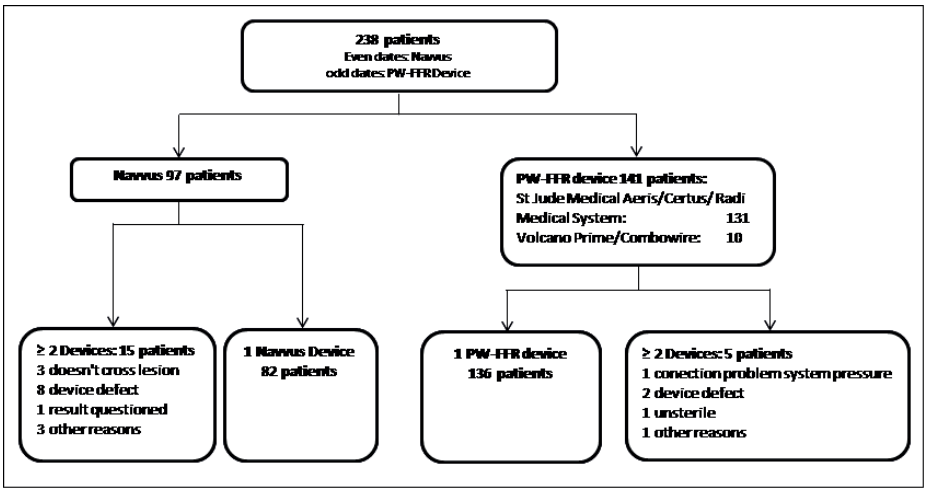



**Figure 1.** Study Design and Enrollment. PW-FFR Device (pressure-wire based FFR- device)

A total of 238 patients were enrolled, 97 patients in Navvus group vs 141 in the PW-FFR group. In twenty of these patients more than one FFR-device was used, 15 in the Navvus group versus 5 in the PW-FFR group. The reason for the use of multiple devices was: device failure (8 vs 2), inability of the device to cross the lesion (3 vs 0), unsterile device (0 vs 1) and other reasons (3 vs 1) respectively for Navvus and PW-FFR. In order to eliminate bias induced by the use of multiple devices, final analyses were performed on the cohort in which only 1 device was used (82 Navvus procedures vs. 136 PW-FFR procedures).

## 2.2. Primary and secondary endpoints

The primary endpoints were: 1) contrast volume 2) total radiation and 3) total procedural costs. Secondary endpoints included device failure or need for a second device, procedure time. Exploratory subgroup analyses were performed in patients with multivessel disease, multivessel PCI and influence of either a positive or negative FFR.

## 2.3 Endpoint definitions

Procedural time was defined as the difference in time (minutes) between start of the procedure (patient on the table) until removal of the access sheath. Total radiation burden was represented as “Sum total area dose” in centiGray*$cm^2$. (10) Total costs are presented based on local list prices

(Euros) of individual materials used during each procedure. In order to objectively compare both FFR systems, FFR device price was set to €0,-. Console and maintenance costs for either device were not taken into consideration.

### 2.4 Statistical analysis

Given the exploratory nature of the study along with the lack of comparative data, no power calculation was performed. Continuous variables are presented as mean ±standard deviation. All continuous variables were normally distributed. Categorical variables are expressed as counts and percentages. Comparisons among the two groups were performed by the F-test from an analysis of variance for continuous variables and Pearson's Chi-Square test for categorical variables. All statistical tests are 2-tailed. Linear regression analyses were performed to correct for confounding factors. The number of co-variables in the final stepwise multiple linear regression model was limited to variables ($p<0.10$) in the univariate model.

## RESULTS

### 3.1 Physiological and procedural baseline characteristics

Baseline and procedural characteristics are summarized in Tables 1 and 2. Mean age was 64 years in both cohorts. There were no significant differences in baseline risk profile and procedural characteristics with the exception of a higher number of small vessels in the Navvus group. Multivessel disease was present in 52.4% in the Navvus group vs. 40.4% in the PW-FFR group (p=0.09) leading to multivessel FFR in 22% vs 24.2% (p=0.70) in both groups respectively. Not including the PW-FFR wire, the mean number of additional guidewires used was obviously higher in the Navvus group as compared to the PW-FFR group (2.5±1.2 vs 2.0±1.8 respectively; p=0.03). However, when disregarding the first wire needed to use the Navvus system, the average number of additional wires needed was lower when the Navvus system was used, namely 1.5 vs 2.0; p=0.02.

The mean number of FFR measurements was comparable (1.57±0.84 vs 1.52±0.77; p=0.69) in the Navvus and PW-FFR group respectively. Mean FFR values were slightly though non-significantly lower in the Navvus as compared to the PW-FFR group (0.82±0.08 vs 0.83±0.10 respectively; p=0.42) leading to a somewhat higher number of positive FFR measurement in the Navvus group (51.9%) as compared to the PW-FFR group (43.8%; p=0.25). No procedural complications occurred in any of the groups.

**Table 1.** Baseline characteristics. Procedures in which only one device was used.

| | NAVVUS (n = 82) | PW-FFR (n = 136) | p-Value |
|---|---|---|---|
| Mean age (y) | 64.3 ± 10.6 | 64.2 ± 9.6 | 0.93 |
| Male sex, n (%) | 57 (69.5) | 92 (67.6) | 0.77 |
| Risk factors for CVD, n (%) | | | |
| Hypertension | 46 (61.3) | 70 (55.6) | 0.49 |
| Hyperlipidemia | 45 (54.9) | 74 (54.4) | 0.95 |
| Diabetes Mellitus | 27 (32.9) | 38 (27.9) | 0.44 |
| Smoker | 18 (19.6) | 26 (19.5) | 0.88 |
| BMI (mean (±SD)) | 27.9 ± 4.6 | 28.0 ± 5.5 | 0.94 |
| Co-morbidity | | | |
| Previous MI, n (%) | 42 (51.2) | 88 (64.7) | 0.05 |
| Previous PCI, n (%) | 36 (43.9) | 78 (57.8) | 0.05 |
| Previous CABG, n (%) | 4 (4.9) | 7 (5.2) | 0.92 |
| Renal insufficiency, n (%) | 10 (12.2) | 21 (15.8) | 0.47 |
| COPD, n (%) | 7 (8.5) | 15 (11.2) | 0.53 |
| Hemoglobine (mmol/L) (±SD) | 8.3 ± 1.1 | 8.5 ± 1.1 | 0.23 |

PW-FFR (conventional pressure-wire based FFR)

## 3.2 Primary and secondary endpoints

### *3.2.1 Procedural-related costs*

Including only those patients in which only 1 device was used (FFR device price set to €0,-) no significant differences were found in procedural costs (€1994±1696,- vs. €1930±2099,- in the Navvus and PW-FFR group respectively; p=0.32) (Figure 2).

As expected the total procedural costs were higher in procedures with positive as compared to negative FFR-measurements. In the FFR positive population, procedural costs increased to €2.280±1817,- in the Navvus group as compared to €2.442±2546,- in the PW-FFR group; p=0.72. In the negative FFR cohort costs appeared to be comparable, €1.634±1570,- vs. €1.452±1553,- respectively; p=0.56. There were 98 cases of multivessel disease in which only one FFR-device was used. Total procedural costs were €2.649±1838,- vs. €2.819±2765,- in the Navvus vs. PW-FFR group respectively; p=0.73. Similar results were found in patients with multivessel FFR (Figure 2)

### *3.2.2 Contrast*

Total contrast volume was identical between both groups (150±77 vs 147±79ml in the Navvus and PW-FFR groups respectively, p=0.81). The presence of multivessel disease or the performance of multivessel FFR did not significantly impact the difference in contrast use between both cohorts (Table 3).

**Table 2.** Procedural characteristics. Procedures in which only one device was used.

| | NAVVUS (n = 82) | PW-FFR (n = 136) | p-Value |
|---|---|---|---|
| Approach radial, n (%) | 62 (75.6) | 97 (72.4) | 0.60 |
| Multivessel disease, n (%) | 43 (52.4) | 55 (40.4) | 0.09 |
| Multivessel FFR, n (%) | 18 (22) | 32 (24.2) | 0.70 |
| OCT, n (%) | 11 (13.4) | 26 (19.1) | 0.28 |
| IVUS, n (%) | 5 (6.1) | 14 (10.3) | 0.29 |
| *Treated vessel, n (%)* | | | |
| Right coronary artery (RCA) | 30 (36.6) | 50 (37) | 0.95 |
| Ramus descendens anterior (LAD) | 54 (65.9) | 79 (58.5) | 0.28 |
| Ramus circumflexus (LCX) | 28 (34.1) | 47 (34.8) | 0.92 |
| Left Main (LM) | 4 (4.9) | 7 (5.2) | 0.92 |
| Vessel diameter ≤ 2.5 mm (%) | 37 (45.1) | 42 (30.9) | 0.034 |
| *Lesion's characteristics, n (%)* | | | |
| Ostial | 6 (7.3) | 7 (5.1) | 0.51 |
| Bifurcation | 13 (15.9) | 12 (8.8) | 0.26 |
| Calcification | 8 (9.8) | 16 (11.8) | 0.60 |
| *Number of material used, (mean ± SD)* | | | |
| Guidewires | 2.5 ± 1.2 | 2.0 ± 1.8 | 0.03 |
| Balloons | 1.5 ± 1.7 | 1.2 ± 1.6 | 0.27 |
| Stents | 1.3 ± 1.4 | 1.1 ± 1.4 | 0.18 |
| *FFR parameters (mean ± SD)* | | | |
| Number of FFR measurments | 1.57 ± 0.84 | 1.52 ± 0.77 | 0.69 |
| Mean FFR value | 0.82 ± 0.08 | 0.83 ± 0.10 | 0.42 |
| Positive FFR, n (%) | 41 (51.9) | 54 (43.8) | 0.25 |

PW-FFR (conventional pressure-wire based FFR)

### *3.2.3 Radiation*

There was no significant difference in the cumulative total area dose between both cohorts, 6200±4601centiG*cm$^2$ vs. 5076±4655 centiG*cm$^2$; p=0.09, neither was there a difference when the impact of multivessel disease (7203 vs. 6609 centiG*cm$^2$) was taken into account.

### *3.2.4 Procedural Time*

Total procedural time was identical between both cohorts, 72±26 minutes in the Navvus vs. 73±40 minutes in the PW-FFR group; p=0.79. A slight heterogeneity appeared to exist in patients with multivessel disease and multivessel FFR in which procedural time was numerically shorter in the Navvus cohort (Table 3).

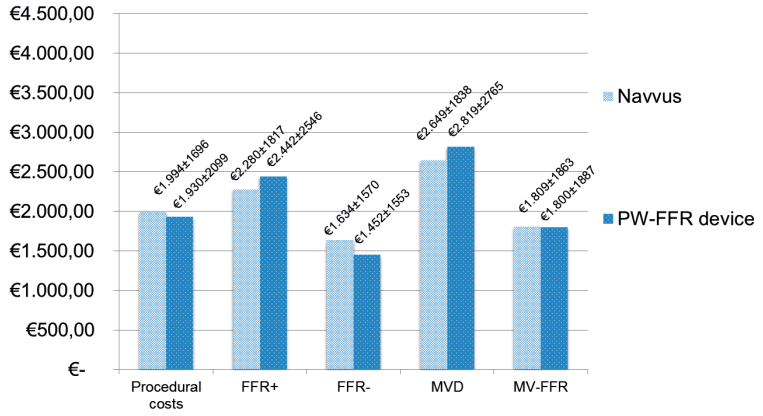



**Figure 2.** Total procedural costs (means), according to FFR price standardized to €0,-. Analysis in patients in which only one device was used. FFR+ (positive FFR value), FFR- (negative FFR value), MVD (multivessel disease), MV-FFR (multivessel FFR), PW-FFR (conventional pressure-wire based FFR)

**Table 3.** Radiation exposure, contrast use and procedural time in procedures in which only one

| | NAVVUS (n = 82) | PW-FFR (n = 136) | p-Value |
|---|---|---|---|
| *Radiation exposure, (mean ± SD)* | | | |
| Average fluoro voltage (kV) | 87 ± 7 | 88 ± 8 | 0.45 |
| Average fluoro current (mAmpere) | 224 ± 20 | 216 ± 23 | 0.01 |
| Cumulative total area dose (centiG * cm2) | 6200 ± 4601 | 5076 ± 4655 | 0.09 |
| Average total time (min) | 16 ± 9 | 16 ± 15 | 0.96 |
| Contrast use (ml ± SD) | 150 ± 77 | 147 ± 79 | 0.81 |
| Single vessel FFR (n = 160) | 152 ± 72 | 140 ± 73 | 0.35 |
| Multivessel FFR (n = 50) | 144 ± 95 | 156 ± 84 | 0.66 |
| Multivessel disease (n = 98) | 174 ± 91 | 180 ± 84 | 0.72 |
| Procedure time (min ± SD) | 72 ± 26 | 73 ± 40 | 0.79 |
| Multivessel FFR (n = 50) | 72 ± 23 | 79 ± 38 | 0.45 |
| Multivessel disease (n = 98) | 77 ± 24 | 88 ± 47 | 0.16 |

PW-FFR (conventional pressure-wire based FFR)

### *3.2.5 Predictors of cost, contrast and radiation*

Multivariable regression analyses identified bifurcation treatment, the use of OCT and the number of stents and balloons used as independent predictors of procedural costs. Independent predictors for the use of contrast were multivessel disease, the use of OCT and the number of stents and balloons while BMI, bifurcation treatment and number of balloons used were independent predictors of radiation as expressed by total area dose. Use of the Navvus system did not significantly impact procedural costs, radiation use and contrast use when these potential confounders were taken into account (Table 4).

**Table 4.** Predictors of cost, contrast and radiation

| Predictors | Univariate | | Multivariable | |
|---|---|---|---|---|
| | Beta-value | p-Value | Beta-value | p-Value |
| ***Procedural costs*** | | | | |
| Multivessel disease (MVD) | 0.366 | <0.001 | 0.043 | 0.10 |
| Bifurcation | 0.227 | 0.001 | -0.098 | 0.001 |
| Calcification | 0.248 | <0.001 | 0.040 | 0.12 |
| Vessel diameter ≤ 2.5 mm | 0.238 | <0.001 | 0.001 | 0.98 |
| Nr stents | 0.886 | <0.001 | 0.762 | <0.001 |
| Nr balloons | 0.738 | <0.001 | 0.186 | <0.001 |
| OCT | 0.210 | 0.002 | 0.243 | <0.001 |
| Navvus | 0.016 | 0.81 | -0.010 | 0.68 |
| ***Contrast*** | | | | |
| Multivessel disease (MVD) | 0.338 | <0.001 | 0.155 | 0.009 |
| Bifurcation | 0.221 | 0.001 | -0.071 | 0.27 |
| Calcification | 0.171 | 0.012 | 0.003 | 0.96 |
| Vessel diameter ≤ 2.5 mm | 0.244 | <0.001 | 0.040 | 0.5 |
| Nr stents | 0.525 | <0.001 | 0.23 | 0.007 |
| Nr balloons | 0.549 | <0.001 | 0.340 | <0.001 |
| OCT | 0.308 | <0.001 | 0.288 | <0.001 |
| Navvus | 0.017 | 0.809 | -0.039 | 0.47 |
| ***Radiation (cumulative total area dose)*** | | | | |
| Multivessel disease (MVD) | 0.223 | 0.001 | 0.220 | <0.001 |
| Bifurcation | 0.269 | <0.001 | 0.090 | 0.15 |
| Calcification | 0.192 | 0.005 | -0.203 | 0.003 |
| Vessel diameter ≤ 2.5 mm | 0.234 | 0.001 | 0.035 | 0.56 |
| Nr stents | 0.181 | 0.008 | 0.040 | 0.52 |
| Nr balloons | 0.477 | <0.001 | 0.060 | 0.49 |
| OCT | 0.573 | <0.001 | 0.581 | <0.001 |
| Navvus | 0.117 | 0.087 | 0.070 | 0.22 |

## DISCUSSION

The CONTRACT study demonstrated that the use of the ACIST RXi™ Rapid Exchange FFR system to perform FFR in an everyday PCI proved to be similar to conventional, wire based FFR systems with respect to cost and the use of contrast and radiation.

The RXi and Navvus MicroCatheter FFR has several distinct features as compared to the conventional pressure wire systems. (8) First, the system allows the operator to use a first choice guidewire to deal with all kinds of lesions, including vessels with excessive tortuosity, acute angu-

lation and calcification, without the need to rely on the sometimes suboptimal characteristics of conventional non-hydrophilic pressure wires. In theory, the latter might safe time, radiation and contrast and avoid the need to replace the FFR wire or use a more supportive guidewire in case needed. Second, the system allows multiple pullbacks while maintaining wire access.

The hypothesis of the CONTRACT study was that the use of the Navvus system would reduce procedural cost, total contrast volume and radiation dose as compared to PW-FFR. In the present study however, we were not able to confirm our hypothesis. Instead the use of both systems resulted in virtually identical procedural costs and use of contrast and radiation. The use of the Navvus system however, was left at the discretion of the operator and the number of measurements performed in the Navvus and PW-FFR groups (1.6 vs. 1.5 respectively; p=0.68) were similar suggesting that the specific benefits of the system were not fully utilized. Looking into specific subgroups, a trend was seen in patients with positive FFR and multivessel disease in which the Navvus system proved to be associated with slightly lower procedural costs (6.4% and 5.1% lower in the positive FFR- and multivessel disease subgroups respectively, p=ns) and shorter procedure time, which was on average 11 minutes (12.5%) shorter than in multivessel disease cases where a PW-FFR was used. Furthermore there was a trend towards less contrast use in multivessel disease cases and more contrast in single vessel disease cases when the Navvus system was used. Vessel diameter (i.e. diameter < 2.5mm) did not appear to impact the likelihood of measuring a positive FFR in either cohort. The higher proportion of small vessel disease in the Navvus group was most likely due to a play of chance.

Small previous studies demonstrated a good correlation between Navvus and PW-FFR based measurements however also suggested an overestimation of FFR by Navvus compared to conventional wire-based FFR measurements.(9) Mean FFR values were numerically lower when the Navvus system was used as compared to conventional pressure wire FFR systems (0.79±0.12 vs. 0.81±0.11 respectively), a similar finding was observed in the present study in which use of the Navvus system tended to result in a higher number of positive FFR values (51.9%) as compared to conventional FFR systems (43.8%). However, no QCA/IVUS or OCT analyses were performed to identify and compare minimum luminal dimensions between both groups to correct for potential confounding by differences in luminal dimensions between both cohorts. Larger studies are currently ongoing to further study the correlation between Navvus and conventional wire-based FFR measurements (ACIST-FFR, NCT02577484)

A higher rate of device failure was observed when the Navvus system was used. In 15.5% of the procedures the use of a second device was deemed necessary while this percentage was 3.5% in the conventional FFR systems group. Further scrutinizing the rationale for the relative high rate of device failure in the Navvus group revealed that the device failed to cross the lesion in 3/97 (3.1%) of the cases. Review of the respective cases showed extreme tortuosity and calcification

in 2/3 cases. Additionally, 8 devices (8.2%) appeared to be defect. A device/LOT number check in 6 catheters revealed that 5/6 catheters suffered from a manufacturing issue that was resolved quickly thereafter.

FFR has become the gold standard to determine the severity of epicardial coronary stenoses and myocardial ischaemia. (5) It has become an important instrument in detecting haemodynamic significant lesions in patients with stable coronary disease. While FFR-guided PCI compared to QCA-guided PCI improves PCI outcomes (4,11-13) the need for newer and more user-friendly devices remains relevant. The Navvus system has the theoretical potential to overcome several of PW-FFR limitations. The present study was the first to assess the implications of the use of the system on the use of resources during every day PCI. Larger randomized studies are needed to confirm the potential advantages of the system in subgroups that might benefit the most, such a cases with multivessel disease and more complex anatomy.

## LIMITATIONS

Our study was not designed to assess differences in the device specific performance of measuring FFR since no simultaneous measurements with both systems were performed. No statements can be made also on the accuracy and validation of the FFR values derived from measurements with the individual systems used (yet validation studies have been performed previously). Furthermore, the individual unique features of the Navvus system (like the possibility to do multiple pullbacks and measurements without the need to exchange the wire) were not assessed on a specific level as the use to device was left at the operators discretion.

Analyses on procedural costs were based on local list prices with the device price set to €0,- making that these results might slightly differ in other institutions with different individual device prices.

One of the expected differences in use between both devices was potentially more FFR measurements in Navvus group. However, this did not appear to be the case in our study, in which both devices were used in the same manner which might have influenced our results.

Finally our study population was relatively small and there was an unequal distribution of patients between both groups; 82 vs 136 patients, in the Navvus and PW-FFR respectively. The number of even and odd dates during the inclusion period was equal (108 vs 110 days), as were the number of FFR procedures performed during those days. Therefore, the difference cannot be explained by unequal amount of even and odd dates. A lack of compliance to the protocol was found to

be the most likely explanation of the difference between the amount of patients in Navvus vs PW-FFR group.

## CONCLUSION

The RXi Navvus FFR system as compared to conventional pressure wire based FFR in daily clinical practice was associated with comparable procedural costs, amount of radiation and contrast used.

## REFERENCES

1. Authors/Task Force m, Windecker S, Kolh P et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014.
2. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. Circulation 1993;87:1354-67.
3. Pijls NH, De Bruyne B, Peels K et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med 1996;334:1703-8.
4. Pijls NH, van Schaardenburgh P, Manoharan G et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 2007;49:2105-11.
5. Tonino PA, De Bruyne B, Pijls NH et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213-24.
6. De Bruyne B, Fearon WF, Pijls NH et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 2014;371:1208-17.
7. Levine GN, Bates ER, Blankenship JC et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. J Am Coll Cardiol 2011;58:e44-122.
8. Diletti R, Van Mieghem NM, Valgimigli M et al. Rapid exchange ultra-thin microcatheter using fibre-optic sensing technology for measurement of intracoronary fractional flow reserve. EuroIntervention 2015;11:428-32.
9. Menon M, Jaffe W, Watson T, Webster M. Assessment of coronary fractional flow reserve using a monorail pressure catheter: the first-in-human ACCESS-NZ trial. EuroIntervention 2015;11:257-63.
10. Vano E, Gonzalez L, Fernandez JM, Guibelalde E. Patient dose values in interventional radiology. Br J Radiol 1995;68:1215-20.
11. Berger A, Botman KJ, MacCarthy PA et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. J Am Coll Cardiol 2005;46:438-42.
12. Pijls NH, Fearon WF, Tonino PA et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 2010;56:177-84.
13. Sels JW, Tonino PA, Siebert U et al. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. JACC Cardiovasc Interv 2011;4:1183-9.

# Chapter

# 4

# Routine Fractional Flow Reserve Measurement After Percutaneous Coronary Intervention: The FFR-SEARCH Study

Rutger J. van Bommel, MD, PhD; **Kaneshka Masdjedi, MD**; Roberto Diletti, MD, PhD; Miguel E. Lemmert, MD, PhD; Laurens van Zandvoort, BSc; Jeroen Wilschut, MD; Felix Zijlstra, MD, PhD; Peter de Jaegere, MD, PhD; Joost Daemen, MD, PhD; Nicolas M. van Mieghem, MD, PhD.

**Thorax Center, Erasmus Medical Center, Rotterdam, the Netherlands.**

**Journal:** Circulation: Cardiovascular Interventions; 2019;12:e007428.

## ABSTRACT

**Background:** Fractional flow reserve (FFR) is the current gold standard to determine hemodynamic severity of angiographically intermediate coronary lesions. Much less is known about the prognostic effects of FFR measured directly after percutaneous coronary intervention (PCI). The aims of this study were to evaluate post-PCI FFR values, identify predictors for a low post-PCI FFR, and to investigate whether a relationship between post procedural FFR and outcome during 30-day follow-up exists.

**Methods and Results:** The FFR-SEARCH (Fractional Flow Reserve—Stent Evaluated at Rotterdam Cardiology Hospital) is a prospective registry in which FFR measurements were performed after PCI in 1000 consecutive patients. All FFR measurements were performed under maximum hyperemia with intravenous adenosine with the Navvus RXi system (ACIST Medical Systems, Eden Prairie, MN). The clinical end point was defined as a composite of death, target vessel revascularization, or nonfatal myocardial infarction at 30-day follow-up. Measurement of post-PCI FFR was successful in 959 patients (96%), and a total of 1165 lesions were assessed. There were no complications related to the microcatheter. A total of 322 ST-segment–elevation myocardial infarction patients with 371 measured lesions were excluded leaving 637 patients with 794 measured lesions for the final analysis. Overall post-PCI FFR was 0.90±0.07. In 396 lesions (50%), post-PCI FFR was >0.90. A total of 357 patients (56%) had ≥1 lesion(s) with a post-PCI FFR ≤0.90, and 73 patients (11%) had ≥1 lesion(s) with a post-PCI FFR ≤0.80 with post-PCI FFR ≤0.80 in 78 lesions (9.8%). Complex lesion characteristics, use of multiple stents and smaller reference vessel diameter was associated with post-PCI FFR ≤0.90. During follow-up, 11 patients (1.8%) reached the clinical end point. There was no significant relationship between post-PCI FFR and the clinical end point at 30-day follow-up (P=0.636).

**Conclusions:** Routine measurement of post-PCI FFR using a monorail microcatheter is safe and feasible. Several lesion and patient characteristics were associated with a low post-PCI FFR. Post-PCI FFR did not correlate with clinical events at 30 days.

## WHAT IS KNOWN

- Fractional flow reserve (FFR) is the current gold standard to determine the hemodynamic severity of angiographically intermediate coronary lesions.
- Previous studies, using mainly pressure wires, suggested a relationship between low FFR after coronary stenting and future adverse cardiac events but were either small in sample-size or used selected patients.

## WHAT THE STUDY ADDS

- Routine measurement of FFR after coronary stenting using a dedicated monorail microcatheter is safe and feasible.
- Both lesion and patient characteristics are associated with a low FFR after coronary stenting.
- Low FFR after coronary stenting is not associated with clinical events at 30-day follow-up.

## INTRODUCTION

Fractional flow reserve (FFR) is the current gold standard to determine hemodynamic severity of angiographically intermediate coronary lesions. Large randomized studies have established the superiority of FFR and even demonstrated beneficial effects on long-term outcome (death, myocardial infarction [MI], and repeat revascularization) in patients treated with FFR-guided percutaneous coronary intervention (PCI) as compared to angiography-guided PCI alone.1–3 As a result, the use of FFR in patients with intermediate coronary lesions and no previously documented ischemia has been given a class I recommendation in current European Society of Cardiology guidelines.4 Although it has been widely established that angiographic evaluation is not consistent with the hemodynamic severity of a lesion, coronary physiology is not used to assess PCI results. Several previous studies suggested a relationship between low post-PCI FFR and future adverse cardiac events (mainly repeat target vessel revascularization), but most of them were retrospective by nature, contained only limited numbers of selected patients and were inconsistent in reporting an optimal cutoff value for post-PCI FFR.5–11 Also, most of these studies used selected cases with stable, intermediate coronary lesions in which also pre-PCI FFR was performed. Subsequently, the aims of the current study were (1) to prospectively evaluate FFR values after angiographically successful PCI in a large cohort of consecutive patients, (2) to identify predictors of a low post-PCI FFR, and (3) to investigate whether there is a relationship between postprocedural FFR and clinical outcome during 30-day follow-up.

## METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

### Patient Population and Study Protocol

The FFR-SEARCH (Fractional Flow Reserve—stent Evaluated at Rotterdam Cardiology Hospital) is a prospective registry in which FFR measurements were performed after angiographically successful PCI in 1000 consecutive patients. Post-PCI FFR was measured in all patients, regardless of the clinical presentation or whether FFR or intravascular imaging was performed before PCI. However, patients presenting with cardiogenic shock, high-risk PCI with mechanical circulatory support or an estimated vessel size <2.25 mm were excluded.

PCI was performed according to standard techniques and in accordance with the European Society of Cardiology guidelines. Unfractionated heparin (70–100 U/kg) was used to achieve an activated clotting time >250 seconds. Coronary artery lesion characteristics were classified according to the American College of Cardiology/American Heart Association lesion classification.12

The decision to perform a diagnostic hemodynamic assessment with instantaneous free wave ratio or FFR, pre-intravascular or post-intravascular imaging, thrombus aspiration, predilatation or postdilatation was left at the discretion of the operator.

All FFR measurements were performed with the Navvus RXi system (ACIST Medical Systems, Eden Prairie, MN). This rapid exchange monorail microcatheter uses fiber optic-based sensor technology to assess FFR and is compatible with all standard 0.014 inches guidewires.13,14 The microcatheter technology allows easy access over any coronary guidewire which makes it particularly useful for assessment of post-PCI FFR. In addition, it permits multiple pullbacks while maintaining wire access to the vessel. After angiographically successful PCI, the Navvus RXi was inserted over the previously used coronary guidewire to ≈20 mm distal of the most distal stent edge, this location was defined as P1, Figure 1. Then, hyperemia was achieved with a continuous intravenous infusion of adenosine at a rate of 140 µg/kg per minute through an antecubital vein. Post-PCI FFR values were measured under hyperemia after a minimum of 2 minutes of intravenous adenosine infusion. The lowest value of hyperemic Pd/Pa of any single beat was used.

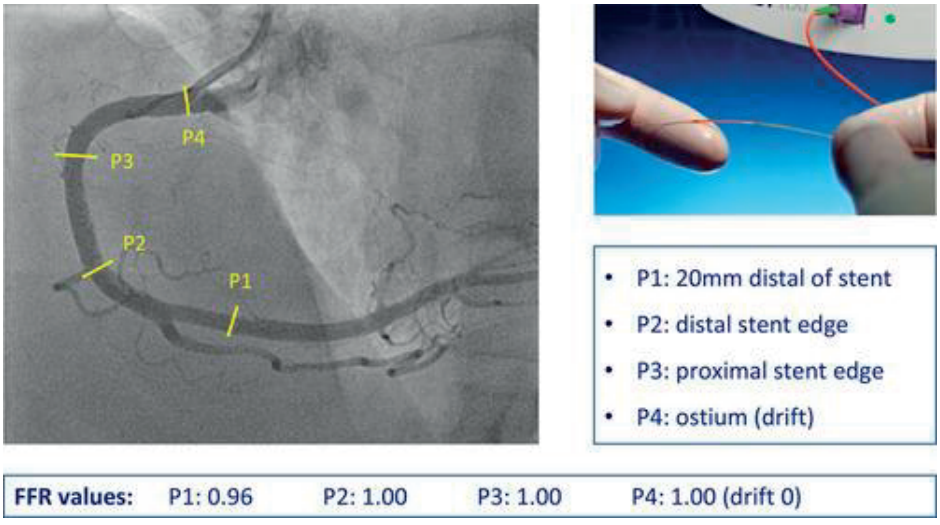



**Figure 1.** Example of post-percutaneous coronary intervention (PCI) fractional flow reserve (FFR) measurements as performed in FFR-SEARCH (Fractional Flow Reserve—Stent Evaluated at Rotterdam Cardiology Hospital), in this case in the right coronary artery in a patient presenting with a non–ST-segment–elevation myocardial infarction (NSTEMI).
After successful PCI, the Navvus RXi was inserted over the previously used coronary guidewire ( upper right). Then post-PCI FFR measurements were collected 20 mm distal of the most distal stent edge (P1), the distal stent edge (P2), the proximal stent edge (P3), and finally at the ostium (P4) to check for signal drift ( left). The values for this case are shown in the bar below.

Next, the microcatheter was pulled back to the most distal stent edge, this location was defined as P2, Figure 1 and the FFR value at that location was noted. The microcatheter was then pulled back to the most proximal stent edge, defined as P3 and again the FFR value at that location was noted. Finally, the microcatheter was pulled back to the ostium to check for pressure drift, this location was named P4, Figure 1. Using the FFR values at these 4 locations, pressure drop gradients were calculated from 3 segments; the distal segment (ΔFFR P2–P1), the stented segment (ΔFFR P3–P2), and the proximal segment (ΔFFR P4–P3). A significant pressure drop was defined as a ΔFFR >0.05.

For all later lesion and patient comparisons, only the FFR values measured 20 mm distal of the most distal stent edge (P1) were used.

Irrespective of the final post-PCI FFR value, and as directed by the study protocol, no further treatment was performed. The latter was directed in order not to bias the predictive value of post-PCI FFR on future adverse cardiac events. All angiograms and FFR pullbacks were checked to confirm protocol adherence. Based on previous studies, comparisons were made between lesions (and patients with lesions) with a low post-PCI FFR ≤0.90 versus a high post-PCI FFR >0.90.11

For this specific study, patients who presented with ST-segment–elevation myocardial infarction (STEMI) were excluded from further analysis as measuring FFR in patients with STEMI can be considered unreliable, mainly caused by incomplete hyperemia because of endothelial dysfunction and microvascular injury and obstruction in STEMI.15–17 Consequently, patients with STEMI are more likely to have a high-FFR value which does not necessarily reflect a better procedural result or outcome. Specific analysis on FFR-SEARCH patients with STEMI will be presented separately.

The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee. All patients provided written informed consent for the procedure and the use of anonymous data sets for research purposes in alignment with the Dutch Medical Research Act.

### Quantitative Coronary Angiography

Two-dimensional quantitative coronary angiography analysis was performed pre-stent and post-stent implantation in all treated lesions. An angiographic view with minimal foreshortening of the lesion and minimal overlap with others vessels was selected, and similar angiographic views were used pre-stent and post-stent implantation. Measurements included lesion length, reference diameter, minimal lumen diameter, and diameter stenosis. In case of preprocedural total occlusion of the treated lesion (in patients presenting with STEMI or a chronic total occlusion), the minimal lumen diameter value was considered 0% and stenosis 100%. Reference diameter and lesion length were calculated from the first angiographic view with restored flow.

### Follow-Up and Outcome Analysis

Clinical follow-up data were obtained from electronic medical records of the hospital, general practitioner, and the municipal civil records databases. In addition, all patients were contacted personally by letter or telephone contact. The clinical end point was defined as a composite of cardiac death, nonfatal MI, or target vessel revascularization at 30 days. Clinical events including all-cause mortality, cardiac mortality, MI, target lesion revascularization and target vessel revascularization, any revascularization, stent thrombosis, stroke, and bleeding were collected. Target lesion revascularization was defined as repeat PCI or bypass grafting for restenosis at the lesion treated during the index procedure. Target vessel revascularization was defined as repeat PCI or bypass grafting for a stenosis outside the stented area of the index procedure.

### Statistical Analysis

Continuous data are presented as mean±SD. Categorical data are presented as numbers and percentages. Comparison of data between lesions and patient groups was performed using the independent samples t test for continuous data. Fisher exact tests or $\chi 2$ tests were used as appropriate to compare categorical data. All analyses were performed with SPSS statistics for Windows, version 24.0 (SPSS, Chicago, IL). All statistical tests were 2-sided. A $P<0.05$ was considered statistically significant.

## RESULTS

### Patient Characteristics and Procedural Results

Baseline characteristics of the patient population are presented in Table 1. A total of 1000 patients were included in the study. In 28 patients, the microcatheter was not able to cross the treated lesion, in 11 patients there was another technical issue and in 2 patients a severe response to the intravenous adenosine occurred, leaving 959 patients (96%) with at least 1 successfully treated and FFR assessed lesion. In these 959 patients, a total of 1348 lesions were treated. In 14 of these lesions, the microcatheter was not able to cross and in 1 there was another technical issue. Furthermore, in 109 lesions, the distal vessel was considered too small for the microcatheter. In 9 lesions, the patient was too unstable to administer intravenous adenosine, in 22 cases the operator decided not to perform the FFR measurement. Finally, in 28 cases post-PCI FFR measurement was not performed for other reasons, leaving 1165 successfully treated and measured lesions (Figure 2). Out of these 959 patients with 1165 lesions, 322 STEMI patients with 371 measured lesions were excluded leaving a total of 637 patients with 794 measured lesions for the final analysis.

**Table 1.** Patient Baseline Characteristics

| Variable | n=1000 |
|---|---|
| Age, y | 64.6±11.8 |
| Male sex, n (%) | 725 (73) |
| Hypertension, n (%) | 515 (52) |
| Hypercholesterolemia, n (%) | 451 (45) |
| Diabetes mellitus, n (%) | 191 (19) |
| Smoking history, n (%) | 499 (50) |
| Prior stroke, n (%) | 77 (8) |
| Peripheral artery disease, n (%) | 76 (8) |
| Prior myocardial infarction, n (%) | 203 (20) |
| Prior PCI, n (%) | 264 (26) |
| Prior CABG, n (%) | 57 (6) |
| Hb level, mmol/L | 8.7±1.0 |
| Creatinine, µmol/L | 92±51 |
| **Indication for PCI, n (%)** | |
| Stable angina | 304 (30) |
| Unstable angina/NSTEMI | 367 (37) |
| Acute myocardial infarction | 329 (33) |
| No. of lesions treated | 1.40±0.6 |
| No. of lesions measured | 1.21±0.5 |

CABG indicates coronary artery bypass graft; Hb, hemoglobin; NSTEMI, non–ST-segment–elevation myocardial infarction; and PCI, percutaneous coronary intervention.

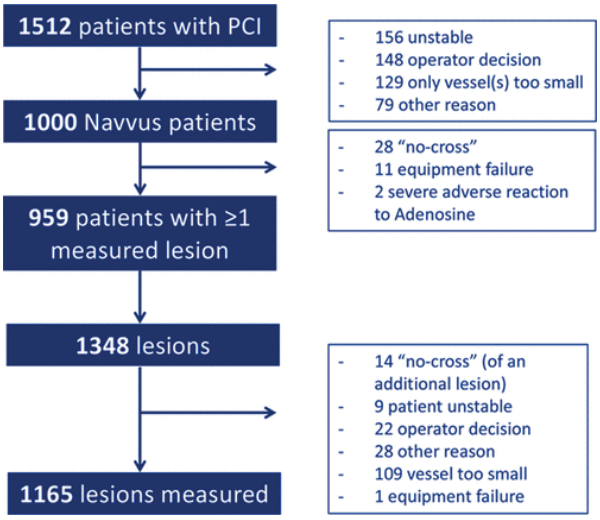



**Figure 2.** Flowchart showing all included and excluded patients and lesions in FFR-SEARCH (Fractional Flow Reserve—Stent Evaluated at Rotterdam Cardiology Hospital).
Measurement of ≥1 post-percutaneous coronary intervention (PCI) FFR was successful in 959 patients (96%).

## FFR Results

The mean time to perform post-PCI FFR was 5.0±1.4 minutes per lesion. No complications related to the microcatheter occurred. The mean Pd/Pa in resting condition was 0.96±0.04, while the mean post-PCI FFR under maximal hyperemia was 0.90±0.07 (as measured at P1). The mean post-PCI FFR at P2 was 0.95±0.05 and mean post-PCI FFR at P3 was 0.98±0.04. Finally, mean drift at P4 was 0.011±0.014 with 50 lesions (6.3%) having a significant drift >0.03, Figure 3. This resulted in an ΔFFR 0.04±0.05 along the distal segment, an ΔFFR 0.03±0.04 over the stented segment, and finally an ΔFFR 0.02±0.04 along the proximal segment. Interestingly, a significant pressure drop (>0.05) was observed in 32% of the distal segments, in 18% of the stented segments, and finally in 15% of the proximal segments.

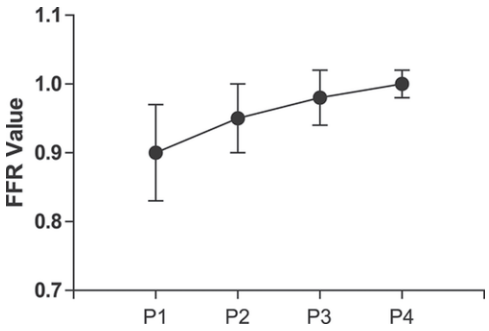



**Figure 3.** Mean post-percutaneous coronary intervention fractional flow reserve (FFR) values as measured at the 4 different locations in the coronary artery.

Distribution of post-PCI FFR values at P1 is shown in Figure 4. Although a satisfactory angiographic result was achieved in all cases, post-PCI FFR remained ≤0.80 in 78 lesions (9.8%). Conversely, post-PCI FFR was >0.90 in 396 lesions (50%). Comparison of post-PCI FFR in 3 predefined sub-

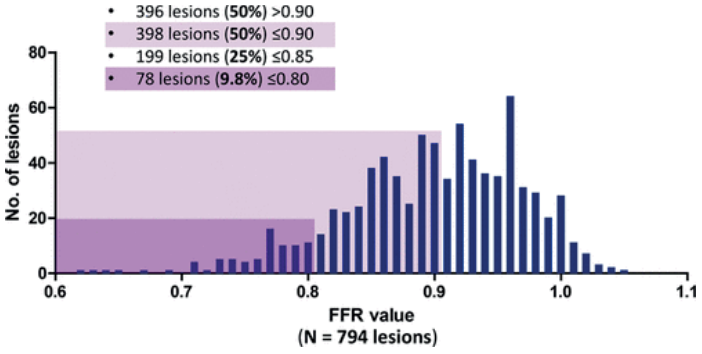



**Figure 4.** Post-percutaneous coronary intervention (PCI) fractional flow reserve (FFR) results on lesion level. In 398 lesions (50%), a post-PCI FFR ≤0.90 was found (light purple box), while in 78 lesions (9.8%), the post-PCI FFR was even ≤0.80 (dark purple box).

groups revealed no differences in men and women (0.89±0.07 versus 0.90±0.06, P=0.134) or in patients presenting with a non-STEMI versus stable angina (0.90±0.06 versus 0.89±0.07, P=0.100) but did show a significant difference in patients with diabetes mellitus and patients without diabetes mellitus (0.88±0.07 versus 0.90±0.06, P=0.027).

Characteristics of lesions with a post-PCI ≤0.90 versus lesions with a post-PCI FFR >0.90 are displayed in Table 2. Lesions with a post-PCI ≤0.90 were more complex lesions and more frequently included bifurcation lesions (18% versus 10%, P=0.002) or calcified lesions (47% versus 35%, P=0.001).

**Table 2.** Lesion Characteristics With FFR ≤0.90 Versus FFR >0.90

| Variable | All Lesions (n=794) | FFR ≤0.90 (n=398) | FFR >0.90 (n=396) | P Value |
|---|---|---|---|---|
| Lesion type, n (%) | | | | 0.003 |
| A | 100 (13) | 35 (9) | 65 (16) | |
| B1 | 163 (21) | 78 (20) | 85 (21) | |
| B2 | 232 (29) | 132 (33) | 100 (25) | |
| C | 299 (37) | 153 (38) | 146 (37) | |
| Bifurcation, n (%) | 109 (14) | 70 (18) | 39 (10) | 0.002 |
| Calcified, n (%) | 328 (41) | 188 (47) | 140 (35) | 0.001 |
| In-stent restenosis, n (%) | 30 (4) | 19 (5) | 11 (3) | 0.140 |
| Thrombus, n (%) | 81 (10) | 26 (7) | 55 (14) | 0.001 |
| Stent thrombosis, n (%) | 5 (1) | 3 (1) | 2 (1) | 0.658 |
| Ostial, n (%) | 84 (11) | 37 (9) | 47 (12) | 0.239 |
| CTO, n (%) | 39 (5) | 25 (6) | 14 (4) | 0.073 |
| Stenosis pre, % | 60±20 | 57±19 | 63±20 | <0.001 |
| Ref diameter pre, mm | 2.6±0.6 | 2.5±0.5 | 2.7±0.5 | <0.001 |
| Length pre, mm | 21±11 | 20±11 | 21±12 | 0.631 |
| MLD pre, mm | 1.0±0.5 | 1.1±0.5 | 1.0±0.6 | 0.044 |
| Predilatation, n (%) | 553 (70) | 289 (73) | 264 (67) | 0.068 |
| Postdilatation, n (%) | 499 (63) | 272 (68) | 227 (57) | 0.001 |
| IVUS, n (%) | 87 (11) | 65 (16) | 22 (6) | <0.001 |
| Stenosis post, % | 3.5±14 | 2.8±14 | 4.2±13 | 0.153 |
| Ref diameter post, mm | 2.7±0.5 | 2.5±0.5 | 2.7±0.5 | <0.001 |
| Length post, mm | 24±14 | 24±14 | 23±14 | 0.345 |
| MLD post, mm | 2.6±0.5 | 2.5±0.5 | 2.7±0.5 | <0.001 |
| No. of stent, n | 1.4±0.7 | 1.5±0.7 | 1.3±0.6 | 0.022 |
| Stent length, mm | 29±18 | 31±19 | 28±16 | 0.015 |
| Stent diameter, mm | 3.1±0.5 | 3.1±0.4 | 3.2±0.5 | <0.001 |

CTO indicates chronic total occlusion; FFR, fractional flow reserve; IVUS, intravascular ultrasound; and MLD, minimum luminal diameter.

Conversely, lesions with a post-PCI FFR >0.90 were more frequently thrombotic lesions (14% versus 7%, P=0.001), had a higher stenosis grade pre (63±20% versus 57±19%, P<0.001), higher reference diameter pre (2.7±0.5 versus 2.5±0.5 mm, P<0.001), and smaller minimal lumen diameter pre (1.0±0.6 versus 1.1±0.5 mm, P=0.044). Furthermore, postdilatation was more frequently performed in lesions with a post-PCI FFR ≤0.90 (68% versus 57%, P=0.001). Also, intravascular ultrasound was more frequently used in lesions with a post-PCI FFR ≤0.90 (16% versus 6%, P<0.001). In lesions with a post-PCI FFR ≤0.90 more stents were used (1.5±0.7 versus 1.3±0.6, P=0.022), with a smaller mean diameter (3.1±0.4 versus 3.2±0.5 mm, P<0.001), and a greater stent length (31±19 versus 28±16 mm, P=0.015). Finally, lesions with a post-PCI FFR >0.90 had a higher reference diameter post (2.7±0.5 versus 2.5±0.5 mm, P<0.001) and larger minimal lumen diameter post (2.7±0.5 versus 2.5±0.5 mm, P<0.001). Of note, in lesions with a post-PCI FFR ≤0.90, a significant pressure drop (>0.05) was observed in 57% of the distal segments, in 33% of the stented segments, and finally in 29% of the proximal segments (as compared to 9% of the distal segments, 4% of the stented segments, and 3% of the proximal segments in lesions with post-PCI FFR >0.90).

*Patients With All Measured Post-PCI FFR >0.90 Versus Any FFR ≤0.90*

In a total of 280 patients (44%), all measured lesions had a post-PCI FFR >0.90. There were 357 patients (56%) with ≥1 lesion ≤0.90, 182 patients (29%) with ≥1 lesion ≤0.85, and 73 patients (11%) with ≥1 lesion ≤0.80 despite an angiographically satisfactory result of the procedure. Baseline and procedural characteristics of patients with ≥1 lesion ≤0.90 versus patients with all lesions >0.90 are shown in Table 3. Patients with ≥1 lesion ≤0.90 were more likely to have diabetes mellitus (28% versus 19%, P=0.007) or peripheral arterial disease (11% versus 6%, P=0.038) as compared to patients with all lesions >0.90. Conversely, patients with all lesions >0.90 more frequently had prior coronary artery bypass graft (12% versus 5%, P=0.002). Finally, patients with ≥1 lesion ≤0.90 had more lesions treated (1.59±0.7 versus 1.31±0.6, P<0.001) and measured (1.36±0.6 versus 1.11±0.4, P<0.001) as compared to patients with all lesions >0.90.

## Follow-Up

Clinical follow-up at 30 days was available in 618 patients (97%). In total, 11 patients (1.8%) experienced a clinical end point. All separate end points and corresponding incidences are displayed in Table 4. No significant difference was found for the occurrence of the combined end point between the groups (2.0% in patients with ≥1 lesion ≤0.90 versus 1.5% in the patients with all lesions >0.90, P=0.636), or in any of the separate end points. Finally, no differences were found in event rates between men and women (2.0% versus 1.1%, P=0.385), patients with or without diabetes mellitus (2.7% versus 1.5%, P=0.316) and patients presenting with a non-STEMI versus patients with stable angina (2.7% versus 0.7%, P=0.064).

**Table 3.** Patient Baseline Characteristics With Any FFR ≤0.90 Versus FFR >0.90

| Variable | FFR ≤0.90 (n=357) | FFR >0.90 (n=280) | P Value |
|---|---|---|---|
| Age, y | 65.8±10.6 | 65.6±12.1 | 0.878 |
| Male sex, n (%) | 261 (73) | 185 (66) | 0.054 |
| Hypertension, n (%) | 215 (60) | 164 (59) | 0.684 |
| Hypercholesterolemia, n (%) | 202 (57) | 145 (52) | 0.476 |
| Diabetes mellitus, n (%) | 99 (28) | 52 (19) | 0.007 |
| Smoking history, n (%) | 152 (43) | 131 (47) | 0.303 |
| Prior stroke, n (%) | 35 (10) | 17 (6) | 0.088 |
| Peripheral artery disease, n (%) | 40 (11) | 18 (6) | 0.038 |
| Prior myocardial infarction, n (%) | 92 (26) | 69 (25) | 0.745 |
| Prior PCI, n (%) | 113 (32) | 95 (34) | 0.543 |
| Prior CABG, n (%) | 18 (5) | 33 (12) | 0.002 |
| Hb level, mmol/L | 8.6±1.0 | 8.5±1.1 | 0.519 |
| Creatinine, µmol/L | 99±75 | 92±32 | 0.192 |
| Indication for PCI, n (%) | | | 0.243 |
| Stable angina | 167 (47) | 118 (42) | |
| Unstable angina/NSTEMI | 190 (53) | 162 (58) | |
| No. of lesions treated | 1.59±0.7 | 1.31±0.6 | <0.001 |
| No. of lesions measured | 1.36±0.6 | 1.11±0.4 | <0.001 |

CABG indicates coronary artery bypass graft; FFR, fractional flow reserve; Hb, hemoglobin; NSTEMI, non–ST-segment–elevation myocardial infarction; and PCI, percutaneous coronary intervention.

**Table 4.** Thirty-Day Clinical Outcome

| | **All Patients (n=618)** | **FFR ≤0.90 (n=350)** | **FFR >0.90 (n=268)** | **P Value** |
|---|---|---|---|---|
| Combined end point, n (%) | 11 (1.8) | 7 (2.0) | 4 (1.5) | 0.636 |
| All-cause mortality, n (%) | 5 (0.8) | 4 (1.1) | 1 (0.4) | 0.290 |
| Cardiac mortality, n (%) | 4 (0.6) | 3 (0.9) | 1 (0.4) | 0.457 |
| Nonfatal MI, n (%) | 4 (0.6) | 4 (1.1) | 0 (0) | 0.079 |
| TLR, n (%) | 1 (0.2) | 1 (0.3) | 0 (0) | 0.380 |
| TVR, n (%) | 2 (0.3) | 1 (0.3) | 1 (0.4) | 0.851 |
| Any revascularization, n (%) | 7 (1.1) | 4 (1.1) | 3 (1.1) | 0.978 |
| Stent thrombosis, n (%) | 1 (0.2) | 1 (0.3) | 0 (0) | 0.380 |
| Stroke, n (%) | 0 (0) | 0 (0) | 0 (0) | 1.000 |
| Bleeding, n (%) | 1 (0.2) | 1 (0.3) | 0 (0) | 0.380 |

FFR indicates fractional flow reserve; MI, myocardial infarction; TLR, target lesion revascularization; and TVR, target vessel revascularization.

## DISCUSSION

The main findings of FFR-SEARCH at 30-day follow-up can be summarized as follows: (1) Routine measurement of post-PCI FFR is safe and feasible. (2) Mean post-PCI FFR was 0.90±0.07, with 73 patients (11%) having ≥1 lesion(s) with a post-PCI FFR ≤0.80 despite angiographically successful PCI and 357 patients (56%) having a low post-PCI FFR ≤0.90. (3) A significant pressure drop (>0.05) was found in 32% of the segments distal of the stent, while only in 18% of the stented segments and 15% of the proximal segments. (4) Several factors were associated with a low post-PCI FFR, including bifurcations or calcified lesions. Furthermore, patients with diabetes mellitus or peripheral arterial disease were more likely to have ≥1 lesion with a post-PCI FFR ≤0.90. (5) Finally, no significant relationship was found between post-PCI FFR and the combined clinical end point at 30-day follow-up.

Since the beginning of coronary angioplasty, interventional cardiologists have been on an ever-continuing search to further optimize outcome in patients undergoing PCI. In the last decade, intracoronary physiological assessment with FFR has become an established diagnostic tool to measure the hemodynamic importance of intermediate coronary lesions and guide the need for revascularization.1–3 However, FFR is only rarely used to assess the functional result after PCI. The angiographic result after PCI does not correlate with FFR post-PCI.5–8,10,18 Pijls et al19 studied 750 patients with post-PCI FFR measurements and a total of 44 patients (6%) had an FFR <0.80. In our study, more complex lesion phenotypes like bifurcations lesion or extensive calcification were associated with a post-PCI FFR ≤0.90. Furthermore, balloon postdilatation and invasive imaging were more frequently performed in lesions with a post-PCI FFR ≤0.90.

On a patient level, diabetes mellitus and peripheral arterial disease were more prevalent in patients with ≥1 lesion with a post-PCI FFR ≤0.90.

Currently, no substantial data on the exact mechanism of a suboptimal result after PCI (as measured with FFR) exist. There are several potential explanations for a low FFR value after PCI, including incomplete stent deployment, underexpansion or malapposition, protruding struts in bifurcations, small edge dissection or plaque shift proximally or distally to the stent and remaining nontreated atherosclerotic disease throughout the coronary artery. In the present study, a significant pressure drop (>0.05) was found almost twice as often in the segments distal of the stent, as compared to the stented segments and the proximal segments (32% versus 18% and 15%, respectively). In patients with post-PCI FFR ≤0.90, a significant pressure drop was found in over 57% of the distal segments as compared to only 30% of the stented and proximal segments. This could be indicative that diffuse atherosclerotic disease distal to the stent may play an important role in low FFR after PCI. Although this is currently hypothetical, invasive imaging may complement conventional coronary angiography to help elucidate the etiopathology of low FFR post-PCI.

In the DOCTORS trial (Does Optical Coherence Tomography Optimize Results of Stenting), which randomized 240 patients to either optical coherence tomography (OCT)-guided PCI or angiography-guided PCI,20 post-PCI OCT revealed stent under expansion in 42% of patients, stent malapposition in 32%, incomplete lesion coverage in 20%, and edge dissection in 37.5%. This resulted in more frequent use of postdilatation in the OCT-guided group versus the angiography-guided group (43% versus 12.5%, P<0.0001). More importantly, the mean post-PCI FFR in the OCT-guided group was significantly higher as compared to the angiography-guided group (0.94±0.04 versus 0.92±0.05, P=0.005). These findings are consistent with data from the earlier ILUMIEN I study (Observational Study of Optical Coherence Tomography in Patients Undergoing Fractional Flow Reserve and Percutaneous Coronary Intervention).21 In this specific study, OCT and FFR were performed pre-PCI and post-PCI in 418 patients with stable or unstable angina or non-STEMI. Not only did post-PCI OCT uncover 14.5% malapposition, 7.6% under expansion, and 2.7% edge dissection, but it resulted in further stent optimization in 25% of patients with additional postdilatation in 81% of the cases and placement of additional stents in 12%. As a result, post-PCI FFR values improved from 0.86±0.07 to 0.90±0.10 after optimization.

From this data, it may be concluded that post-PCI FFR could signal a suboptimal PCI result, unnoticeable by angiography alone. The most important question raised by these findings is: “can post-PCI FFR be used to detect and optimize procedural results and consequently improve patient outcome?” Agarwal et al22 demonstrated in 574 consecutive patients with stable angina that 143 of the 664 treated lesions (21%) had an FFR of ≤0.80 despite optimal angiographic PCI results (mean post-PCI FFR 0.87±0.08). After optimization of these lesions (42% received further postdilation of the implanted stent, 33% additional stenting, and 18% underwent additional stenting and postdilation), 80 lesions (56%) improved to an FFR >0.80, leaving 63 lesions (9.5%) with a persistently ischemic FFR of ≤0.80. A final post-PCI FFR >0.86 was considered as the optimal cutoff, and this was associated with improved outcome (major adverse cardiovascular event) during a mean follow-up of for 31±16 months. As the percentage of patients in this optimal post-PCI FFR group increased from 60% to 74% after the additional optimization, the authors concluded these subsequent interventions not only improved the overall functional outcome as measured with FFR but also likely reduced major adverse cardiovascular event during follow-up. As this study was a retrospective nonrandomized study, it remains unclear whether routine FFR assessment, followed by additional optimization in case of low post-PCI FFR may actually improve patient outcome. This hypothesis is currently studied in the FFR-REACT trial (Dutch trial register: NTR6711) that will randomize 290 patients with post-PCI FFR <0.90 to intravascular ultrasound-guided PCI optimization or control.

## LIMITATIONS

Some limitations of the study need to be addressed. First, this is a single-center, observational study and, therefore, reflects local practice. Second, pressure measurements were performed with the Navvus microcatheter. The microcatheter may enhance luminal narrowing and thus affect coronary flow and result in a lower FFR as compared to wire-based FFR.23,24 However, in FFR-SEARCH coronary physiology was assessed after successful PCI which makes the obstructive effect of the microcatheter less relevant, especially because only vessels >2.25 mm were eligible. Nonetheless, in ≈8% of the cases, the distal vessel was considered too small for the microcatheter. In addition, in 3.4% of the attempted lesions, the microcatheter was not able to cross the stented segment. Finally, this analysis was restricted to a 30-day clinical follow-up. The association of post-PCI FFR with clinical events may only appear during longer-term follow-up. The primary clinical end point of FFR-SEARCH is, therefore, set at 2 years.

## CONCLUSIONS

Routine measurement of post-PCI FFR using a monorail microcatheter is safe and feasible. Mean post-PCI FFR was 0.90±0.07, with 73 patients (11%) having ≥1 lesion(s) with a post-PCI FFR ≤0.80 despite angiographically successful PCI. Post-PCI FFR did not correlate with clinical events at 30 days.

## REFERENCES

1. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease.N Engl J Med. 2012; 367:991–1001. doi: 10.1056/NEJMoa1205361CrossrefMedlineGoogle Scholar
2. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nüesch E, Jüni P; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI for stable coronary artery disease.N Engl J Med. 2014; 371:1208–1217. doi: 10.1056/NEJMoa1408758CrossrefMedlineGoogle Scholar
3. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention.N Engl J Med. 2009; 360:213–224. doi: 10.1056/NEJMoa0807611CrossrefMedlineGoogle Scholar
4. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A, Authors/Task Force members. 2014 ESC/EACTS guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI).Eur Heart J. 2014; 35:2541–2619. doi: 10.1093/eurheartj/ehu278CrossrefMedlineGoogle Scholar
5. Ishii H, Kataoka T, Kobayashi Y, Tsumori T, Takeshita H, Matsumoto R, Shirai N, Nishioka H, Hasegawa T, Nakata S, Shimada Y, Ehara S, Muro T, Yoshiyama M. Utility of myocardial fractional flow reserve for prediction of restenosis following sirolimus-eluting stent implantation.Heart Vessels. 2011; 26:572–581. doi: 10.1007/s00380-010-0105-1CrossrefMedlineGoogle Scholar
6. Nam CW, Hur SH, Cho YK, Park HS, Yoon HJ, Kim H, Chung IS, Kim YN, Kim KB, Doh JH, Koo BK, Tahk SJ, Fearon WF. Relation of fractional flow reserve after drug-eluting stent implantation to one-year outcomes.Am J Cardiol. 2011; 107:1763–1767. doi: 10.1016/j.amjcard.2011.02.329CrossrefMedline Google Scholar
7. Agarwal SK, Kasula S, Almomani A, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Clinical and angiographic predictors of persistently ischemic fractional flow reserve after percutaneous revascularization.Am Heart J. 2017; 184:10–16. doi: 10.1016/j.ahj.2016.10.016CrossrefMedlineGoogle Scholar
8. Doh JH, Nam CW, Koo BK, Lee SY, Choi H, Namgung J, Kwon SU, Kwak JJ, Kim HY, Choi WH, Lee WR. Clinical relevance of poststent fractional flow reserve after drug-eluting stent implantation.J Invasive Cardiol. 2015; 27:346–351.MedlineGoogle Scholar
9. Kimura Y, Tanaka N, Okura H, Yoshida K, Akabane M, Takayama T, Hirayama A, Tada T, Kimura T, Takano H, Mizuno K, Inami T, Yoshino H, Yamashina A. Characterization of real-world patients with low fractional flow reserve immediately after drug-eluting stents implantation.Cardiovasc Interv Ther. 2016; 31:29–37. doi: 10.1007/s12928-015-0342-4CrossrefMedlineGoogle Scholar
10. Leesar MA, Satran A, Yalamanchili V, Helmy T, Abdul-Waheed M, Wongpraparut N. The impact of fractional flow reserve measurement on clinical outcomes after transradial coronary stenting.EuroIntervention. 2011; 7:917–923. doi: 10.4244/EIJV7I8A145CrossrefMedlineGoogle Scholar

11. Wolfrum M, Fahrni G, de Maria GL, Knapp G, Curzen N, Kharbanda RK, Fröhlich GM, Banning AP. Impact of impaired fractional flow reserve after coronary interventions on outcomes: a systematic review and meta-analysis.BMC Cardiovasc Disord. 2016; 16:177. doi: 10.1186/s12872-016-0355-7CrossrefMedlineGoogle Scholar
12. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB, Loop FD, Peterson KL, Reeves TJ, Williams DO, Winters WL. Guidelines for percutaneous transluminal coronary angioplasty. a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty).Circulation. 1988; 78:486–502.CrossrefMedlineGoogle Scholar
13. Diletti R, Van Mieghem NM, Valgimigli M, Karanasos A, Everaert BR, Daemen J, van Geuns RJ, de Jaegere PP, Zijlstra F, Regar E. Rapid exchange ultra-thin microcatheter using fibre-optic sensing technology for measurement of intracoronary fractional flow reserve.EuroIntervention. 2015; 11:428–432. doi: 10.4244/EIJY15M05_09CrossrefMedlineGoogle Scholar
14. Menon M, Jaffe W, Watson T, Webster M. Assessment of coronary fractional flow reserve using a monorail pressure catheter: the first-in-human ACCESS-NZ trial.EuroIntervention. 2015; 11:257–263. doi: 10.4244/EIJV11I3A51CrossrefMedlineGoogle Scholar
15. Rezkalla SH, Kloner RA. No-reflow phenomenon.Circulation. 2002; 105:656–662.CrossrefMedline-Google Scholar
16. Bulluck H, Foin N, Tan JW, Low AF, Sezer M, Hausenloy DJ. Invasive assessment of the coronary microcirculation in reperfused ST-segment-elevation myocardial infarction patients: where do we stand?Circ Cardiovasc Interv. 2017; 10:e004373. doi: 10.1161/CIRCINTERVENTIONS.116.004373Link Google Scholar
17. Cuculi F, De Maria GL, Meier P, Dall'Armellina E, de Caterina AR, Channon KM, Prendergast BD, Choudhury RP, Choudhury RC, Forfar JC, Kharbanda RK, Banning AP. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction.J Am Coll Cardiol. 2014; 64:1894–1904. doi: 10.1016/j.jacc.2014.07.987CrossrefMedlineGoogle Scholar
18. Tonino PA, Johnson NP. Why is fractional flow reserve after percutaneous coronary intervention not always 1.0?JACC Cardiovasc Interv. 2016; 9:1032–1035. doi: 10.1016/j.jcin.2016.04.001CrossrefMedli neGoogle Scholar
19. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, Escaned J, Tsurumi Y, Akasaka T, Samady H, De Bruyne B; Fractional Flow Reserve (FFR) Post-Stent Registry Investigators. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation. 2002; 105:2950–2954.LinkGoogle Scholar
20. Meneveau N, Souteyrand G, Motreff P, Caussin C, Amabile N, Ohlmann P, Morel O, Lefrançois Y, Descotes-Genon V, Silvain J, Braik N, Chopard R, Chatot M, Ecarnot F, Tauzin H, Van Belle E, Belle L, Schiele F. Optical coherence tomography to optimize results of percutaneous coronary intervention in patients with non-ST-elevation acute coronary syndrome: results of the multicenter, randomized DOCTORS Study (Does Optical Coherence Tomography Optimize Results of Stenting).Circulation. 2016; 134:906–917. doi: 10.1161/CIRCULATIONAHA.116.024393LinkGoogle Scholar
21. Wijns W, Shite J, Jones MR, Lee SW, Price MJ, Fabbiocchi F, Barbato E, Akasaka T, Bezerra H, Holmes D. Optical coherence tomography imaging during percutaneous coronary intervention impacts physician decision-making: ILUMIEN I study.Eur Heart J. 2015; 36:3346–3355. doi: 10.1093/eurheartj/ehv367CrossrefMedlineGoogle Scholar

22. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing post-intervention fractional flow reserve to optimize acute results and the relationship to long-term outcomes.JACC Cardiovasc Interv. 2016; 9:1022–1031. doi: 10.1016/j.jcin.2016.01.046CrossrefMedlineGoogle Scholar
23. Wijntjens GW, van de Hoef TP, Kraak RP, Beijk MA, Sjauw KD, Vis MM, Madera Cambero MI, Brinckman SL, Plomp J, Baan J, Koch KT, Wykrzykowska JJ, Henriques JP, de Winter RJ, Piek JJ. The IMPACT Study (Influence of Sensor-Equipped Microcatheters on Coronary Hemodynamics and the Accuracy of Physiological Indices of Functional Stenosis Severity).Circ Cardiovasc Interv. 2016; 9:e004645. doi: 10.1161/CIRCINTERVENTIONS.116.004645LinkGoogle Scholar
24. Pouillot C, Fournier S, Glasenapp J, Rambaud G, Bougrini K, Vi Fane R, Geyer C, Adjedj J. Pressure wire versus microcatheter for FFR measurement: a head-to-head comparison.EuroIntervention. 2018; 13:e1850–e1856. doi: 10.4244/EIJ-D-17-00238CrossrefMedlineGoogle Scholar

# Chapter

# 5

# Impact of Post-Stenting Fractional Flow Reserve on Long Term Clinical Outcomes: The FFR-SEARCH study

**Kaneshka Masdjedi, MD*1;** Roberto Diletti, MD, PhD*[1]; Joost Daemen, MD, PhD[1]; Laurens J.C. van Zandvoort, BSc[1]; Tara Neleman, BSc[1]; Jeroen Wilschut, MD[1], Wijnand K. Den Dekker, MD, PhD[1]; Rutger J. van Bommel, MD, PhD[2]; Miguel Lemmert, MD, PhD[3]; Isabella Kardys, MD, PhD[1]; Paul Cummins, BSc[1]; Peter de Jaegere, MD PhD;MD[1]; Felix Zijlstra MD PhD[1]; Nicolas M. Van Mieghem, MD PhD[1]

[1] Department of Interventional Cardiology, Thoraxcenter, Erasmus University Medical Centre, Rotterdam, the Netherlands.
[2] Department of Cardiology, Tergooi Hospital, Tergooi, the Netherlands
[3] Department of Cardiology, Isala Hospital, Zwolle, the Netherlands

*These two authors contributed equally to this study

**Journal:** Circulation: Cardiovascular Interventions. 2021;14:e009681

## ABSTRACT

**Background:** Fractional flow reserve (FFR) guided treatment has been demonstrated to improve percutaneous coronary intervention (PCI) results. However, little is known on the long-term impact of low post PCI FFR

**Methods:** This is a large prospective all comers study evaluating the impact of post-PCI FFR on clinical outcomes. All patients undergoing successful PCI were eligible for enrollment. FFR measurements were performed immediately after PCI when the operator considered the angiographic result acceptable and final. No further action was undertaken based on the post-PCI result. Suboptimal post-PCI FFR was defined as FFR<0.90. The primary endpoint was major adverse cardiac events (MACE), a composite of cardiac death, any myocardial infarction or any revascularization at 2-year follow-up. Secondary end-points were target vessel revascularizations (TVR) and stent thrombosis (ST) and the separate components of the primary endpoint.

**Results:** A total of 1000 patients were enrolled. Post PCI FFR was successfully measured in 1165 vessels from 959 patients. A post-stenting FFR<0.90 was observed in 440 vessels (37.8%). A total of 399 patients had at least 1 vessel with FFR<0.90 post-PCI. At 2-year follow-up, a patient level analysis showed no association between post PCI FFR and MACE (HR1.08 [95%CI, 0.73-1.60], p=0.707), cardiac death (HR1.55 [95%CI, 0.72-3.36], p=0.261), any myocardial infarction (HR1.53 [95%CI, 0.78-3.02], p=0.217). A vessel level analysis showed a higher rate of TVR (HR1.91 [95%CI, 1.06-3.44], p=0.030) and a tendency towards higher rate of ST (HR2.89 [95%CI, 0.88-9.48],p=0.081) with final post-PCI FFR<0.90.

**Conclusion:** Suboptimal Post-PCI FFR has only a moderate impact on MACE but coronary arteries with a post-PCI FFR<0.90 have a higher rate of TVR.

**Keywords:** percutaneous coronary intervention, stenting, fractional flow reserve.

### What is known

- Fractional flow reserve (FFR) is a reliable index of functional severity for epicardial vessel stenosis
- FFR immediately after stenting to assess the impact of the treatment on coronary flow and the possible residual stenosis has been poorly investigated and data on this specific FFR application are sparse
- The impact of Microcatheter based post PCI FFR has been not evaluated in large prospective studies

## What the Study Adds

- Microcatheter based suboptimal Post-PCI FFR has only a moderate impact on MACE but is associated with a higher rate of target vessel revascularizations.

## INTRODUCTION

Fractional flow reserve (FFR) is a reliable index of functional severity for epicardial vessel stenosis.[1] This diagnostic tool facilitates the correct identification of hemodynamically significant coronary artery disease, translating into increased intervention appropriateness and improved clinical outcomes.[2, 3]

Therefore, the ESC/EACTS guidelines on myocardial revascularization formulated strong recommendations towards FFR guidance for percutaneous coronary interventions (PCI) .[4]

Conversely, the significance of FFR immediately after stenting to assess the impact of the treatment on coronary flow and the possible residual stenosis has been poorly investigated and data on this specific FFR application are sparse.[5]

In particular, a relationship between post-PCI FFR and clinical outcomes has mainly been derived from retrospective studies and post-hoc analyses of randomized studies, with unclear results in terms of optimal cut-off values for the identification and definition of sub-optimal post-stenting FFR.[6-8]

Given this background, we performed the FFR-SEARCH prospective study, to investigate the clinical impact of post-PCI FFR values on long terms clinical outcomes using a cut-off value for the definition of sub-optimal FFR (FFR <0.90) already hypothesized in the FAME 1 and FAME 2 trials[7, 9] and supported by large meta-analyses[10] but never evaluated in a prospective fashion.

## METHODS

### Patient population

The FFR-SEARCH (Fractional Flow Reserve Stent Evaluated at Rotterdam Cardiology Hospital) is a large prospective, open label, all comers study evaluating the impact of post stenting FFR on long-term clinical outcomes.

Consecutive patients undergoing coronary intervention with stent implantation, irrespectively of the clinical presentation were considered for the study. Culprit lesions in patients presenting with ST- elevation or non ST-elevation acute coronary syndromes were included in the analysis. Exclusion criteria comprised age <18 years, cardiogenic shock, high-risk PCI with mechanical circulatory support, vessel size <2.25 mm by visual estimation, uncertain neurological outcome after cardiopulmonary resuscitation, planned CABG as a staged procedure (hybrid) within 12 months of the index procedure. The data that support the findings of this study are available from the corresponding author upon reasonable request

## Post stenting FFR measurements and analysis

Functional assessments were performed at the end of the procedure when the operator considered the angiographic result acceptable and final.

The Guide-wire access to the vessel was maintained and was used to advance a monorail microcatheter with an optical pressure FFR sensor technology (Navvus RXi, ACIST Medical Systems, Eden Prairie, MN).[11]

For post-stenting FFR values the microcatheter sensor was positioned in the mid-distal segment of the investigated vessel and at least 20 mm distal of the most distal stent edge and hyperaemia was induced with a continuous intravenous infusion of adenosine at 140 µg/kg/minute for at least 2 minutes.

As per study protocol and in order not to bias the predictive value of post-PCI FFR no additional interventions were performed regardless of the final post-PCI FFR value.[12]

Based on previous reports, comparisons in terms of long-term clinical outcomes were made using a post-PCI FFR cut-off value of 0.90. [7, 10] In the patient-level analysis, patients were stratified based on the presence at least one post-PCI FFR value <0.90. Therefore, for the patient-level analysis the patients were divided into two groups: 1) at least one FFR<0.90 and 2) No any FFR<0.90. In addition a vessel level analysis was performed.

The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee. All patients provided written informed consent for the procedure and the use of anonymous data-sets for research purposes in alignment with the Dutch Medical Research Act.

## Quantitative Coronary Angiography

Two-dimensional quantitative coronary angiography (2D-QCA) was performed for descriptive purposes, pre- and post-stent implantation in all treated lesions, using angiographic projections with minimal foreshortening of the lesion and minimal overlap with others coronary vessels. Analyses were performed with a dedicated quantitative coronary angiography (QCA) analysis software (CAAS Workstation, Pie Medical Imaging, Maastricht, the Netherlands). QCA measurements included lesion length, reference diameter, minimal lumen diameter, and diameter stenosis. In case of totally occluded vessels either acutely or chronically the minimal lumen diameter value was considered 0% and diameter stenosis 100% in the pre-stenting analysis and reference vessel diameter and lesion length were calculated from the first angiographic view with restored flow.

## Clinical Follow-up and definitions

Clinical follow-up was obtained for each patient from electronic medical records of the hospital, general practitioner, and the municipal civil records databases. In addition, all patients were contacted personally by letter or telephone. Clinical events including all-cause mortality, cardiac mortality, any spontaneous myocardial infarction, target vessel revascularization, any revascularization and stent thrombosis, were collected.

The primary endpoint was major adverse cardiac events (MACE), defined as a composite of cardiac death, any spontaneous myocardial infarction or any revascularization. The secondary end-points were target vessel revascularizations (TVR), Target vessel myocardial infarction (TVMI), stent thrombosis (ST) and the separate components of the primary endpoint. Cardiac death was defined as any death in which a cardiac cause could not be excluded. [13] Myocardial infarction (MI) was defined according to the fourth universal definition of myocardial infarction.[14] Target vessel revascularization (TVR) was defined as a re-intervention driven by any lesion located in the same epicardial vessel. Target vessel myocardial infarction (TVMI), was defined as a re-MI driven by any lesion located in the same epicardial vessel. Stent thrombosis was defined according to the ARC 2 definitions [13]. Event adjudication was performed by two independent cardiologists unaware of the final physiological assessment.

## Statistical analysis

Baseline, categorical variables are reported as counts and percentages and compared using the Chi Squared test on patient level and generalized linear mixed models (GLMM) with random intercepts on vessel level. Baseline, continuous data are presented as mean with standard deviation for normally distributed variables and as medians with interquartile range for variable that were not normally distributed. Differences between both groups for continuous data were assessed using the independent t-test on patient level and GLMM with random intercepts on vessel level.

The Kaplan-Meier method was applied to show the cumulative incidence of clinical endpoints. The association between post PCI FFR and clinical endpoints was analysed by Cox proportional hazard regression analysis. First the analysis was performed univariably. Then all models were adjusted for a set of potential confounders, which were chosen based on clinical relevance. Specifically. in the 'patient level' analyses the associations of post PCI FFR with MACE, cardiac death, MI and any revascularization were adjusted for gender, hypertension, dyslipidaemia, diabetes, smoking, peripheral arty disease, prior PCI, prior infarction, prior CABG, STEMI, NSTEMI and stable angina.

For the analysis on a vessel level, Cox regression with robust standard errors was used to account for the correlation between the vessels in case multiple vessels were assessed within one patient. In these analyses, the associations of post PCI FFR with TVR and Stent thrombosis were adjusted for bifurcation, severe calcification, in-stent restenosis, thrombotic culprit lesion in STEMI, CTO

and stented region located in the left anterior descending artery. Data are presented as Hazard-Ratios (HRs) with 95% confidence intervals (CI 95%).

All tests were two-tailed and a P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS statistics for Windows, version 24.0 (SPSS, Chicago, IL, USA) and R (version 3.4.1).

## RESULTS

A total of 1512 patients were screened and 1000 patients with 1207 treated vessels were included. Post-PCI FFR measurement was successfully performed in 959 patients and 1165 vessels (Table 1, Table 2, Figure 1). No complications related to the use of the FFR microcatheter were observed (Table 3). A post-PCI FFR <0.90 was reported in 440 vessels (37.8%), and ≤0.80 in 90 (7.7%) vessels (Figure 2). Baseline clinical characteristics are reported in Table 1.

**Table 1.** Baseline clinic characteristics

| | All patients (n=959) | FFR <0.90 (n=399) | FFR ≥0.90 (n=560) | p-value |
|---|---|---|---|---|
| Age (years) | 64.6±11.8 | 64.7±11.3 | 64.2±12.4 | 0.335 |
| Male gender (n) | 725 (76) | 301 (75) | 424 (75) | 0.090 |
| **Cardiovascular risk factors, n(%)** | | | | |
| Hypertension | 515 (54) | 228 (57) | 287 (51) | 0.005 |
| Hypercholesterolemia | 451 (45) | 206 (52) | 245 (44) | 0.001 |
| Diabetes | 191 (20) | 97 (24) | 94 (17) | 0.001 |
| Current smoker | 499 (52) | 184 (46) | 315 (56) | 0.056 |
| Prior stroke | 77 (8) | 37 (9) | 40 (7) | 0.128 |
| Peripheral art. Disease | 76 (8) | 42 (11) | 34 (6) | 0.004 |
| **Comorbidity, n(%)** | | | | |
| Prior myocardial infarction | 203 (21) | 100 (25) | 103 (18) | 0.002 |
| Prior PCI | 264 (28) | 120 (30) | 144 (28) | 0.032 |
| Prior CABG | 57 (6) | 17 (4) | 40 (7) | 0.110 |
| Hb level (mmol/L), mean±SD | 8.7±1.0 | 8.6±1.0 | 8.7±1.0 | 0.568 |
| Creatinine (µmol/L), median (IQR) | 84 (72-99) | 85 (73-98) | 83 (71-99) | 0.030 |
| **Presentation, n(%)** | | | | <0.001 |
| Stable angina | 304 (32) | 151 (38) | 153 (27) | |
| Unstable angina / NSTEMI | 367 (38) | 167 (42) | 200 (36) | |
| STEMI | 329 (34) | 81 (20) | 248 (44) | |

BMI= body mass index; CABG= coronary artery bypass graft; Hb= haemoglobin; IQR= Interquartile range; (N) STEMI= (non) ST-elevation myocardial infarction; PCI= percutaneous coronary intervention.

**Table 2.** Procedural Characteristics

| | All vessels with post-PCI FFR (n=1165) | FFR <0.90 (n=440) | FFR ≥0.90 (n=725) | p-value |
|---|---|---|---|---|
| **Lesion type, n(%)** | | | | |
| A | 125 (11) | 34 (8) | 91 (13) | 0.012 |
| B1 | 233 (20) | 84 (19) | 149 (21) | 0.557 |
| B2 | 379 (33) | 150 (34) | 229 (32) | 0.380 |
| C | 428 (37) | 172 (39) | 256 (35) | 0.198 |
| Bifurcation | 138 (12) | 78 (18) | 60 (8) | <0.001 |
| Calcified | 402 (35) | 196 (45) | 206 (28) | <0.001 |
| In-stent restenosis | 39 (3) | 24 (6) | 15 (2) | 0.003 |
| Thrombus | 214 (18) | 47 (11) | 167 (23) | <0.001 |
| Stent thrombosis | 14 (1) | 7 (1) | 7 (1) | 0.351 |
| Ostial | 97 (8) | 38 (9) | 59 (8) | 0.783 |
| CTO | 42 (4) | 24 (6) | 18 (3) | 0.011 |
| **Measured vessel, n (%)** | | | | |
| Right coronary artery | 331 (28) | 57 (5) | 274 (24) | <0.001 |
| Left Main | 19 (2) | 12 (1) | 7 (1) | 0.029 |
| Left anterior descending artery | 593 (51) | 339 (29) | 254 (35) | <0.001 |
| Left circumflex artery | 211 (18) | 32 (3) | 179 (15) | <0.001 |
| Coronary Artery Bypass Graft | 10 (1) | 0 (0) | 10 (1) | * |
| **2D-QCA measurements;** median (IQR) | | | | |
| Stenosis Pre, %; | 63 (50-78) | 56 (44-70) | 67 (53-86) | <0.001 |
| Stenosis Post, % | 4 (-4-13) | 4 (-5-13) | 5 (-3-13) | 0.190 |
| MLD Pre, mm | 0.92 (0.56-1.34) | 1.0 (0.7-1.4) | 0.9 (0.4-1.3) | <0.001 |
| MLD Post, mm | 2.60 (2.25-2.93) | 2.5 (2.2-2.8) | 2.7 (2.3-3.0) | <0.001 |
| Stent length, mm | 23 (15-36) | 26 (15-40) | 22 (15-35) | 0.004 |
| Stent diameter, mm | 3 (3-4) | 3 (2.75-3.5) | 3 (2-5) | <0.001 |
| No. of Stents, n mean±SD | 1.4±0.6 | 1.4±0.7 | 1.3±0.6 | 0.007 |
| Pre-dilation, n (%) | 769 (66) | 328 (75) | 441 (38) | <0.001 |
| Post-dilation, n (%) | 691 (59) | 305 (69) | 386 (53) | <0.001 |
| FFR, mean±SD | 0.91±0.07 | 0.84±0.05 | 0.95±0.03 | <0.001 |

Vessel-based analysis: CTO= chronic total occlusion; IQR= Interquartile range; MLD= minimum luminal diameter; *Not tested due to complete separation. Data are reported as mean ± SD or median and IQR

In brief the mean age was 64.6±11.8 years, 19% of patients had diabetes, 70% of the coronary lesions were B2 (33%), or C (37%) with a median stent length of 23mm (IQR 15-36) and a median post-stenting MLD of 2.6mm (IQR 2.25-2.93). Patients with a final post-stenting FFR<0.90 more frequently had hypertension (58% vs 49%, p=0.005), hypercholesterolemia (52% vs 42%, p=0.001), diabetes, (24% vs 16%, p=0.001). Patients with a final post-stenting FFR ≥0.90 presented more often with a STEMI (20% vs 41%, p <0.001) (Table 1). Vessels with a final post-stenting FFR <0.90

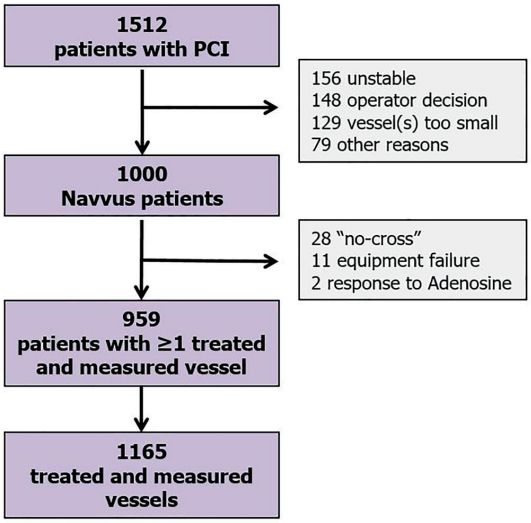



**Figure 1.** Study flow-chart

were more often calcified (45% vs 28%, p<0.001) and less frequently thrombotic (11% vs 23%, p<0.001).

Vessels with post-stenting FFR ≥0.90 showed a smaller pre-intervention MLD of 0.9mm (IQR 0.4-1.3) vs 1.0 (IQR 0.7-1.4), p<0.001) by QCA, but a larger post-procedure MLD (median 2.7 vs 2.5mm, p<0.001).

Mean follow-up was 655±183 days. Complete 2-year follow-up was available in 849 patients (88,5%), 39 had at least 1-year follow-up, 59 patients had follow up between 1-365 days, 12 patients were lost at follow up.

**Table 3.** Post-stenting FFR measurements and microcatheter performance

| | **All vessels (n=1207)** |
|---|---|
| Successful post-PCI FFR, mean±SD | 96.5% (1165) |
| Average Pd/Pa 20mm distal of stent, mean±SD | 0.96 ± 0.04 |
| Average FFR value 20mm distal of stent, mean±SD | 0.91 ± 0.07 |
| Average FFR value distal stent edge, mean±SD | 0.95 ± 0.06 |
| Average FFR value proximal stent edge, mean±SD | 0.98 ± 0.04 |
| Average drift value, median (IQR) | 0.01 (0.00-0.02) |
| Average time per lesion (minutes) , mean±SD | 5.0 ± 1.4 |
| FFR microcatheter related complications, n (%) | 0 (0) |

Data are reported as mean ± SD or median and IQR

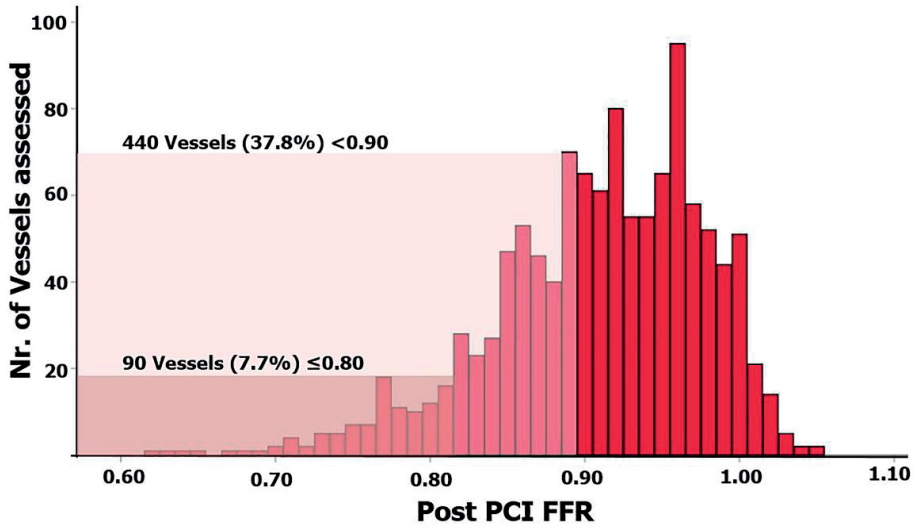



**Figure 2.** Vessels distribution per 0.01 FFR increment

At the univariate analysis and after adjustment for confounders, in the patient level analysis, no associations were found between post PCI FFR and MACE (HR 1.08, [95% CI, 0.73-1.60] p=0.707), cardiovascular death (HR 1.55 [95% CI, 0.72-3.36] p=0.261) and any myocardial infarction (HR 1.53 [95% CI, 0.78-3.02] p=0.217) (Table 4, Figure 3).

In the individual vessel level analysis, a higher rate of TVR (HR 1.91, [95%CI, 1.06-3.44], p=0.030) and a tendency towards higher rate of ST (HR 2.89, [95%CI, 0.88-9.48], p=0.081) was observed with a final post-stenting FFR <0.90 (Table 4, Figure 4).

After performing the predefined analysis we evaluated in an exploratory fashion several different cut-off values including post-PCI FFR 0.85. However results on overall MACE did not changed in terms of significant differences between groups.

In addition a separate analysis was performed excluding patients presenting with ST-elevation myocardial infarction (STEMI). After adjusting for confounders, no differences between groups were observed in both patient and vessel level analyses (Supplemental Table 1, Supplemental Table 2, Supplemental Table 3).

**Table 4.** Clinical outcomes at 2-year follow-up

| | Total | FFR <0.90 | | FFR ≥0.90 | | Univariate | | Multivariate | |
|---|---|---|---|---|---|---|---|---|---|
| | | Patients with event n (%) | KM estimate at 2 yr (%) | Patients with event n (%) | KM estimate at 2 yr (%) | HR [95% CI] | p-value | HR [95% CI] | p-value |
| **Patient-based analysis** | **959** | **N=399 (41.6%)** | | **N=560 (58.4%)** | | | | | |
| MACE | 113 (11.8) | 52 (13.0) | 13.7 | 61 (10.9) | 11.8 | 1.17 [0.81-1.70] | p=0.40 | 1.08 [0.73-1.60] | p=0.71 |
| Cardiovascular Death | 30 (3.1) | 16 (4.0) | 4.2 | 14 (2.5) | 2.7 | 1.58 [0.77-3.23] | p=0.21 | 1.55 [0.72-3.36] | p=0.26 |
| Any Myocardial Infarction | 28 (2.9) | 21 (5.3) | 5.6 | 7 (1.3) | 3.3 | 1.72 [0.91-3.27] | p=0.10 | 1.53 [0.78-3.02] | p=0.22 |
| Any Revascularization | 87 (9.1) | 41 (10.3) | 11 | 46 (8.2) | 9.0 | 1.23 [0.81-1.88] | p=0.33 | 1.10 [0.71-1.73] | p=0.67 |
| **Vessel-based analysis** | **1165** | **N=440(37.8%)** | | **N=725 (62.2%)** | | | | | |
| TVR | 49 (4.2) | 25 (5.7) | 6.2 | 24 (3.3) | 3.7 | 1.71 [0.98-2.99] | p=0.06 | 1.91 [1.06-3.44] | p=0.03 |
| TVMI | 24 (2.1) | 12 (2.7) | 2.9 | 12 (1.7) | 1.8 | 1.64 [0.76-3.52] | p=0.21 | 1.45[0.66-3.18] | p=0.35 |
| Stent thrombosis | 26 (2.2) | 10 (2.3) | 2.4 | 16 (2.2%) | 0.9 | 2.71 [0.99-7.46] | p=0.05 | 2.89 [0.88-9.48] | p=0.08 |

Data are presented as Hazard ratio (HR) [95% Confidence Interval (CI)] p-value. MACE= Composite endpoint of cardiac death, myocardial infarction and any revascularization; TVR= Target vessel revascularization; TVMI= target vessel myocardial infarction. KM= Kaplan-Meier, in the KM estimate column percentages are cumulative incidence rates. Extended Cox regression with time-dependent covariate modelling was performed.

- Adjusted confounders on patient-based level: gender, hypertension, dyslipidaemia, diabetes, smoking, peripheral arty disease, prior PCI, prior infarction, prior CABG, STEMI, NSTEMI and stable angina.
- Adjusted confounders on vessel-based level: bifurcation, severe calcification, in-stent restenosis, thrombotic culprit lesion in STEMI, CTO and stented region located in the left anterior descending artery.

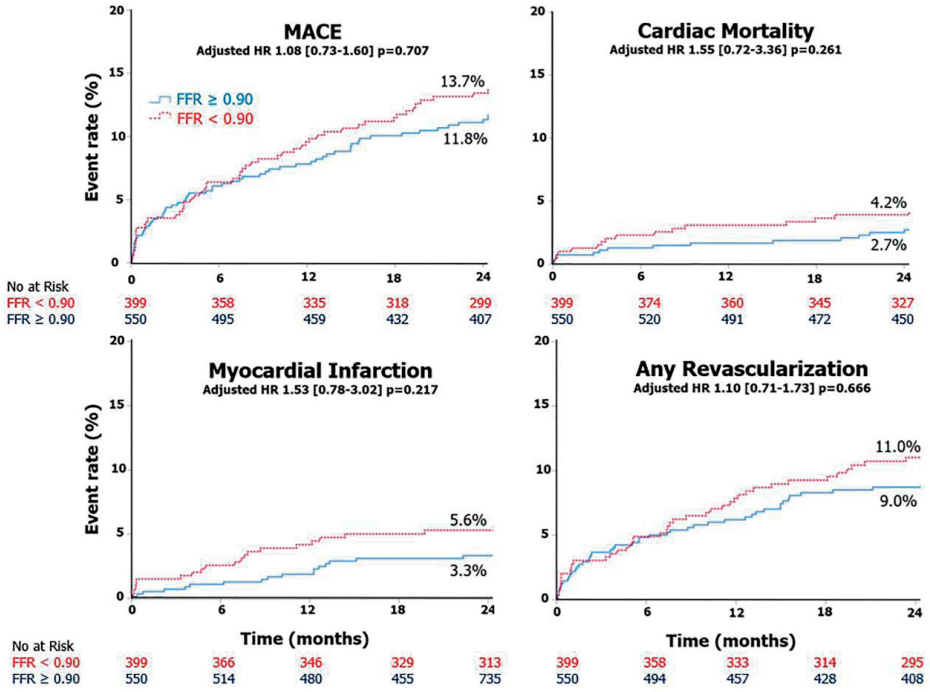



**Figure 3.** Kaplan-Meier curves for MACE, cardiovascular mortality, myocardial infarction and any revascularization. Patient-based analysis.

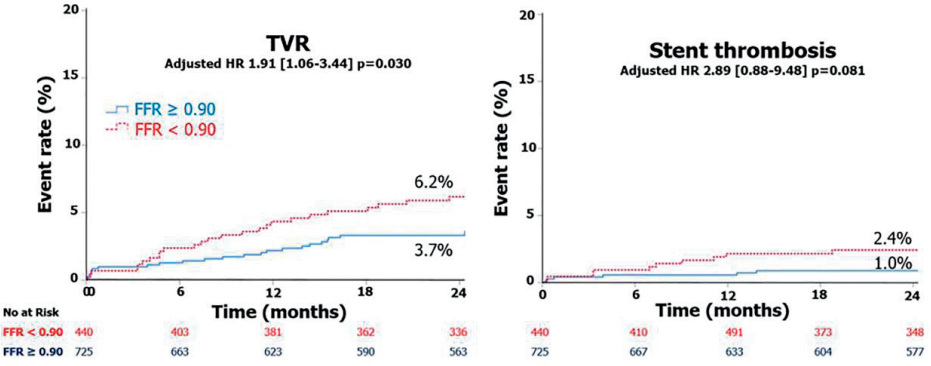



**Figure 4.** Kaplan-Meier curves for target vessel revascularization and stent thrombosis. Vessel-level analysis.

## DISCUSSION

FFR SEARCH is the largest prospective study to date evaluating the impact of microcatheter based post-stenting FFR on long-term clinical outcomes. The main findings of our study are: 1) post-stenting FFR is safe, feasible and can be easily performed when using a rapid exchange micro-catheter maintaining wire access. 2) Impaired coronary physiology expressed by FFR < 0.90 was common (37.8% of patients). 3) Post PCI FFR < 0.90 was not associated with overall MACE. But on a vessel level analysis FFR < 0.90 post PCI resulted into a higher rate of target vessel revascularizations and a trend towards higher rate of stent thrombosis during a follow up of 2 years.

A large body of evidence has cemented FFR as the standard for invasive ischemia detection in the catheterization laboratory and both American and European clinical guidelines have formulated strong recommendations for FFR evaluation in intermediate coronary stenosis [4, 15]. Conversely, not much is known about the relevance of coronary physiology to address PCI results.

Post-PCI FFR with a rapid exchange microcatheter appeared safe and easy to execute over the coronary guidewire that was previously used for PCI mitigating the need for additional wire manipulations and concomitant risk of wire passage behind stent struts and coronary dissections.[11]

The FFR cut-off < 0.90 was derived from a post-hoc analysis of the FAME Trials [9] and was supported by a large meta-analysis[10], however, never tested in a prospective fashion. Using this threshold more than one third of the final results judged as acceptable by angiography were categorized as sub-optimal, highlighting its clinical relevance. On the other hand we cannot exclude that lower cut-off values might have a similar or even higher association with clinical events.

The comparison of clinical outcomes on a patient-level analysis showed a consistent numerical, although non-statistically significant, increase in clinical events in subjects with suboptimal post-PCI FFR values. Such results are in line with previous retrospective studies or post-hoc analyses suggesting a moderate impact of sub-optimal post PCI FFR on hard clinical end-points and a more relevant impact on vessel-specific end-points.[7, 8] Piroth Z. and collegues, comparing the 2-year outcome of lower and upper tertiles of post-PCI FFR reported a significant increase of the vessel oriented composite end point (VOCE), defined as the composite of vessel-related cardiovascular death, vessel-related spontaneous (nonperiprocedural) MI, and ischemia-driven target vessel revascularization (9.2%vs3.8%, p=0.037) [7]. Lee J.M. showed in patients with low post-PCI FFR a higher risk of 2-year TVF compared with those with high post-PCI FFR (9.1% vs. 2.6%, p . 0.006)[8]. Similarly in the DKCRUSH prospective registry Post-DES FFR strongly correlated with TVF rate[16]. Importantly, lesions with FFR <0.90 post PCI were associated with more TVR and a numerical increase of definite stent thrombosis, this analysis might be able to better capture the real impact of a single post-stenting FFR values on a specific vessel.

From a mechanistic point of view, post-stenting FFR indicates residual flow impairment during maximal hyperaemia[7]. Various factors that may not be appreciated by conventional angiography might contribute to the flow impairment, such as proximal or distal residual focal stenosis, stent underexpansion, or diffuse atherosclerotic disease [17-19]. Invasive coronary imaging may help elucidate the pathophysiologic mechanism of impaired coronary flow and guide corrective measures including high-pressure balloon post-dilation, additional stenting or drug eluting balloon therapy.

Optimization of a suboptimal post PCI FFR may be challenging and FFR pullbacks can help identifying focal drops or more gradual decreases.[1, 20] Still, FFR pullbacks are not devoid of limitations, such as the absence of a clear threshold [21], the need for prolonged adenosine infusion, with possible patients discomfort and unstable hyperaemia, the occurrence of pressure recovery affecting pressure gradients and often increasing the proportion of focal lesion identification [20, 22] and finally cases with no clear FFR drop but a diffuse pressure loss indicating a diffuse disease, particularly challenge to treat with local therapies.[21] therefore, intravascular coronary imaging may complement post PCI FFR.

In this context the currently on-going FFR REACT Trial (NTR6711) [23] is randomizing patients with a post PCI FFR <0.90 to either standard of care (no additional intervention) or intravascular ultrasound (IVUS) directed optimization. The primary end point is the composite of cardiac death, target vessel MI and clinically driven target vessel revascularisation (target vessel failure) at 1 year.

## LIMITATIONS

FFR SEARCH is a single centre study. The sample size is limited and might be not sufficient to highlight differences in terms of hard clinical outcomes. The present study was performed in an all-comers population with a relevant number of patients presenting with acute myocardial infarction. The occurrence of microvascular dysfunction in the myocardial territory supplied by the infarct-related artery might often results in higher post-PCI FFR values. Given the observational nature of the analysis, the results do not evaluate the clinical benefit of additional intervention in vessels with sub-optimal post-PCI FFR. No direct comparisons between microcathter based and wire based FFR was performed in terms of stented lesion crossability. Further large randomized trials are needed to fully investigate the relation between sub-optimal post-PCI FFR and clinical events and to elucidate PCI optimization strategies.

## CONCLUSIONS

FFR< 0.90 occurs in approximately one third of patients post stenting. Suboptimal Post-PCI FFR has only a moderate impact on MACE. Post PCI FFR <0.90 is associated with a higher rate of target vessel revascularizations.

## REFERENCES

1. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek JKJJ and Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703-8.
2. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-24.
3. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, Engstrom T, Kaab S, Dambrink JH, Rioufol G, et al. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *N Engl J Med*. 2018;379:250-259.
4. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
5. Hakeem A and Uretsky BF. Role of Postintervention Fractional Flow Reserve to Improve Procedural and Clinical Outcomes. *Circulation*. 2019;139:694-706.
6. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF and Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. *JACC Cardiovasc Interv*. 2016;9:1022-31.
7. Piroth Z, Toth GG, Tonino PAL, Barbato E, Aghlmandi S, Curzen N, Rioufol G, Pijls NHJ, Fearon WF, Juni P et al. Prognostic Value of Fractional Flow Reserve Measured Immediately After Drug-Eluting Stent Implantation. *Circ Cardiovasc Interv*. 2017;10:1-10.
8. Lee JM, Hwang D, Choi KH, Rhee TM, Park J, Kim HY, Jung HW, Hwang JW, Lee HJ, Jang HJ, et al. Prognostic Implications of Relative Increase and Final Fractional Flow Reserve in Patients With Stent Implantation. *JACC Cardiovasc Interv*. 2018;11:2099-2109.
9. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, Escaned J, Tsurumi Y, Akasaka T, Samady H, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. *Circulation*. 2002;105:2950-4.
10. Rimac G, Fearon WF, De Bruyne B, Ikeno F, Matsuo H, Piroth Z, Costerousse O and Bertrand OF. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis. *Am Heart J*. 2017;183:1-9.
11. Diletti R, Van Mieghem NM, Valgimigli M, Karanasos A, Everaert BR, Daemen J, van Geuns RJ, de Jaegere PP, Zijlstra F and Regar E. Rapid exchange ultra-thin microcatheter using fibre-optic sensing technology for measurement of intracoronary fractional flow reserve. *EuroIntervention*. 2015;11:428-32.
12. van Bommel RJ, Masdjedi K, Diletti R, Lemmert ME, van Zandvoort L, Wilschut J, Zijlstra F, de Jaegere P, Daemen J and van Mieghem NM. Routine Fractional Flow Reserve Measurement After Percutaneous Coronary Intervention. *Circ Cardiovasc Interv*. 2019;12:e007428.
13. Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel MA, van Es GA, Zuckerman B, et al. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. *Eur Heart J*. 2018;39:2192-2207.
14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD and Group ESCSD. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40:237-269.
15. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ and Smith PK. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease: A Report of the American College of Cardiology Appropriate Use

Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;69:2212-2241.

16. Li SJ, Ge Z, Kan J, Zhang JJ, Ye F, Kwan TW, Santoso T, Yang S, Sheiban I, Qian XS, et al. Cutoff Value and Long-Term Prediction of Clinical Events by FFR Measured Immediately After Implantation of a Drug-Eluting Stent in Patients With Coronary Artery Disease: 1- to 3-Year Results From the DKCRUSH VII Registry Study. *JACC Cardiovasc Interv*. 2017;10:986-995.
17. van Zandvoort LJC, Masdjedi K, Witberg K, Ligthart J, Tovar Forero MN, Diletti R, Lemmert ME, Wilschut J, de Jaegere PPT, Boersma E, et al. Explanation of Postprocedural Fractional Flow Reserve Below 0.85. *Circ Cardiovasc Interv*. 2019;12:e007030.
18. Baranauskas A, Peace A, Kibarskis A, Shannon J, Abraitis V, Bajoras V, Bilkis V, Aidietis A, Laucevicius A and Davidavicius G. FFR result post PCI is suboptimal in long diffuse coronary artery disease. *EuroIntervention*. 2016;12:1473-1480.
19. Wolfrum M, De Maria GL, Benenati S, Langrish J, Lucking AJ, Channon KM, Kharbanda RK and Banning AP. What are the causes of a suboptimal FFR after coronary stent deployment? Insights from a consecutive series using OCT imaging. *EuroIntervention*. 2018;14:e1324-e1331.
20. Collet C, Sonck J, Vandeloo B, Mizukami T, Roosens B, Lochy S, Argacha JF, Schoors D, Colaiori I, Di Gioia G, et al. Measurement of Hyperemic Pullback Pressure Gradients to Characterize Patterns of Coronary Atherosclerosis. *J Am Coll Cardiol*. 2019;74:1772-1784.
21. Tonino PA and Johnson NP. Why Is Fractional Flow Reserve After Percutaneous Coronary Intervention Not Always 1.0? *JACC Cardiovasc Interv*. 2016;9:1032-5.
22. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med*. 2017;376:1824-1834.
23. van Zandvoort LJC, Masdjedi K, Tovar Forero MN, Lenzen MJ, Ligthart J, Diletti R, Lemmert ME, Wilschut J, de Jaegere PPT, Zijlstra F, et al. 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. *Am Heart J*. 2019;213:66-72.

# Chapter

# 6

# Explanation of post-procedural Fractional Flow Reserve below 0.85: A comprehensive ultrasound analysis of the FFR SEARCH registry

Laurens J.C. van Zandvoort BSc, **Kaneshka Masdjedi MD,** Karen Witberg RN, Jurgen Ligthart RT, Natalia Forero Tovar MD, Roberto Diletti MD PhD, Miguel E. Lemmert MD PhD, Jeroen Wilschut MD, Peter P.T. de Jaegere MD PhD, Eric Boersma MSc PhD, Felix Zijlstra MD PhD, Nicolas M. Van Mieghem MD PhD, Joost Daemen MD PhD

**Department of cardiology, Thoraxcenter, Erasmus Medical Center**

**Journal:** Circulation Cardiovascular Interventions; 2019;12:e007030.

## ABSTRACT

**Background:** Fractional flow reserve (FFR) after percutaneous coronary intervention (PCI) is a predictor of adverse cardiovascular events during follow-up. However the rationale for low post procedural FFR values remains often elusive based on angiographic findings alone.

**Methods and Results:** FFR SEARCH is a prospective single center registry in which post PCI FFR was assessed in 1,000 consecutive all-comer patients. FFR measurements were performed with a microcatheter ±20 mm distal to the most distal stent edge. In 100 vessels with a post procedural FFR ≤0.85, and 20 vessels >0.85 high definition intravascular ultrasound analysis (IVUS) was performed.

In 100 vessels with a post PCI FFR ≤0.85, mean post procedural FFR was 0.79±0.05. Minimal lumen area was 2.19 (1.81-3.19) $mm^2$, mean lumen area was 5.95 (5.01-7.03) $mm^2$ and minimal stent area was 4.01 (3.09-5.21) $mm^2$. Significant residual focal proximal lesions were found in 29% of the assessed vessels while focal distal lesions were found in 30% of the vessels. Stent underexpansion and malapposition were found in 74% and 22% of vessels respectively. Clear focal signs of luminal narrowing were found in 54% of the vessels analysed. While incidences of focal lesions, underexpansion and malapposition were similar between both cohorts, minimal stent area was significantly smaller in vessels with a post PCI FFR ≤0.85 as compared to those with an FFR >0.85.

**Conclusions:** In patients with a post procedural FFR ≤0.85, IVUS revealed focal signs of luminal narrowing in a significant number of cases.

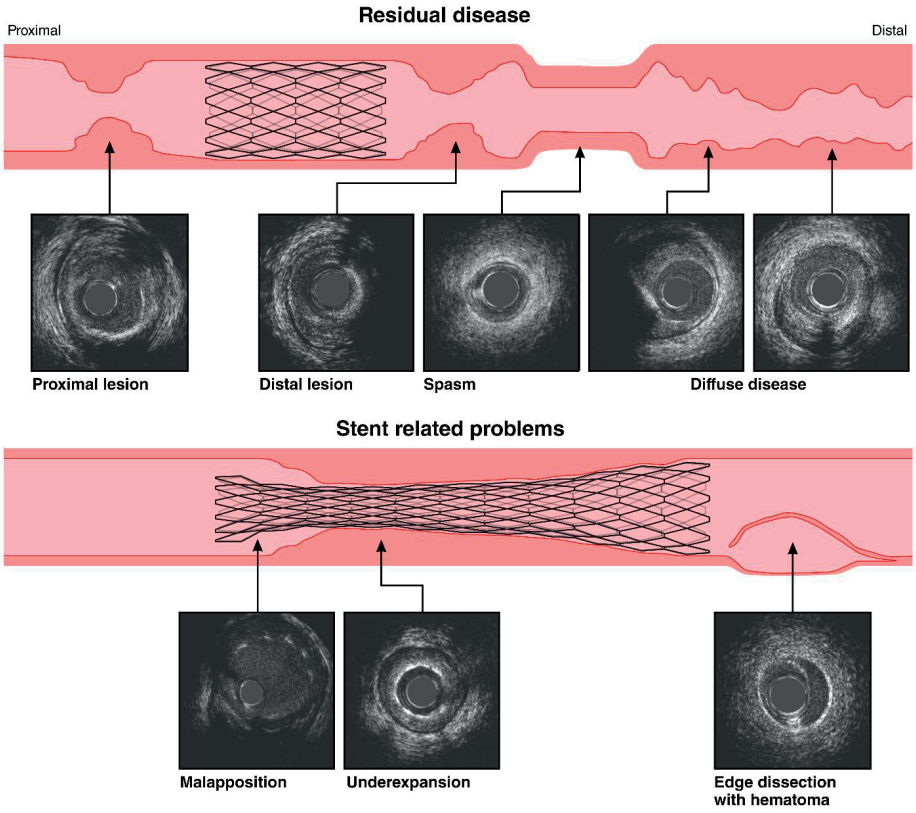
**Key words**: Percutaneous coronary intervention, post PCI FFR, IVUS

### What's known?

- FFR after stenting is a strong and independent predictor of major adverse cardiac events.
- Unfortunately, the rationale for low post procedural FFR values often remains elusive based on angiographic findings alone.

### What the study adds?

- Residual treatable lesions or lumen compromising hematomas were present in 54% in vessels with a post PCI FFR ≤0.85.
- Underexpansion was present in 75% of the treated vessel
- More data on the use of post-PCI FFR values, their association with intravascular findings and potential further treatment in order to improve clinical outcome is warranted.




**Central illustration.** IVUS detected causes of post PCI FFR ≤ 0.85.

## INTRODUCTION

In order to overcome the limitations of angiographic lesion assessment, fractional flow reserve (FFR) has proven to be a useful tool to identify the hemodynamic impact of a coronary artery stenosis[1]. Several randomized trials have demonstrated that a routine pre-procedural FFR measurement in patients with multivessel coronary artery disease undergoing percutaneous coronary intervention (PCI) significantly reduces the composite endpoint of death, nonfatal myocardial infarction, and repeat revascularization at 1 year as compared to angiographic guidance alone[2]. More recently, FFR after stenting has proved to be a strong and independent predictor of major adverse cardiac events (MACE) up to 2 years[3-5]. The actual scope of the problem of low post PCI FFR was illustrated by recent work from our group demonstrating that in up to 43% of the cases, post PCI FFR values ≤0.90 were found while in 20% of the cases post PCI FFR even dropped below 0.85[6].

Unfortunately, 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[7-11]. The primary objective of the current study was to look for morphological reasons for a post procedural FFR ≤0.85 in a real world patient cohort with the help of high definition intravascular ultrasound (HD-IVUS).

## METHODS

### Patient selection

The FFR SEARCH (Stent Evaluated at Rotterdam Cardiology Hospital) study is a prospective, all comer registry, enrolling 1512 consecutive patients who underwent successful PCI between March 2016 and May 2017. Among them, 512 patients were excluded due to several reasons (156 were unstable, in 129 patients the treated vessel was too small, in 148 cases it was operators decision not to perform an FFR and in 79 cases for other reasons). In a total of 1000 patients after angiographic confirmation of treatment success, FFR was measured. In 41 cases, no FFR measurements were performed because of failure of the microcatheter to cross the stented segment, equipment failure or the occurrence of an adverse reaction to adenosine. Finally, FFR was measured in at least one lesion in a total of 959 patients. A total of 1165 post PCI FFR measurements were performed. For the present prespecified subgroup analysis, IVUS analysis were performed in 100 consecutive vessels with a post procedural FFR ≤ 0.85 as well as 20 consecutive vessels with a post procedural FFR >0.85 between August 2016 and October 2017 in respectively 95 and 20 patients. No complications due to FFR measurements were encountered. The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee. All patients provided written informed consent for the procedure

and the use of anonymous datasets for research purposes in alignment with the Dutch Medical Research Act. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

### FFR and IVUS acquisition

After angiographic confirmation of treatment success, post procedural FFR measurements were performed using the Navvus rapid exchange monorail microcatheter (ACIST Medical Systems, Inc., Eden Prairie, MN, USA). Measurements were performed in all stented segments after an intracoronary bolus of nitrates (200 µg). Results were based on single FFR measurement performed at approximately 20 mm distal to the distal stent edge as well as single measurements at the distal stent edge, proximal stent edge and ostium. Whenever multiple vessels were treated, this method was performed in all treated vessels. Pd/Pa was defined as the ratio of mean distal coronary artery pressure to mean aortic pressure in the resting state during the whole cardiac cycle. FFR was 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 µg/kg/min through an antecubital vein. Pullback analyses were performed under hyperemic conditions measuring FFR at the distal stent edge, proximal stent edge and the ostium to test for drift.

IVUS imaging was performed with the multi frequency HD-IVUS Kodama catheter (ACIST Medical Systems, Inc., Eden Prairie, MN, USA) at 60Mhz with a pullback speed of 2.5 mm/sec (24 frames per mm). Imaging assessment was performed off-line every 0.5 mm using dedicated software (QCU-CMS, Leiden University Medical Centre, LKEB, Division of Image Processing, version 4.69) by three dedicated academic intravascular imaging specialists, blinded to the final FFR results. Focal lesions were manually detected and defined as treatable lesions with an appropriate landing zone either proximal or distal to the stented segment. Proximal focal lesions were defined as lesions proximal to the stented segment with a minimal lumen area (MLA) <4.0 $mm^2$ or <6.0 $mm^2$ in case of left main (LM) lesions. Additionally, the MLA at the residual proximal stenosis had to be smaller than the distal reference external elastic membrane (EEM) diameter [12, 13](figure 1). Distal focal lesions were assessed based solely on the criteria involving the size of the distal reference EEM diameter[12, 13]. Underexpansion, according to the MUSIC criteria, was defined as an in-stent MLA <90% of the average reference lumen area (LA)[14]. Reference LAs were measured 5 mm proximal and 5 mm distal to the implanted stent. If one of these locations could not be accounted for as a reference lumen due to a bifurcation, it was excluded and only one reference area was used. Stent malapposition was defined as incomplete strut apposition of at least one strut to the lumen wall, without involvement of side branches, thus permitting blood to flow between the struts and the underlying wall[15].

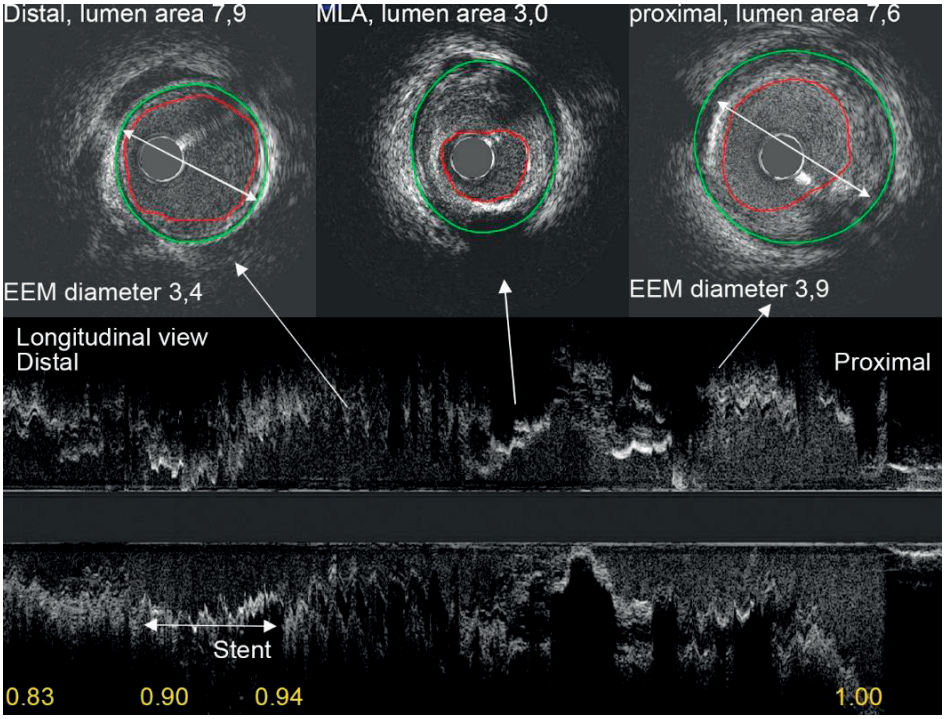



**Figure 1.** IVUS analysis of a focal lesion
Lumen areas are in $mm^2$ and diameters are in mm. EEM = External Elastic Membrane. MLA = minimum luminal area. The EEM, distal of the MLA, is smaller than the MLA, therefor, the luminal narrowing in this example can be categorised as a focal lesion. Values in yellow at the bottom of the figure represent the FFR measurements, from left to right: 15mm distal , distal stent edge, proximal stent edge and ostium respectively.

An intramural hematoma was defined as a severe lumen narrowing due to a intravascular stent edge dissection filled with blood within the medial space, displacing the internal elastic membrane inward and the external elastic membrane outward[15]. Non flow-limiting edge dissections were not assessed in this study.

Coronary vasospasm was defined as severe diffuse intimal thickening and a think media, often accompanied by negative remodelling, even in the absence of a significant coronary stenosis[16, 17].

### Quantitative coronary angiography

Angiographic success was assessed, offline, with the use of quantitative coronary angiography (QCA)( CAAS workstation 8.0, Pie Medical Imaging, Maastricht, The Netherlands). The treated vessels were divided into four segments: proximal segment (ostium to proximal stent edge); stented segment (in-stent analysis); stented segment with (including an additional 5 mm proximal and 5 mm distal to stent edges; in-segment analysis); the distal segment (distal stent edge to position where FFR was measured, at least 20mm from distal stent edge). If multiple stents were

implanted with a gap of more than 10 mm in-between, the gap segment was considered as a proximal segment. For each segment, length, minimal diameter (mm), diameter stenosis (%), reference diameter (mm), maximal diameter (mm) and mean diameter (mm) were calculated.

### Statistical analysis

Statistical analyses were performed by using R (version 3.5.1, packages: Hmisc, lme4 and nlme). Baseline, categorical variables are reported as either counts or percentages and compared using the Chi Squared test on patient level. Normality for continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables are reported as mean ± standard deviation (SD), Non-Gaussian variables are reported as median (interquartile range (IQR)). Normally distributed continuous variable were compared using a generalized linear mixed-effects model with a random effect for patients and a fixed effect for FFR groups, non-Gaussian variable were log transformed preparatory to the generalized linear mixed-effects model.

## RESULTS

Patient demographics and baseline characteristics are depicted in table 1. In the cohort of patients with a post PCI FFR ≤0.85, mean age was 65±12 years and 85% of the patients were male. Clinical presentation was stable angina in 42%, unstable angina or non ST elevated myocardial infarction (NSTEMI) in 45% and ST segment elevation myocardial infarction (STEMI) in 13% of the patients. In the vessels assessed an average of 1.6±0.8 stents were used with a median stent diameter of 3 (2.75-3.25) mm. Median total stented length was 28 (15-46) mm.

Comparable baseline characteristics were observed in the >0.85 cohort, with the exception of a lower total stented length. Mean post procedural Pd/Pa and FFR were 0.91±0.04 and 0.79±0.05 in the ≤0.85 cohort and 0.96±0.03 and 0.90±0.03 in patients with a post PCI FFR >0.85 respectively.

**Table 1.** Baseline characteristic

| | FFR ≤0.85 (n=95) (100 vessels) | FFR >0.85 (n=20) (20 vessels) | p value |
|---|---|---|---|
| Age, years | 65±12 | 66±12 | 0.67 |
| Gender, male | 81 (85) | 19 (95) | 0.29 |
| Hypertension | 58 (61) | 14 (70) | 0.40 |
| Hypercholesterolemia | 50 (53) | 50 (53) | 0.29 |
| Diabetes | 24 (25) | 6 (30) | 0.57 |
| Smoking history | 39 (41) | 6 (30) | 0.32 |
| Prior stroke | 11 (12) | 0 (0) | 0.23 |
| Peripheral art. disease | 6 (6) | 1 (5) | 0.86 |

**Table 1.** Baseline characteristic (continued)

| | FFR ≤0.85 (n=95) (100 vessels) | FFR >0.85 (n=20) (20 vessels) | p value |
|---|---|---|---|
| Prior PCI | 29 (31) | 7 (35) | 0.66 |
| Prior CABG | 3 (3) | 1 (5) | 0.65 |
| Indication | | | |
| Stable angina | 41 (43) | 9 (45) | 0.80 |
| Unstable angina or NSTEMI | 41 (43) | 8 (40) | 0.68 |
| STEMI | 13 (14) | 3 (15) | 0.81 |
| Target vessel | | | |
| Left anterior descending artery (LAD) | 81 (81) | 12 (60) | 0.24 |
| Left circumflex artery(LCX) | 7 (7) | 3 (15) | 0.25 |
| Left main artery (LM) | 3 (3) | 1 (5) | 0.65 |
| Right coronary artery (RCA) | 9 (9) | 4 (20) | 0.16 |
| Predilatation | 74 (74) | 10 (50) | 0.04 |
| High pressure post dilatation (NC balloon) | 74 (74) | 13 (65) | 0.41 |
| Mean post PCI Pd/Pa | 0.91±0.04 | 0.96±0.03 | <0.001 |
| Mean post PCI FFR | 0.79±0.05 | 0.90±0.03 | <0.001 |
| No. of vessels with a post PCI FFR ≤0.80 | 56 (56) | | |
| No. of vessels with a post PCI FFR ≤0.75 | 22 (22) | | |
| No. of stents | 1 (1-2) | 1 (1-1) | <0.001 |
| Mean stent diameter, mm | 3 (2.75-3.25) | 3.25 (3.0-3.5) | 0.13 |
| Total stent length, mm | 28 (15-46) | 21 (16-25) | 0.12 |

Values are n (%), mean±SD or median (IQR), PCI = Percutaneous Coronary Artery and CABG = Coronary Artery Bypass Grafting, NSTEMI = non ST elevated myocardial infarction, STEMI =ST elevated myocardial infarction. NC = non-compliant, Pd/Pa = the Pressure in the Distal coronary artery to the Pressure in the Aorta ratio, FFR = Fractional Flow Reserve under maximum hyperemia.

## IVUS analysis in the post PCI FFR ≤0.85 cohort

IVUS analyses showed a mean LA of 5.95 (5.01-7.03)$mm^2$ with an MLA of 2.19 (1.81-3.19) $mm^2$ and minimal stent area was 4.01 (3.09-5.21)$mm^2$ (table 2). Significant focal lesions proximal or distal to the stented segment were found in 29% and 30% of the vessels respectively. With an average of 1.6±0.8 stents implanted, a total of 115 nonadjacent stented segments were analysed. According to the MUSIC criteria stent underexpansion was present in 88% of these segments (74% of the vessels). Mean stent expansion rate in the segments was 78.7%. Malapposition was found in 21% of the segments (23% of the vessels). In 54% of the vessels clear focal signs of luminal narrowing were found due to residual focal lesions or lumen compromising hematoma (3%). Spasm was present in 9% of the vessels analysed and in 8% of the vessels diffuse disease was present.

**Table 2.** IVUS findings in 100 vessels with an FFR ≤0.85 and 20 vessel >0.85

| | FFR ≤0.85 (n=100) | FFR >0.85 (n=20) | p value |
|---|---|---|---|
| Mean lumen area, $mm^2$ | 5.95 (5.01-7.03) | 6.24 (5.12-8.10) | 0.15 |
| Minimal lumen area, $mm^2$ | 2.19 (1.81-3.19) | 2.92 (1.96-4.10) | 0.02 |
| Minimal stent area, $mm^2$ | 4.01 (3.09-5.21) | 5.11 (3.05-7.41) | 0.01 |
| Focal lesion (proximal) | 29 (29) | 3 (15) | 0.78 |
| MLA at proximal lesion, $mm^2$ | 2.98 (2.24-3.36) | 2.60 (2.30-2.60) | 0.98 |
| Focal lesion (distal) | 30 (30) | 6 (30) | 1.00 |
| MLA at distal lesion, $mm^2$ | 2.01 (1.68-2.12) | 2.51 (1.88-3.26) | 0.02 |
| Lumen compromising hematoma | 3 (3) | 0 (0) | 0.69 |
| MLA lumen compromising hematoma, $mm^2$ | 1.97 (1.22-1.97) | - | - |
| Underexpansion | 74 (74) | 15 (75) | 0.93 |
| Malapposition | 23 (23) | 1 (5) | 0.1 |
| Spasm | 9 (9) | 0 (0) | 0.31 |
| Diffuse diseased | 8 (8) | 0 (0) | 0.68 |
| Any focal lesion | 51 (51) | 9 (45) | 0.63 |
| Any focal lesion or lumen compromising hematoma | 54 (54) | 9 (45) | 0.37 |
| Any focal lesion, underexpansion, lumen compromising hematoma or malapposition | 84 (84) | 18 (90) | 0.99 |

Values are n (%) or median (IQR)

In 87% of the vessels, either a focal lesion, underexpansion, a lumen compromising hematoma or malapposition were present. A dedicated sub-analysis on vessels with FFR values ≤0.75 and ≤0.80 can be found in table 3.

## IVUS analysis in the post FFR PCI > 0.85 cohort

IVUS analysis of the 20 vessels with a post PCI FFR >0.85 showed a median LA 6.24 (5.12-8.10) $mm^2$ with an MLA of 2.92 (1.96-4.10) $mm^2$ and minimal stent area was 5.11 (3.05-7.41) $mm^2$ (table 2). Significant focal lesions proximal or distal to the stented segment were found in 15% and 30% of the vessels respectively. With an average of 1.0±0.0 stent implanted. According to the MUSIC criteria stent underexpansion was present in 75% of the vessels with a mean stent expansion rate of 79.6%. Malapposition was found in 1 vessel (5%). In 45% of the vessels clear focal signs of luminal narrowing were found due to residual focal lesions or lumen compromising hematoma (0 instances). Spasm and diffuse disease were not present in this cohort.

## Pressure drops per segment in the total cohort

FFR pullback data were available for 107/120 vessels. A significantly higher pressure drop over the proximal segment was found in vessels with residual proximal focal lesions as compared to segments with no residual proximal focal lesions (0.06±0.09 vs 0.03±0.06 respectively, p=0.004).

**Table 3.** IVUS findings according to incrementing groups of post PCI FFR

| | FFR ≤0.75 (n=22) | FFR ≤0.80 (n=56) | FFR ≤0.85 (n=100) | FFR >0.85 (n=20) |
|---|---|---|---|---|
| Mean lumen area, $mm^2$ | 5.99 (4.53-6.78) | 5.79 (4.68-6.95) | 5.95 (5.01-7.03) | 6.24 (5.12-8.10) |
| Minimal lumen area, $mm^2$ | 2.04 (1.49-2.92) | 2.14 (1.59-3.17) | 2.19 (1.81-3.19) | 2.92 (1.96-4.10) |
| Minimal stent area, $mm^2$ | 3.59 (4.53-6.78) | 3.87 (2.83-4.94) | 4.01 (3.09-5.21) | 5.11 (3.05-7.41) |
| Focal lesion (proximal) | 10 (46) | 18 (32) | 29 (29) | 3 (15) |
| MLA at proximal lesion, $mm^2$ | 3.12 (2.26-4.83) | 3.00 (2.26-3.51) | 2.98 (2.24-3.36) | 2.60 (2.30-2.60) |
| Focal lesion (distal) | 3 (14) | 13 (23) | 30 (30) | 6 (30) |
| MLA at distal lesion, $mm^2$ | 1.71 (1.40-1.71) | 2.03 (1.54-2.28 | 2.01 (1.68-2.12) | 2.51 (1.88-3.26) |
| Lumen compromising hematoma | 0 (0) | 1 (1.8) | 3 (3) | 0 (0) |
| MLA lumen compromising hematoma, $mm^2$ | - | 1.22 | 1.97 (1.22-1.97) | - |
| Underexpansion | 18 (82) | 40 (71) | 74 (74) | 15 (75) |
| Malapposition | 6 (27) | 17 (23) | 23 (23) | 1 (5) |
| Spasm | 2 (9) | 8 (14) | 9 (9) | 0 (0) |
| Diffuse diseased | 2 (9) | 6 (11) | 8 (8) | 0 (0) |
| Any focal lesion | 11 (50) | 27 (48) | 51 (51) | 9 (45) |
| Any focal lesion or lumen compromising hematoma | 11 (50) | 28 (50) | 54 (54) | 9 (45) |
| Any focal lesion, underexpansion, lumen compromising hematoma or malapposition | 19 (86) | 49 (88) | 84 (84) | 18 (90) |

Values are median (IQR) or absolute numbers (%). MLA is minimal lumen area

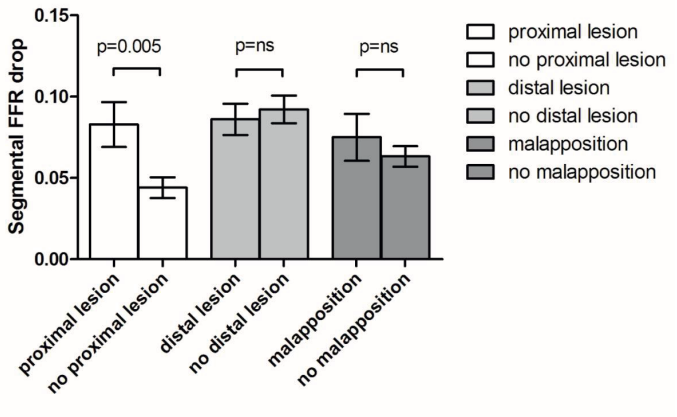



**Figure 2.** FFR drop by presence of residual lesions or malapposition
Values are means with error bars of the standard error of the mean

No significant differences in FFR drop were found in case of residual distal lesions (0.06±0.05 in the presence of a distal lesion vs. 0.05±0.06 in the absence of a distal lesion, p=0.92) or malapposition (0.06±0.06 with malapposition vs 0.05±0.06 without malapposition, p=0.22)(figure 2).

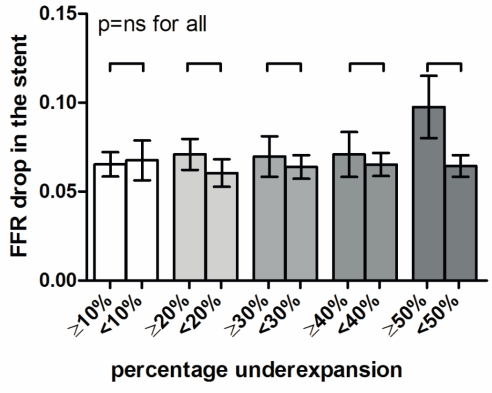



**Figure 3.** FFR drop by % of underexpansion
Values are means with error bars of the standard error of the mean

No significant changes in pressure drops over the stented segment were found in case of underexpansion according to either the MUSIC criteria or criteria with modified underexpansion limits, however, a trend was observed towards higher pressure drops along with more severe underexpansion rates (figure 3).

**Table 4.** Quantitative coronary angiography of the proximal and distal segment as well as in-segment and in-stent analysis.

| **Proximal segment** | | | | | | |
|---|---|---|---|---|---|---|
| | **FFR ≤0.85 (n=87)** | **FFR >0.85 (n=16)** | **p value** | **Proximal lesion* (n=31)** | **No proximal lesion* (n=72)** | **p value** |
| Length, mm | 17.20 (11.43-27.70) | 16.31 (12.01-30.77) | 0.99 | 27.01 (12.90-39.58) | 15.42 (9.02-24.74) | 0.19 |
| Minimal diameter, mm | 2.38 (1.97-2.99) | 2.43 (2.22-2.94) | 0.90 | 1.98 (1.67-2.21) | 2.52 (2.27-3.02) | <0.001 |
| Diameter stenosis, % | 20 (11-30) | 20.50 (12.25-28.00) | 0.91 | 29 (19-34) | 17.50 (11-25) | 0.17 |
| Stenosis>50%, % | 0 (0) | 0 (0) | - | 0 (0) | 0 (0) | - |
| Reference diameter, mm | 3.05 (2.69-3.56) | 3.20 (2.85-3.31) | 0.91 | 2.81 (2.24-3.36) | 3.17 (2.80-3.64) | 0.03 |
| Maximal diameter, mm | 3.92 (3.06-4.29) | 3.89 (3.70-4.61) | 0.72 | 3.59 (2.84-4.14) | 3.94 (3.30-4.38) | 0.09 |
| Mean diameter, mm | 2.96 (2.54-3.50) | 3.34 (2.87-3.61) | 0.78 | 2.54 (2.30-3.11) | 3.20 (2.78-3.57) | 0.009 |
| **Distal segment** | | | | | | |
| | **FFR ≤0.85 (n=90)** | **FFR >0.85 (n=19)** | **p value** | **Distal lesion* (n=34)** | **No distal lesion* (n=75)** | **p value** |
| Length, mm | 25.11 (17.16-36.02) | 29.49 (19.17-41.18) | 0.78 | 30.54 (21.11-41.13) | 24.52 (17.17-34.76) | 0.10 |
| Minimal diameter, mm | 1.37 (1.23-1.57) | 1.69 (1.23-1.89) | 0.59 | 1.39 (1.23-1.60) | 1.44 (1.23-1.69) | 0.82 |
| Diameter stenosis, % | 29.50 (18-38) | 29 (11-37) | 0.77 | 33.50 (28.25-43.25) | 24 (13-34) | 0.02 |
| Stenosis>50%, % | 5 (6%) | 0 (0) | 0.29 | 3 (9) | 2 (3) | 0.16 |
| Reference diameter, mm | 1.97 (1.69-2.20) | 2.06 (1.76-2.55) | 0.68 | 2.10 (1.84-2.37) | 1.93 (1.63-2.16) | 0.02 |
| Maximal diameter, mm | 2.43 (2.16-2.73) | 2.86 (2.45-3.44) | 0.51 | 2.51 (2.18-2.85) | 2.45 (2.20-2.87) | 0.90 |
| Mean diameter, mm | 1.87 (1.70-2.07) | 2.13 (1.84-2.46) | 0.004 | 1.92 (1.71-2.12) | 1.90 (1.70-2.15) | 0.71 |
| **In-segment** | | | | | | |
| | **FFR ≤0.85 (n=104)** | **FFR >0.85 (n=19)** | **p value** | **>20% underexpansion* (n=62)** | **≤20% underexpansion* (n=61)** | **p value** |
| Length, mm | 33.41 (24.04-46.07) | 27.74 (23.18-32.34) | 0.93 | 33.36 (24.72-43.52) | 30.29 (22.48-45.56) | 0.35 |
| Minimal diameter, mm | 1.82 (1.56-2.04) | 1.91 (1.69-2.31) | 0.41 | 1.79 (1.55-1.99) | 1.91 (1.63-2.18) | 0.07 |
| Diameter stenosis, % | 23 (17-30) | 21 (16-28) | 0.65 | 22 (17-30) | 22 (17.50-30.50) | 0.82 |
| Stenosis>50% | 0 (0) | 0 (0) | - | 0 (0) | 0 (0) | - |
| Reference diameter, mm | 2.34 (2.11-2.70) | 2.66 (2.19-2.89) | 0.32 | 2.30 (2.03-2.57) | 2.58 (2.16-2.80) | 0.02 |

**Table 4.** Quantitative coronary angiography of the proximal and distal segment as well as in-segment and in-stent analysis. (continued)

| **Proximal segment** | | | | | | |
|---|---|---|---|---|---|---|
| Maximal diameter, mm | 3.22 (2.87-3.74) | 3.34 (3.04-3.55) | 0.44 | 3.19 (2.91-3.76) | 3.30 (2.92-3.74) | 0.92 |
| Mean diameter, mm | 2.61 (2.38-2.90) | 2.71 (2.45-2.99) | 0.32 | 2.59 (2.33-2.85) | 2.70 (2.42-2.94) | 0.19 |
| **In-stent** | | | | | | |
| | **FFR ≤0.85 (n=104)** | **FFR >0.85 (n=19)** | **p value** | **>20% underexpansion* (n=62)** | **≤20% underexpansion* (n=61)** | **p value** |
| Length, mm | 23.77 (14.57-37.01) | 17.56 (14.42-23.79) | 0.96 | 23.78 (15.76-35.60) | 21.27 (13.26-36.36) | 0.31 |
| Minimal diameter, mm | 2.08 (1.86-2.47) | 2.31 (2.08-2.67) | 0.35 | 2.07 (1.83-2.41) | 2.15 (1.91-2.57) | 0.19 |
| Diameter stenosis, % | 15 (9-20) | 13 (3-19) | <0.001 | 15 (8.75-19) | 13 (8-21) | 0.65 |
| Stenosis>50%, % | 0 (0) | 0 (0) | - | 0 (0) | 0 (0) | - |
| Reference diameter, mm | 2.42 (2.14-2.81) | 2.80 (2.34-3.05) | 0.3 | 2.37 (2.10-2.82) | 2.65 (2.25-2.90) | 0.06 |
| Maximal diameter, mm | 3.21 (2.88-3.59) | 3.16 (2.97-3.54) | 0.37 | 3.18 (2.86-3.58) | 3.28 (2.98-3.65) | 0.30 |
| Mean diameter, mm | 2.68 (2.43-2.99) | 2.81 (2.58-3.01) | 0.28 | 2.65 (2.43-2.97) | 2.79 (2.50-3.03) | 0.15 |

*as detected by IVUS.

Values are median (IQR) or absolute numbers (%)

### QCA analysis

A total of 103 proximal segments, 123 stented segments and 109 distal segments were analysed with QCA (Table 4). In brief, in the proximal segments, QCA did not reveal any significant differences in luminal dimensions in the two FFR cohorts, whereas in the distal segments diameters were significantly larger in the cohort with a post PCI FFR >0.85. As expected, in the presence either proximal- or distal focal lesions on IVUS, angiographic luminal dimensions differed significantly as compared to segments without residual lesions on IVUS. However, diameter stenosis did not exceed 50% in any of the proximal residual lesions detected by IVUS and/or FFR. In 5 cases QCA detected a diameter stenosis>50% (range 51 to 61%), corresponding to 3 cases with an IVUS detected distal focal lesion. Stented length was significantly larger in vessels with a post PCI FFR<0.85 as compared to vessels with a post PCI>0.85. Finally, QCA was not able to detect a difference in luminal dimensions of stented segments with 20% underexpansion or more.

## DISCUSSION

In this IVUS sub-study of the FFR SEARCH registry we demonstrated, for the first time, that clear signs of residual luminal narrowing, including focal lesions, underexpansion and malapposition, were present in a significant amount of vessels with an impaired post PCI FFR. Findings that were not readily apparent on QCA. Several recent studies demonstrated the value of low post PCI FFR in predicting late adverse cardiac events[3, 4]. Unfortunately, details on the actual rationale for these low PCI FFR values often remained elusive since no data on residual angiographically apparent disease were reported, nor were details presented on intravascular imaging findings. In our study meticulous intravascular ultrasound analysis revealed specific morphologic explanations for the suboptimal post PCI FFR.

First, in the low FFR cohort, we found residual focal lesions in 51% of the vessels. We found MLAs in focal proximal and distal lesions of 2.88 (2.29-3.37) mm and 2.03 (1.74-2.21) mm respectively. Several previous studies already indicated the strong correlation of IVUS derived low post PCI MLA with both low post PCI FFR values (<0.80) and worse outcome [18-22]. With QCA conversely, diameter stenosis in proximal and distal lesions were 29 (19-34) % and 33.5 (28.25-43.25) % respectively. Interestingly, in only 3 of the segments with residual focal lesions on IVUS, QCA detected a diameter stenosis >50%.

Secondly, in the low FFR cohort, we found underexpanded stents in 74% of the vessels with an FFR ≤0.85, a significantly higher percentage as would be expected post stenting in general, with expected underexpansion rates of 20-44%[23]. Again, these underexpansion figures appreciated with IVUS were not apparent with QCA. The latter might illustrate the potential of post PCI FFR to expose more severe forms of underexpansion and also fits with previous data showing a clear

correlation between underexpansion and increased rates of early stent thrombosis and restenosis[24-27].

Thirdly, in the low FFR cohort, malapposition was identified in 23% of the cases. Since we could not demonstrate a direct correlation between malapposition and a drop in FFR, in most cases malapposition was found in combination with underexpansion (87%), residual focal lesions or lumen compromising hematoma (52%) and only occurred isolated in one patient. Furthermore, the malapposition rate of 23% found in our study fits with previous imaging studies post DES implantation, showing rates of malapposition in 7-39% of the cases with no significant correlation to either stent thrombosis or restenosis[24, 28-30]. Nevertheless, stent malapposition is suboptimal and is associated with stent thrombosis in intravascular imaging studies and adequate strut apposition might help to avoid long-term stent related complications[31].

Although we only enrolled 20 cases with a post PCI FFR >0.85 as a reference a clear trend was seen towards larger minimal stent areas, a lower number of residual proximal focal lesions, less stents with malapposition and a lower incidence of diffuse disease. Additionally, the incidence of patients presenting with STEMI was significantly lower in patients with post PCI FFR<0.85 as compared to those with higher post PCI values[32]. Nevertheless, also in the STEMI cohort, IVUS revealed residual luminal narrowing in a significant proportion of patients.

Despite accumulating outcome data supporting the use of IVUS, its adoption in daily clinical practice remains low[33]. IVUS has the reputation to be costly and time-consuming, and insufficient IVUS knowledge might hamper ad-hoc image interpretation. Conversely, FFR allows a faster and more easily interpretable assessment of the hemodynamic importance of coronary artery disease.

In the present study we attempted to link a lower than expected FFR to morphological findings by IVUS and QCA. FFR pressure drops were more pronounced in vessels with residual proximal focal lesions but not with distal lesions. Previous work already alluded to the lack of correlation between anatomic and functional severity of stenosis in small vessels, probably due to the small myocardial territory at risk[34]. On the other hand, FFR guided PCI resulted in significantly superior outcomes as compared to angiography guided PCI also in studies focussing on small vessels[35]. Finally, we demonstrated that milder forms of underexpansion might remain unnoticed on FFR pullbacks while larger, and perhaps more clinically relevant rates of underexpansion might be associated with significant pressure gradients.

While the results of the FFR-REACT trial (Dutch trial register: NTR6711), assessing whether FFR directed IVUS guided PCI optimization improves patient outcomes as compared to standard clinical practice, are eagerly awaited, there is a clear need for larger prospective randomized controlled

trials designed to better understand the potential benefit of FFR-guided PCI optimization with or without the focused use of IVUS.

## LIMITATIONS

Several limitations need to be mentioned. First, we only enrolled 20 patients with a post PCI FFR >0.85. The absence of clear significant differences in IVUS findings between both cohorts might have been due to a lack of power. Second, the criteria for underexpansion in this study are based upon the MUSIC criteria[14]. Unlike in the MUSIC study in which only stents with a length of 15 mm were used, the average stented length in the present cohort was 34 mm resulting in significant differences between proximal and distal reference segments which might have impacted the calculation of the percentage underexpansion. This could have resulted in a lower mean reference LA and therefore an overestimation of the degree of expansion. Third, pressure measurements were performed with the Navvus microcatheter, which might underestimate the FFR value as compared to the wire based FFR[36-38]. The latter might mean that the IVUS finding from this study can also be applicable to higher post PCI values, measure with a wired base device. Fourth, maximum hyperemic conditions during continuous intravenous infusion of adenosine might fluctuate and therefore influence pullback assessment in up to 40% of the cases[39]. Fifth, for the present study we used an FFR cut-off of 0.85. While several previous studies demonstrated a clear trend towards increased MACE rates with decreasing post PCI FFR values an exact cut-off for an optimal post PCI FFR, at present, is elusive. Finally since the FFR SEARCH registry was developed to assess the impact of post PCI FFR measured in routine clinical practice, per protocol, no additional interventions were performed based on either FFR or IVUS findings. Whether additional treatment will optimize the longer-term results of these patients is currently being investigated in the FFR REACT trial.

## CONCLUSION

In patients with a post procedural FFR ≤0.85, IVUS revealed focal signs of luminal narrowing in the majority of the cases. Only proximal focal lesions resulted in significant FFR pressure drops during pullback.

## REFERENCES

1. Fearon WF, Bornschein B, Tonino PA, Gothe RM, Bruyne BD, Pijls NH, Siebert U and Fractional Flow Reserve Versus Angiography for Multivessel Evaluation Study I. Economic evaluation of fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *Circulation*. 2010;122:2545-50.
2. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF and Investigators FS. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-24.
3. Wolfrum M, Fahrni G, de Maria GL, Knapp G, Curzen N, Kharbanda RK, Fröhlich GM and Banning AP. Impact of impaired fractional flow reserve after coronary interventions on outcomes: a systematic review and meta-analysis. *BMC Cardiovascular Disorders*. 2016;16:177.
4. Rimac G, Fearon WF, De Bruyne B, Ikeno F, Matsuo H, Piroth Z, Costerousse O and Bertrand OF. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis. *Am Heart J*. 2017;183:1-9.
5. Kasula S, Agarwal SK, Hacioglu Y, Pothineni NK, Bhatti S, Ahmed Z, Uretsky B and Hakeem A. Clinical and prognostic value of poststenting fractional flow reserve in acute coronary syndromes. *Heart*. 2016;102:1988-1994.
6. Diletti R, Van Bommel R, Masdjedi K, Van Zandvoort L, Lemmert ME, Wilschut J, De Jaegere P, Boersma E, Zijlstra F, Daemen J and Van Mieghem NM. Routine Fractional Flow Reserve Measurement after Percutaneous Coronary Intervention The FFR-SEARCH Study. *EuroPCR presentation* 2017.
7. Hanekamp CE, Koolen JJ, Pijls NH, Michels HR and Bonnier HJ. Comparison of quantitative coronary angiography, intravascular ultrasound, and coronary pressure measurement to assess optimum stent deployment. *Circulation*. 1999;99:1015-21.
8. Fearon WF, Luna J, Samady H, Powers ER, Feldman T, Dib N, Tuzcu EM, Cleman MW, Chou TM, Cohen DJ, Ragosta M, Takagi A, Jeremias A, Fitzgerald PJ, Yeung AC, Kern MJ and Yock PG. Fractional flow reserve compared with intravascular ultrasound guidance for optimizing stent deployment. *Circulation*. 2001;104:1917-22.
9. Stempfle HU, Konig A, Drescher E, Siebert U and Klauss V. Discrepancy between morphologic and functional criteria of optimal stent deployment using intravascular ultrasound and pressure derived myocardial fractional flow reserve. *Int J Cardiovasc Intervent*. 2005;7:101-7.
10. Pijls NH, De Bruyne B, Bech GJ, Liistro F, Heyndrickx GR, Bonnier HJ and Koolen JJ. Coronary pressure measurement to assess the hemodynamic significance of serial stenoses within one coronary artery: validation in humans. *Circulation*. 2000;102:2371-7.
11. Kim HL, Koo BK, Nam CW, Doh JH, Kim JH, Yang HM, Park KW, Lee HY, Kang HJ, Cho YS, Youn TJ, Kim SH, Chae IH, Choi DJ, Kim HS, Oh BH and Park YB. Clinical and physiological outcomes of fractional flow reserve-guided percutaneous coronary intervention in patients with serial stenoses within one coronary artery. *JACC Cardiovasc Interv*. 2012;5:1013-8.
12. Ben-Dor I, Torguson R, Deksissa T, Bui AB, Xue Z, Satler LF, Pichard AD and Waksman R. Intravascular ultrasound lumen area parameters for assessment of physiological ischemia by fractional flow reserve in intermediate coronary artery stenosis. *Cardiovasc Revasc Med*. 2012;13:177-82.
13. Ben-Dor I, Torguson R, Gaglia MA, Jr., Gonzalez MA, Maluenda G, Bui AB, Xue Z, Satler LF, Suddath WO, Lindsay J, Pichard AD and Waksman R. Correlation between fractional flow reserve and intravascular ultrasound lumen area in intermediate coronary artery stenosis. *EuroIntervention*. 2011;7:225-33.
14. de Jaegere P, Mudra H, Figulla H, Almagor Y, Doucet S, Penn I, Colombo A, Hamm C, Bartorelli A, Rothman M, Nobuyoshi M, Yamaguchi T, Voudris V, DiMario C, Makovski S, Hausmann D, Rowe S,

Rabinovich S, Sunamura M and van Es GA. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). *Eur Heart J*. 1998;19:1214-23.

15. Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, Pinto FJ, Rosenfield K, Siegel RJ, Tuzcu EM and Yock PG. American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2001;37:1478-92.
16. Koyama J, Yamagishi M, Tamai J, Kawano S, Daikoku S and Miyatake K. Comparison of vessel wall morphologic appearance a sites of focal and diffuse coronary vasospasm by intravascular ultrasound. *American Heart Journal*. 1995;130:440-445.
17. Miyao Y, Kugiyama K, Kawano H, Motoyama T, Ogawa H, Yoshimura M, Sakamoto T and Yasue H. Diffuse intimal thickening of coronary arteries in patients with coronary spastic angina. *J Am Coll Cardiol*. 2000;36:432-7.
18. Takayama T and Hodgson JM. Prediction of the physiologic severity of coronary lesions using 3D IVUS: validation by direct coronary pressure measurements. *Catheter Cardiovasc Interv*. 2001;53:48-55.
19. Briguori C, Anzuini A, Airoldi F, Gimelli G, Nishida T, Adamian M, Corvaja N, Di Mario C and Colombo A. Intravascular ultrasound criteria for the assessment of the functional significance of intermediate coronary artery stenoses and comparison with fractional flow reserve. *Am J Cardiol*. 2001;87:136-41.
20. Takagi A, Tsurumi Y, Ishii Y, Suzuki K, Kawana M and Kasanuki H. Clinical potential of intravascular ultrasound for physiological assessment of coronary stenosis: relationship between quantitative ultrasound tomography and pressure-derived fractional flow reserve. *Circulation*. 1999;100:250-5.
21. Lee SY, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, Jang Y and Hong MK. Intravascular Ultrasound Predictors of Major Adverse Cardiovascular Events After Implantation of Everolimus-eluting Stents for Long Coronary Lesions. *Rev Esp Cardiol (Engl Ed)*. 2017;70:88-95.
22. Ito T, Tani T, Fujita H and Ohte N. Relationship between fractional flow reserve and residual plaque volume and clinical outcomes after optimal drug-eluting stent implantation: insight from intravascular ultrasound volumetric analysis. *Int J Cardiol*. 2014;176:399-404.
23. Mudra H, di Mario C, de Jaegere P, Figulla HR, Macaya C, Zahn R, Wennerblom B, Rutsch W, Voudris V, Regar E, Henneke KH, Schachinger V, Zeiher A and Investigators OS. Randomized comparison of coronary stent implantation under ultrasound or angiographic guidance to reduce stent restenosis (OPTICUS Study). *Circulation*. 2001;104:1343-9.
24. Choi SY, Witzenbichler B, Maehara A, Lansky AJ, Guagliumi G, Brodie B, Kellett MA, Jr., Dressler O, Parise H, Mehran R, Dangas GD, Mintz GS and Stone GW. Intravascular ultrasound findings of early stent thrombosis after primary percutaneous intervention in acute myocardial infarction: a Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) substudy. *Circ Cardiovasc Interv*. 2011;4:239-47.
25. Liu X, Doi H, Maehara A, Mintz GS, Costa Jde R, Jr., Sano K, Weisz G, Dangas GD, Lansky AJ, Kreps EM, Collins M, Fahy M, Stone GW, Moses JW, Leon MB and Mehran R. A volumetric intravascular ultrasound comparison of early drug-eluting stent thrombosis versus restenosis. *JACC Cardiovasc Interv*. 2009;2:428-34.
26. Fujii K, Carlier SG, Mintz GS, Yang YM, Moussa I, Weisz G, Dangas G, Mehran R, Lansky AJ, Kreps EM, Collins M, Stone GW, Moses JW and Leon MB. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. *J Am Coll Cardiol*. 2005;45:995-8.

27. Sonoda S, Morino Y, Ako J, Terashima M, Hassan AH, Bonneau HN, Leon MB, Moses JW, Yock PG, Honda Y, Kuntz RE, Fitzgerald PJ and Investigators S. Impact of final stent dimensions on long-term results following sirolimus-eluting stent implantation: serial intravascular ultrasound analysis from the sirius trial. *J Am Coll Cardiol*. 2004;43:1959-63.
28. Steinberg DH, Mintz GS, Mandinov L, Yu A, Ellis SG, Grube E, Dawkins KD, Ormiston J, Turco MA, Stone GW and Weissman NJ. Long-term impact of routinely detected early and late incomplete stent apposition: an integrated intravascular ultrasound analysis of the TAXUS IV, V, and VI and TAXUS ATLAS workhorse, long lesion, and direct stent studies. *JACC Cardiovasc Interv*. 2010;3:486-94.
29. Kawamori H, Shite J, Shinke T, Otake H, Matsumoto D, Nakagawa M, Nagoshi R, Kozuki A, Hariki H, Inoue T, Osue T, Taniguchi Y, Nishio R, Hiranuma N and Hirata K-i. Natural consequence of post-intervention stent malapposition, thrombus, tissue prolapse, and dissection assessed by optical coherence tomography at mid-term follow-up. *European Heart Journal Cardiovascular Imaging*. 2013;14:865-875.
30. Guo N, Maehara A, Mintz GS, He Y, Xu K, Wu X, Lansky AJ, Witzenbichler B, Guagliumi G, Brodie B, Kellett MA, Jr., Dressler O, Parise H, Mehran R and Stone GW. Incidence, mechanisms, predictors, and clinical impact of acute and late stent malapposition after primary intervention in patients with acute myocardial infarction: an intravascular ultrasound substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. *Circulation*. 2010;122:1077-84.
31. Souteyrand G, Amabile N, Mangin L, Chabin X, Meneveau N, Cayla G, Vanzetto G, Barnay P, Trouillet C, Rioufol G, Range G, Teiger E, Delaunay R, Dubreuil O, Lhermusier T, Mulliez A, Levesque S, Belle L, Caussin C, Motreff P and Investigators P. Mechanisms of stent thrombosis analysed by optical coherence tomography: insights from the national PESTO French registry. *Eur Heart J*. 2016;37:1208-16.
32. Stone GW, Webb J, Cox DA, Brodie BR, Qureshi M, Kalynych A, Turco M, Schultheiss HP, Dulas D, Rutherford BD, Antoniucci D, Krucoff MW, Gibbons RJ, Jones D, Lansky AJ, Mehran R, Enhanced Myocardial E and Recovery by Aspiration of Liberated Debris I. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. *Jama*. 2005;293:1063-72.
33. Ahn J-M, Kang S-J, Yoon S-H, Park HW, Kang SM, Lee J-Y, Lee S-W, Kim Y-H, Lee CW, Park S-W, Mintz GS and Park S-J. Meta-Analysis of Outcomes After Intravascular Ultrasound–Guided Versus Angiography-Guided Drug-Eluting Stent Implantation in 26,503 Patients Enrolled in Three Randomized Trials and 14 Observational Studies. *The American Journal of Cardiology*. 2014;113:1338-1347.
34. Costa MA, Sabate M, Staico R, Alfonso F, Seixas AC, Albertal M, Crossman A, Angiolillo DJ, Zenni M, Sousa JE, Macaya C and Bass TA. Anatomical and physiologic assessments in patients with small coronary artery disease: final results of the Physiologic and Anatomical Evaluation Prior to and After Stent Implantation in Small Coronary Vessels (PHANTOM) trial. *Am Heart J*. 2007;153:296 e1-7.
35. Puymirat E, Peace A, Mangiacapra F, Conte M, Ntarladimas Y, Bartunek J, Vanderheyden M, Wijns W, De Bruyne B and Barbato E. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary revascularization in patients with small-vessel disease. *Circ Cardiovasc Interv*. 2012;5:62-8.
36. Menon M, Jaffe W, Watson T and Webster M. Assessment of coronary fractional flow reserve using a monorail pressure catheter: the first-in-human ACCESS-NZ trial. *EuroIntervention*. 2015;11:257-63.
37. Pouillot C, Fournier S, Glasenapp J, Rambaud G, Bougrini K, Vi Fane R, Geyer C and Adjedj J. Pressure wire versus microcatheter for FFR measurement: a head-to-head comparison. *EuroIntervention*. 2018;13:e1850-e1856.

38. Masdjedi K, Van Mieghem NM, Diletti R, van Geuns RJ, de Jaegere P, Regar E, Zijlstra F, van Domburg RT and Daemen J. Navvus FFR to reduce CONTRAst, Cost and radiaTion (CONTRACT); insights from a single-centre clinical and economical evaluation with the RXi Rapid-Exchange FFR device. *Int J Cardiol*. 2017;233:80-84.
39. Johnson NP, Johnson DT, Kirkeeide RL, Berry C, De Bruyne B, Fearon WF, Oldroyd KG, Pijls NHJ and Gould KL. Repeatability of Fractional Flow Reserve Despite Variations in Systemic and Coronary Hemodynamics. *JACC Cardiovasc Interv*. 2015;8:1018-1027.

**Supplementary table 1.**

| | FFR ≤0.75 (n=22) | FFR ≤0.80 (n=56) | FFR ≤0.85 (n=100) | FFR >0.85 (n=20) |
|---|---|---|---|---|
| Mean lumen area, $mm^2$ | 5.99 (4.53-6.78) | 5.79 (4.68-6.95) | 5.95 (5.01-7.03) | 6.24 (5.12-8.10) |
| Minimal lumen area, $mm^2$ | 2.04 (1.49-2.92) | 2.14 (1.59-3.17) | 2.19 (1.81-3.19) | 2.92 (1.96-4.10) |
| Minimal stent area, $mm^2$ | 3.59 (4.53-6.78) | 3.87 (2.83-4.94) | 4.01 (3.09-5.21) | 5.11 (3.05-7.41) |
| Focal lesion (proximal) | 10 (46) | 18 (32) | 29 (29) | 3 (15) |
| MLA at proximal lesion, $mm^2$ | 3.12 (2.26-4.83) | 3.00 (2.26-3.51) | 2.98 (2.24-3.36) | 2.60 (2.30-2.60) |
| Focal lesion (distal) | 3 (14) | 13 (23) | 30 (30) | 6 (30) |
| MLA at distal lesion, $mm^2$ | 1.71 (1.40-1.71) | 2.03 (1.54-2.28 | 2.01 (1.68-2.12) | 2.51 (1.88-3.26) |
| Lumen compromising hematoma | 0 (0) | 1 (1.8) | 3 (3) | 0 (0) |
| MLA lumen compromising hematoma, $mm^2$ | - | 1.22 | 1.97 (1.22-1.97) | - |
| Underexpansion | 18 (82) | 40 (71) | 74 (74) | 15 (75) |
| Malapposition | 6 (27) | 17 (23) | 23 (23) | 1 (5) |
| Spasm | 2 (9) | 8 (14) | 9 (9) | 0 (0) |
| Diffuse diseased | 2 (9) | 6 (11) | 8 (8) | 0 (0) |
| Any focal lesion | 11 (50) | 27 (48) | 51 (51) | 9 (45) |
| Any focal lesion or lumen compromising hematoma | 11 (50) | 28 (50) | 54 (54) | 9 (45) |
| Any focal lesion, underexpansion, lumen compromising hematoma or malapposition | 19 (86) | 49 (88) | 84 (84) | 18 (90) |

Values are median (IQR) or absolute numbers (%)

# Chapter

# 7

# Impact of intravascular ultrasound findings in patients with a post PCI fractional flow reserve ≤0.85 on 2 year clinical outcome

Laurens J.C. van Zandvoort BSc, **Kaneshka Masdjedi MD**, Tara Neleman, BSc, Maria Natalia Tovar Forero MD, Jeroen Wilschut MD, Wijnand den Dekker, MD PhD, Peter de Jaegere MD PhD, Roberto Diletti MD PhD, Felix Zijlstra MD PhD, Nicolas M. Van Mieghem MD PhD, Joost Daemen MD PhD;

**Department of Cardiology, Thoraxcenter, Erasmus Medical Center, The Netherlands**

**Journal:** International journal of cardiology 317 (2020) 33–363

## ABSTRACT

**Background:** Patients with a low post PCI fractional flow reserve (FFR) are at increased risk for future adverse cardiac events. The aims of the present study was to assess the impact of specific intravascular ultrasound (IVUS) findings in patients with a low post percutaneous coronary intervention (PCI) FFR on long-term clinical outcome.

**Methods:** In a subgroup analysis, 100 vessels with an FFR value ≤0.85 underwent post PCI IVUS to further assess the potential determinants for low post PCI FFR. No further action was taken to improve post PCI FFR. The primary endpoint of this study was the event free survival of target vessel failure (TVF) at two years in patients with a post PCI FFR ≤0.85, which was defined as a composite of cardiac death, target vessel myocardial infarction or target vessel revascularization.

**Results:** In patients with a post PCI FFR ≤0.85, TVF free survival rates were 88.5% vs. 95.5% for patients with versus without residual proximal lesions and 88.2% vs. 95.5% for patients with versus without residual distal lesions respectively (HR=2.53, 95% confidence interval (CI) 0.52-12.25, p=0.25 and HR=2.60, 95% CI 0.54-12.59, p=0.24 respectively). TVF free survival was 92.8% vs. 93.5% in patients with versus without stent underexpansion >20% (HR=1.01, 95% CI 0.21-4.88, p=0.99) and 89.3% vs. 97.8% in patients with versus without any residual focal lesion including lumen compromising hematoma (HR=4.64, 95% CI 0.55-39.22, p=0.18).

**Conclusion:** Numerically higher TVF rates were observed in patients with a post PCI FFR ≤0.85 and clear focal residual disease as assessed with IVUS.

**Key words**: post PCI FFR, predictors, IVUS, outcome

## BACKGROUND

FFR after stenting proved to be a strong and independent predictor for MACE (1). Unfortunately, the exact rationale behind this observation remains elusive based on angiographic findings alone let alone the impact on clinical follow-up. Fractional flow reserve (FFR) has proven to be a useful technique to address coronary physiology and the haemodynamic significance of coronary segments both pre- and post-intervention (2).

In the intravascular ultrasound (IVUS) sub-study of the FFR SEARCH registry we demonstrated, for the first time, that clear signs of residual luminal narrowing, including focal lesions, underexpansion and malapposition, were present in a significant amount of vessels with an impaired post percutaneous coronary intervention (PCI) FFR despite optimal angiographic results (3).

Patients with a low post PCI fractional flow reserve (FFR) are at increased risk for future adverse cardiac events. The aims of the present study was to assess the impact of specific IVUS findings in patients with a low post PCI FFR on long-term clinical outcome (FFR ≤0.85).

## METHODS

### Patient selection

The FFR SEARCH (Stent Evaluated at Rotterdam Cardiology Hospital) study is a prospective single center registry in which 1000 consecutive patients underwent FFR evaluation after angiographic successful PCI with a primary endpoint to study the impact of post PCI FFR on major adverse cardiac event rates at 2 years. In a subgroup analysis, 95 consecutive patients (100 vessels) with a post PCI FFR value ≤0.85 and 20 patients (20 vessels) with a post PCI FFR >0.85 underwent post PCI IVUS to further assess the potential determinants for the low post PCI FFR. No further action was taken to improve the post PCI FFR. The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee. All patients provided written informed consent for the procedure and the use of anonymous datasets for research purposes in alignment with the Dutch Medical Research Act.

Specifics on angiographic measurements, FFR assessment and IVUS acquisition are discussed in the initial FFR SEARCH registry study and the IVUS sub-study report (3, 4). In brief, a dedicated FFR Navvus MicroCatheter (ACIST Medical Systems, Inc., Eden Prairie, MN, USA) was advanced over the previously used coronary guidewire approximately 20 mm distal to the most distal stent edge. IVUS imaging was performed with the multi frequency High Definition IVUS Kodama catheter (ACIST Medical Systems, Inc., Eden Prairie, MN, USA).

The primary endpoint of this study was the event free survival of target vessel failure (TVF) at two years, which was defined as a composite of cardiac death, target vessel myocardial infarction or target vessel revascularization.

Myocardial infarction (MI) was defined according to the fourth definition recommended by the European Society of Cardiology (5). Cardiac death was adjudicated if the cause of death was most probable cardiac cause or could not be identified. Clinical follow-up data were collected by hospital visit, chart review or telephone contact.

Categorical variables are reported as either counts or percentages, continuous variables are reported as mean ± standard and compared using a generalized linear mixed model. Survival analyses were performed using the Kaplan-Meier method. In order to evaluate IVUS findings and the impact on TVF at two year follow-up, all 100 vessels were tested univariately using a Cox proportional hazards model which accounted for the multilevel nature of the data. No multivariable model was constructed due to a lack of events. Statistical analyses were performed by using SPPS 25 and R (version 3.5.1, packages: lme4, nlme, surv).

## RESULTS

Baseline characteristics and IVUS findings are depicted in table 1.

In the dedicated IVUS analyses, in patients with a post PCI FFR ≤0.85, significant focal lesions proximal or distal to the treated segment were found in 29% and 30% of the vessels respectively. Underexpansion >20% was present in 50% of the vessels. In 54% of the vessels clear focal signs of luminal narrowing were found due to residual focal lesions or lumen compromising hematoma (3%). In 87% of the vessels, either a focal lesion, underexpansion (>10%), a lumen compromising hematoma or malapposition were present. Baseline characteristics compared in different subgroups are depicted in supplementary table 1.

Complete two-year follow-up was available for 100% of the patients. At two years , the cumulative survival free of TVF was 93.2% in patients with a post PCI FFR ≤0.85.TVF free survival rates were 88.5% vs. 95.5% (n. events=3 vs. 3) for patients with versus without residual proximal lesions and 88.2% vs. 95.5% (n. events=3 vs. 3) for patients with versus without residual distal lesions respectively (hazard ratio (HR)=2.53, 95% confidence interval (CI) 0.52-12.25, p=0.25 and HR=2.60, 95% CI 0.54-12.59, p=0.24 respectively) (figure 1). TVF free survival was 93.8% vs. 93.2%(n. events=3 vs. 3) in patients with versus without stent underexpansion >20% (HR=1.01, 95% CI 0.21-4.88, p=0.99) and 89.3% vs. 97.8% (n. events=5 vs. 1) in patients with versus without any residual focal lesion including lumen compromising hematoma (HR=4.64, 95% CI 0.55-39.22, p=0.16).

**Table 1.** Key characteristic and IVUS findings.

| | FFR ≤0.85 (n=95) (100 vessels) | FFR >0.85 (n=20) (20 vessels) | P value |
|---|---|---|---|
| Patient and vessel characteristic | | | |
| Age, years | 65±12 | 66±12 | 0.67 |
| Gender, male | 81 (85) | 19 (95) | 0.29 |
| Diabetes | 24 (25) | 6 (30) | 0.57 |
| Prior PCI | 29 (31) | 7 (35) | 0.66 |
| Indication | | | |
| Stable angina | 41 (43) | 9 (45) | 0.80 |
| ACS | 54 (57) | 11 (55) | 0.80 |
| Target vessel | | | |
| Left anterior descending artery (LAD) | 81 (81) | 12 (60) | 0.24 |
| Left circumflex artery(LCX) | 7 (7) | 3 (15) | 0.25 |
| Left main artery (LM) | 3 (3) | 1 (5) | 0.65 |
| Right coronary artery (RCA) | 9 (9) | 4 (20) | 0.16 |
| Predilatation | 74 (74) | 10 (50) | 0.04 |
| High pressure post dilatation (NC balloon) | 74 (74) | 13 (65) | 0.41 |
| Mean post PCI Pd/Pa | 0.91±0.04 | 0.96±0.03 | <0.001 |
| Mean post PCI FFR, maximum hyperemia | 0.79±0.05 | 0.90±0.03 | <0.001 |
| No. of stents | 1 (1-2) | 1 (1-1) | <0.001 |
| Mean stent diameter, mm | 3 (2.75-3.25) | 3.25 (3.0-3.5) | 0.13 |
| Total stent length, mm | 28 (15-46) | 21 (16-25) | 0.12 |
| IVUS analysis | | | |
| Minimal lumen area, $mm^2$ | 2.19 (1.81-3.19) | 2.92 (1.96-4.10) | 0.02 |
| Mean lumen area, $mm^2$ | 5.95 (5.01-7.03) | 6.24 (5.12-8.10) | 0.15 |
| Minimal stent area, $mm^2$ | 4.01 (3.09-5.21) | 5.11 (3.05-7.41) | 0.01 |
| Focal lesion (proximal) | 29 (29) | 3 (15) | 0.78 |
| MLA at proximal lesion, $mm^2$ | 2.98 (2.24-3.36) | 2.60 (2.30-2.60) | 0.98 |
| Focal lesion (distal) | 30 (30) | 6 (30) | 1.00 |
| MLA at distal lesion, $mm^2$ | 2.01 (1.68-2.12) | 2.51 (1.88-3.26) | 0.02 |
| Lumen compromising hematoma | 3 (3) | 0 (0) | 0.69 |
| MLA lumen compromising hematoma, $mm^2$ | 1.97 (1.22-1.97) | - | - |
| Underexpansion (>10%) | 74 (74) | 15 (75) | 0.93 |
| Underexpansion (>20%) | 50 (50) | 8 (40) | 0.41 |
| Malapposition | 23 (23) | 1 (5) | 0.10 |
| Spasm | 9 (9) | 0 (0) | 0.31 |
| Diffuse diseased | 8 (8) | 0 (0) | 0.68 |
| Any focal lesion | 51 (51) | 9 (45) | 0.63 |
| Any focal lesion or lumen compromising hematoma | 54 (54) | 9 (45) | 0.37 |
| Any focal lesion, underexpansion (>10%), lumen compromising hematoma or malapposition | 84 (84) | 18 (90) | 0.99 |

Values are n (%) or mean±SD, PCI = Percutaneous Coronary Artery and CABG = Coronary Artery Bypass Grafting, NSTEMI = non ST elevated myocardial infarction, STEMI =ST elevated myocardial infarction. NC = non-compliant, Pd/Pa = the Pressure in the Distal coronary artery to the Pressure in the Aorta ratio, FFR = Fractional Flow Reserve. MLA = minimal lumen area

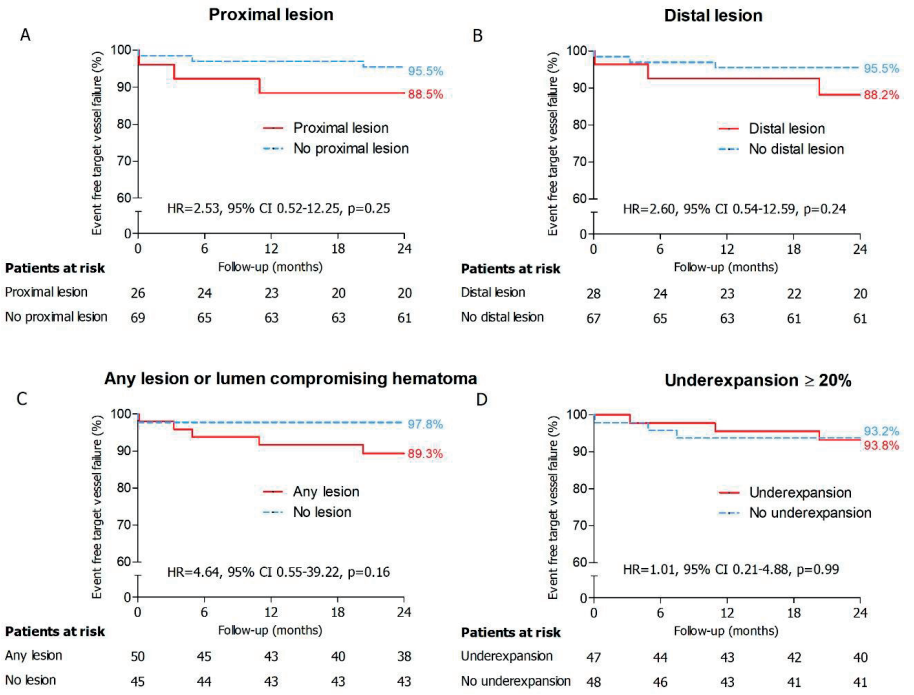



**Figure 1.** Kaplan-Meier curves for separated for the presence of proximal focal lesions, distal focal lesions, any lesion including lumen compromising hematoma and >20% underexpansion.
Event free survival of target vessel failure (TVF).

In contrast to focal residual disease, which clearly tended to impact TVF at 2 years, no events were found related to vessels with diffuse disease (n=8). TVF free survival in patients with a post PCI FFR >0.85 was 90.0% (88.9% and 90.9% in patients with versus without residual lesions or lumen compromising hematoma).

## DISCUSSION

Low post PCI FFR proved to be associated with higher rates of TVF (1). However, the practical implications of low post PCI FFR remain debated since little is known about the exact mechanisms behind the low FFR and potential consequences of further intravascular treatment.

In the FFR SEARCH IVUS study we found a high proportion of IVUS detected anomalies including focal lesions, stent underexpansion and malapposition in vessels with a post PCI FFR ≤0.85; findings that were not readily apparent on coronary angiography (3).

The present predefined long-term follow-up analysis demonstrated a clear trend towards higher rates of TVF at two years when IVUS derived residual lesions were found.

Patients without clear residual disease on IVUS had a 2.2% risk of TVF at 2 year, despite having a post PCI FFR<0.85 (as compared to 10.7% in those with residual disease, HR 4.6).

We therefore believe that IVUS might provide significant benefit in further stratifying those at the highest risk for future adverse events (post PCI FFR<0.85) and guide further treatment optimization.

## LIMITATIONS

The sample size in this sub-study of the FFR SEARCH is registry is limited. Although clear clinical trends were observed, the limited number of patients with a persistent low post PCI FFR and subsequent IVUS withheld us from providing significant hazard ratios. The current study is hypothesis generating and large randomized trials are warranted to further investigate the relation between IVUS detected anomalies and hard clinical endpoints in patients with persistent low post PCI FFR.

Finally, adverse events were adjudicated by investigators blinded to the final FFR values and IVUS findings. No dedicated independent event committee was used

## CONCLUSION

At two years, the cumulative survival free of TVF in patients with a post PCI FFR ≤0.85 was 93.5%. Numerically higher TVF rates were observed in patients with clear focal residual disease as assessed with IVUS.

## FUNDING

The Erasmus Medical centre received institutional support from ACIST medical Inc.

**Supplemenatry table 1.** Baseline characteristic and IVUS findings in vessels with and without proximal lesions, distal lesions underexpansion or any lesion (post PCI FFR ≤0.85.

| | Proximal lesion | | | Distal lesion | | |
|---|---|---|---|---|---|---|
| | present (n=26 patients, 29 vessels) | Not present (n=69 patients, 71 vessels) | P value | Present (n=28 patients, 30 vessels) | No Present (n=67 patients, 70 vessels) | P value |
| Patient and vessel characteristic | | | | | | |
| Age, years | 65±14 | 64±12 | 0.633 | 67±12 | 64±13 | 0.559 |
| Gender, male | 15 (58) | 60 (96) | <0.001 | 26 (93) | 55 (82) | 0.177 |
| Diabetes | 7 (27) | 17 (25) | 0.819 | 9 (32) | 15 (22) | 0.318 |
| Prior PCI | 11 (42) | 18 (26) | 0.126 | 8 (29) | 21 (31) | 0.789 |
| Indication | | | | | | |
| Stable angina | 10 (39) | 31 (45) | 0.571 | 15 (54) | 26 (39) | 0.185 |
| ACS | 16 (61) | 38 (55) | 0.571 | 13 (46) | 41 (61) | 0.185 |
| | | | | | | |
| Target vessel | | | | | | |
| Left anterior descending artery (LAD) | 16 (55) | 65 (92) | <0.001 | 24 (80) | 57 (81) | 0.867 |
| Left circumflex artery(LCX) | 5 (17) | 2 (3) | 0.048 | 2 (7) | 5 (7) | 0.932 |
| Left main artery (LM) | 1 (3) | 2 (3) | 0.866 | 1 (3) | 2 (3) | 0.898 |
| Right coronary artery (RCA) | 7 (24) | 2 (3) | 0.080 | 3 (10) | 6 (9) | 0.819 |
| Predilatation | 19 (66) | 55 (78) | 0.235 | 21 (70) | 53 (76) | 0.551 |
| High pressure post dilatation (NC balloon) | 16 (55) | 58 (82) | 0.032 | 23 (77) | 51 (73) | 0.689 |
| Mean post PCI Pd/Pa | 0.91±0.03 | 0.91±0.06 | 0.943 | 0.91±0.03 | 0.91±0.05 | 0.841 |
| Mean post PCI FFR, maximum hyperemia | 0.77±0.06 | 0.79±0.05 | 0.026 | 0.80±0.04 | 0.78±0.05 | 0.135 |
| No. of stents | 1 (1-2) | 2.0 (1-2) | 0.061 | 2 (1-2) | 1 (1-2) | 0.726 |
| Mean stent diameter, mm | 2.75 (2.5-3) | 3 (3-3.5) | <0.001 | 3 (2.9-3.3) | 3 (2.7-3.5) | 0.528 |
| Total stent length, mm | 15 (13-35) | 30 (22-52) | 0.012 | 28 (19-42) | 28 (15-47) | 0.673 |

| | >20% underexpansion | | | Any lesion or lumen compromising hematoma | | |
|---|---|---|---|---|---|---|
| | Present (n=47 patients, 58 vessels) | Not present (n=48 patients, 62 vessels) | P value | Present (n=33 patients, 36 vessels) | No Present (n=80 patients, 84 vessels) | P value |
| Patient and vessel characteristic | | | | | | |
| Age, years | 64±13 | 65±13 | 0.374 | 67±12 | 64±13 | 0.299 |
| Gender, male | 39 (83) | 42 (88) | 0.534 | 38 (76) | 43 (96) | 0.007 |
| Diabetes | 14 (30) | 10 (21) | 0.315 | 15 (30) | 9 (20) | 0.263 |
| Prior PCI | 15 (32) | 14 (29) | 0.771 | 16 (32) | 13 (29) | 0.742 |
| Indication | | | | | | |
| Stable angina | 22 (47) | 19 (40) | 0.477 | 22 (44) | 19 (42) | 0.861 |
| ACS | 25 (53) | 29 (60) | 0.477 | 28 (56) | 26 (58) | 0.861 |
| Target vessel | | | | | | |
| Left anterior descending artery (LAD) | 38 (76) | 43 (86) | 0.207 | 39 (72) | 42 (91) | 0.021 |
| Left circumflex artery(LCX) | 5 (10) | 2 (4) | 0.255 | 6 (11) | 1 (2) | 0.116 |
| Left main artery (LM) | 2 (4) | 1 (2) | 0.565 | 1 (2) | 2 (4) | 0.479 |
| Right coronary artery (RCA) | 5 (10) | 4 (8) | 0.727 | 8 (15) | 1 (2) | 0.057 |
| Predilatation | 37 (74) | 37 (74) | 0.999 | 38 (70) | 36 (78) | 0.371 |
| High pressure post dilatation (NC balloon) | 38 (76) | 36 (72) | 0.649 | 36 (67) | 38 (83) | 0.074 |
| Mean post PCI Pd/Pa | 0.91±0.05 | 0.91±0.03 | 0.774 | 0.91±0.05 | 0.91±0.04 | 0.833 |
| Mean post PCI FFR, maximum hyperemia | 0.79±0.06 | 0.78±0.04 | 0.578 | 0.79±0.05 | 0.79±0.05 | 0.909 |
| No. of stents | 1 (1-2) | 1 (1-2) | 0.363 | 1 (1-2) | 1 (1-2) | 0.308 |
| Mean stent diameter, mm | 3 (2.8-3) | 3 (2.8-3.5) | 0.090 | 3 (2.6-3) | 3 (3-3.5) | 0.004 |
| Total stent length, mm | 35 (18-52) | 26 (15-42) | 0.118 | 26 (14-40) | 30 (20-53) | 0.083 |

Values are n (%) or mean±SD, PCI = Percutaneous Coronary Artery and CABG = Coronary Artery Bypass Grafting, NSTEMI = non ST elevated myocardial infarction, STEMI =ST elevated myocardial infarction. NC = non-compliant, Pd/Pa = the Pressure in the Distal coronary artery to the Pressure in the Aorta ratio, FFR = Fractional Flow Reserve. MLA = minimal lumen area

## REFERENCES

1. Wolfrum M, Fahrni G, de Maria GL, Knapp G, Curzen N, Kharbanda RK, et al. Impact of impaired fractional flow reserve after coronary interventions on outcomes: a systematic review and meta-analysis. BMC Cardiovascular Disorders. 2016;16(1):177.
2. De Bruyne B, Fearon Wf Fau - Pijls NHJ, Pijls Nh Fau - Barbato E, Barbato E Fau - Tonino P, Tonino P Fau - Piroth Z, Piroth Z Fau - Jagic N, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014(1533-4406 (Electronic)).
3. van Zandvoort LJC, Masdjedi K, Witberg K, Ligthart J, Tovar Forero MN, Diletti R, et al. Explanation of Postprocedural Fractional Flow Reserve Below 0.85. Circ Cardiovasc Interv. 2019;12(2):e007030.
4. van Bommel RJ, Masdjedi K, Diletti R, Lemmert ME, van Zandvoort L, Wilschut J, et al. Routine Fractional Flow Reserve Measurement After Percutaneous Coronary Intervention. Circ Cardiovasc Interv. 2019;12(5):e007428.
5. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). European Heart Journal. 2018:ehy462-ehy.

# Chapter

# 8

# Predictors of post procedural fractional flow reserve – Insights from the FFR-SEARCH study

van Zandvoort LJC, **Masdjedi K,** Neleman T, Tovar Forero MN, Wilschut J, den Dekker WK, de Jaegere PPT, Diletti R, Zijlstra F, van Mieghem NMDA, Daemen J

Erasmus University Medical Center, Thoraxcenter, Department of cardiology, Rotterdam, the Netherlands

**Journal:** REC Interv Cardiol. 2020

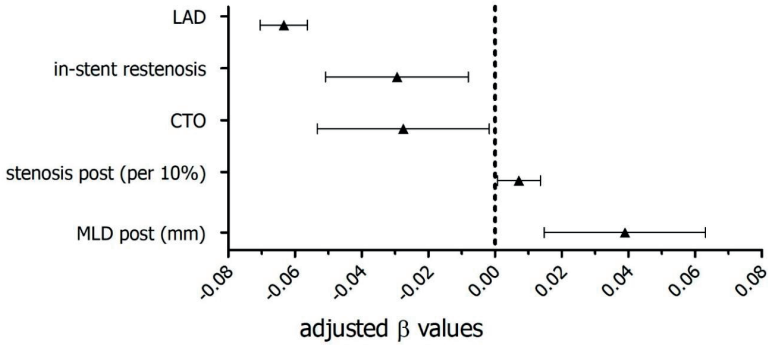
## ABSTRACT

**Introduction and objective:** Patients with a low post percutaneous coronary intervention (PCI) fractional flow reserve (FFR) are at increased risk for future adverse cardiac events. The aim of the current study was to assess specific patient and procedural predictors of post PCI FFR.

**Methods:** The FFR SEARCH study is a prospective single center registry including 1000 consecutive all-comer patients that underwent FFR evaluation after angiographic successful PCI using a dedicated microcatheter. Mixed-effects models were used to search for independent predictors of post PCI FFR.

**Results:** Mean post PCI Pd/Pa (distal pressure divided by the aortic pressure) was 0.96 ± 0.04 and mean post PCI FFR was 0.91 ± 0.07. Adjusting for independent predictors of post PCI FFR, left anterior descending artery as measured vessel was the strongest predictor (adjusted β =-0.063; 95%CI [-0.070 to -0.056]; *P* < .0001), followed by post procedural minimal lumen diameter (adjusted β = 0.039;, 95%CI [0.015 - 0.065]; *P* = .002). Additionally, male sex, in-stent restenosis, chronic total occlusions and pre- and post-dilatation were negatively correlated to the post procedural FFR. Conversely, type A lesions, thrombus containing lesions, post procedural percentage stenosis and stent diameter positively correlated to the post procedural FFR. The $R^2$ for the complete model was 53%.

**Conclusion:** Multiple independent patient and vessel related predictors for post procedural FFR were identified, including gender, LAD as measured vessel and post procedural MLD.




**Central illustration.** Forest plot of most important predictor of the post PCI FFR
Adjusted beta values with 95% confidence intervals. The Figure includes all significant predictors from the multivariate generalized mix model which predicts post PCI FFR, excluding categorical variables with a beta <0.02. LAD = left anterior descending artery; CTO = chronic total occlusion; MLD = minimal lumen diameter.

## INTRODUCTION

Limitations of accurate estimation of the hemodynamic significance of coronary artery lesions by angiographic guidance alone are well known (1). Fractional flow reserve (FFR) instead has proven to be a useful technique to address coronary physiology and the haemodynamic significance of coronary segments both pre- and post-intervention [2-4]. Moreover, FFR after stenting has proven to be a strong and independent predictor of major adverse cardiac events up to 2 years [3-5].

While FFR primarily takes into account the relative luminal narrowing and the amount of viable myocardium perfused by a specific vessel, several factors have been shown to impact pre percutaneous coronary intervention (PCI) FFR values. As such, longer lesion length, high syntax scores, calcifications and tortuosity are associated with significantly lower FFR values while the presence of microvascular dysfunction, chronic kidney disease and female gender have been associated with higher FFR values [6-11].

At present, there is lack of data on independent predictors of post PCI FFR. Therefore, the aim of the present study was to assess both patient and procedural characteristics associated with low post PCI FFR in an all-comer patient population.

## METHODS

The FFR SEARCH study is a prospective single center registry in which all consecutive patients underwent routine Pd/Pa (distal pressure divided by the aortic pressure) and FFR evaluation after angiographic successful PCI with the primary aim to study the impact of post PCI FFR on major adverse cardiac event rates at 2 years. Accordingly, no further actions were taken to improve post PCI FFR. The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee. All patients provided written informed consent for the procedure and the use of anonymous datasets for research purposes in alignment with the Dutch Medical Research Act. A total of 1512 patients treated between March 2016 and May 2017 at the Erasmus Medical Center were available for our study. Among them, 504 patients were excluded due to either haemodynamic instability (n = 156), distal outflow being too small (n = 129), operator's decision not to proceed with post PCI hemodynamic assessment (n = 148) or other reasons (n = 79). A total of 1000 patients were included in the study. The microcatheter was not able to cross the treated lesion in 28 patients, technical issues with the catheter prohibited post PCI assessment in 11 patients and in 2 patients post PCI FFR assessment had to be aborted prematurely due to adenosine intolerance, leaving 959 patients in which post PCI FFR was assessed in at least 1 angiographically successfully treated lesion.

*Quantitative coronary angiography*

Pre procedural lesion type was defined according to the ACC/AHA guidelines and divided in 4 categories: A, B1, B2 and C [12]. Comprehensive quantitative coronary angiography (QCA) analyses were performed pre and post stent implantation in all treated lesions. An angiographic view with minimal foreshortening of the lesion and minimal overlap with others vessels was selected. Similar angiographic views were used pre and post stent implantation. Measurements included: pre and post procedural percent diameter stenosis; reference vessel diameter; lesion length and minimal luminal diameter (MLD). In case of a total occlusion (in patients presenting with ST elevation myocardial infarction (STEMI) or a chronic total occlusion (CTO), the MLD was considered zero and percent diameter stenosis 100%. Reference vessel diameter and lesion length were calculated from the first angiographic view with restored flow. All measurements were performed using CAAS for Windows, version 2.11.2 (Pie Medical Imaging, Maastricht, The Netherlands).

## FFR measurements

All FFR measurements were performed using the Navvus RXi system (ACIST Medical Systems, Eden Prairie, MN, USA), a dedicated FFR microcatheter with optical pressure sensor technology [13, 14]. Measurements were performed after an intracoronary bolus of nitrates (200 µg). The catheter was advanced over the previously used coronary guidewire approximately 20 mm distal to the most distal stent edge. FFR was defined as mean distal coronary artery pressure divided by mean aortic pressure during maximum hyperaemia achieved by continuous intravenous infusion of adenosine at a rate of 140 µg/kg/min through an antecubital vein. No vessels in this study were evaluated using admission of intracoronary adenosine.

## Statistical analysis

Baseline, categorical variables are reported as counts (percentage) and continuous variables are reported as mean ± standard. In order to evaluate independent predictors for post PCI FFR, all patient and vessel characteristics were primarily univariately tested using a mixed-effects model (LME-model) with a random effect for patients and a fixed effect for post PCI FFR. All variables were subsequently inserted in a multivariate LME-model using the enter method, resulting in all significant independent predictors for post PCI FFR values. A forest plot was developed to depict all variables with the corresponding 95% confidence intervals. Beta (β) values indicate the average in-or decrease in FFR in case of a dichotomous variable or the increment per unit increase in case of continuous variables. Statistical analyses were performed by using R (version 3.5.1, packages: Hmisc, lme4 and nlme, RStudio Team (2020), Boston, MA).

## RESULTS

### Demographic characteristics

Mean age was 64.6 ± 11.8 years and 72.5% were males. In 959 patients at least one lesion was measured with a total of 1165 successfully treated and measured lesions. Patient demographics and baseline characteristics are depicted in Table 1. Up to 70% of patients presented with an acute coronary syndrome (ACS), while 18% had confirmed thrombus on angiography. Intravascular imaging was used in 9.6% to guide the procedure. Overall, 1.4 ± 0.6 lesions were treated per patient and in 1.2 ± 0.5 lesions per patient post PCI FFR was successfully assessed. The average total stented length per vessel was 29 ± 17 mm with an average diameter stent of 3.2 ± 0.5 mm.

**Table 1.** Baseline patient and vessel characteristics

| Variable | Total FFR SEARCH registry |
|---|---|
| **Patient characteristics** | (n = 1000) |
| Age | 64.6±11.8 |
| Gender, male | 725 (73) |
| Hypertension | 515 (52) |
| Hypercholesterolemia | 451 (45) |
| Diabetes | 191 (19) |
| Smoking history | 499 (50) |
| Prior Stroke | 77 (8) |
| Peripheral arterial disease | 76 (8) |
| Prior myocardial infarction | 203 (20) |
| Prior PCI | 264 (26) |
| Prior CABG | 57 (6) |
| Indication for PCI | |
| Stable angina | 304 (30) |
| NSTEMI | 367 (37) |
| STEMI | 329 (33) |
| **Vessel characteristics** | (n = 1165) |
| Lesion type | |
| A | 125 (11) |
| B1 | 233 (20) |
| B2 | 379 (33) |
| C | 428 (37) |
| LAD | 593 (51) |
| Bifurcation | 138 (12) |
| Calcified | 402 (35) |
| In-stent restenosis | 39 (3) |
| Thrombus | 214 (18) |

**Table 1.** Baseline patient and vessel characteristics (continued)

| Variable | Total FFR SEARCH registry |
|---|---|
| Stent thrombosis | 14 (1) |
| Ostial | 97 (8) |
| CTO | 42 (4) |
| Stenosis Pre | 69±22 |
| Ref diameter Pre (mm) | 2.6±0.6 |
| Length Pre (cm) | 21±11 |
| MLD Pre (mm) | 0.9±0.6 |
| Predilatation | 769 (66) |
| Post dilatation | 691 (59) |
| Stenosis Post (per 10%) | 4.4±13 |
| Ref diameter Post (mm) | 2.7±0.5 |
| Length Post (cm) | 24±13 |
| MLD Post (mm) | 2.6±0.5 |
| No. Stent | 1.4±0.6 |
| Stent length (cm) | 29±17 |
| Stent diameter (mm) | 3.2±0.5 |
| Mean post PCI Pd/Pa | 0.96 ± 0.04 |
| Mean post PCI FFR | 0.91 ± 0.07 |

Values are mean ± SD or n (%). PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; NSTEMI = non elevated ST segment myocardial infarction; STEMI = ST elevated myocardial infarction; Pd/Pa = Pressure in the Distal coronary artery to the Pressure in the Aorta ratio; FFR = Fractional Flow Reserve.

Mean post PCI FFR was 0.91 ± 0.07 and 7.7% of vessels had a post PCI FFR ≤ 0.80. In the LME-model, adjusting for independent predictors of post PCI FFR, LAD as measured vessel was the strongest predictor (adjusted β = -0.063, 95%CI,-0.070 to -0.056;, *P* < .0001), followed by the post procedural MLD (adjusted β = 0.039, 95%CI, 0.015- 0.065]; *P* = .002). Additionally, male gender, in-stent restenosis, chronic total occlusions (CTO) and pre- and post-dilatation were negatively correlated to the post procedural FFR. Conversely, type A lesions, thrombus containing lesions, post procedural percentage diameter stenosis and stent diameter positively correlated to the post procedural FFR. The $R^2$ for the complete model was 53%. Figure 1 illustrates all significant and non-significant adjusted predictors that were put in the LME-model and Table 2 depicts all adjusted and unadjusted predictors with corresponding β values and 95% confidence intervals. The central illustrations depicts the most important predictors.

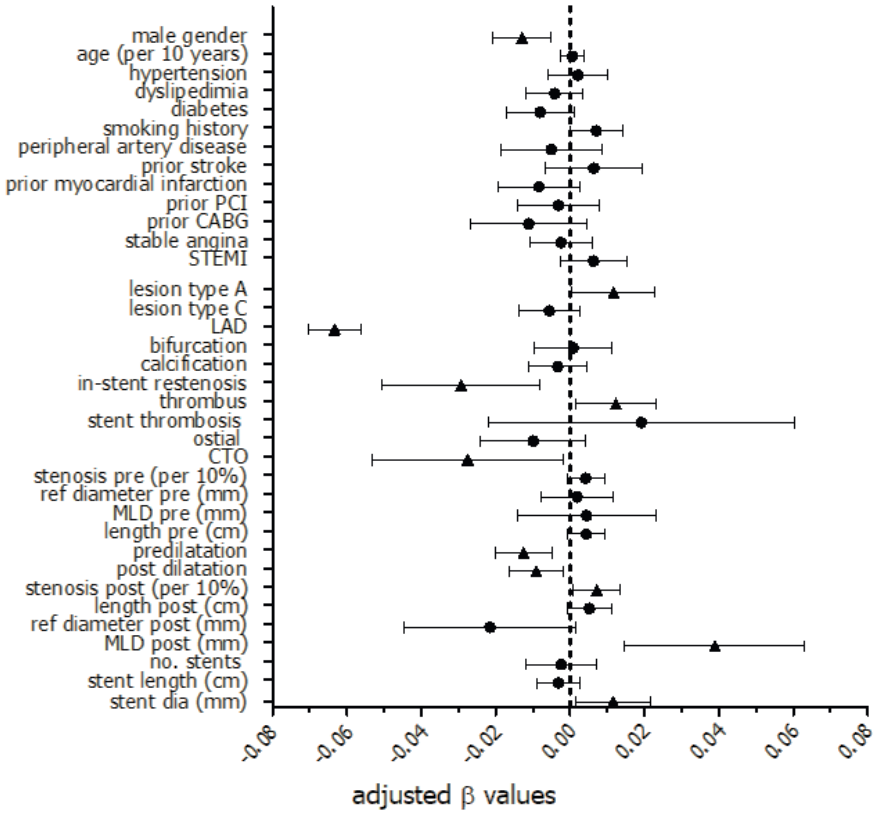



**Figure 1.** Forest plot of independent predictors for post PCI FFR

Adjusted beta values with 95% confidence intervals. Triangles indicate non-significant predictors, while circles indicate significant predictors in the multivariate generalized mix model to predict post PCI FFR. ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; LAD, left anterior descending artery; CTO, chronic total occlusion; MLD, minimal lumen diameter.

**Table 2.** predictors for post PCI FFR

| *Variable* | *unadjusted* | | *adjusted* | |
|---|---|---|---|---|
| | p value | *β (95% CI)* | p value | *β (95% CI)* |
| **Patient characteristics** | | | | |
| Male gender | 0.214 | -0.006 (-0.015 – 0.003) | 0.001 | -0.013 (-0.021 – -0.005) |
| Age (per 10 years) | 0.976 | 0.000 (-0.03 – 0.03) | 0.724 | 0.001 (-0.002 – 0.003) |
| Hypertension | 0.013 | -0.010 (-0.018 – -0.002) | 0.610 | 0.002 (-0.006 – 0.010) |
| Hypercholesterolemia | <0.001 | -0.019 (-0.027 – -0.011) | 0.287 | -0.004 (-0.012 – 0.004) |
| Diabetes | <0.001 | 0.018 (0.008 – 0.042) | 0.081 | -0.008 (-0.017 – 0.001) |
| Smoking history | 0.007 | 0.020 (0.010 – 0.019) | 0.054 | 0.007 (-0.0001 – 0.014) |
| Prior Stroke | 0.831 | -0.002 (-0.017 – 0.013) | 0.342 | 0.006 (-0.0007 – 0.019) |

**Table 2.** predictors for post PCI FFR (continued)

| *Variable* | *unadjusted* | | *adjusted* | |
|---|---|---|---|---|
| | p value | *β (95% CI)* | p value | *β (95% CI)* |
| Peripheral arterial disease | 0.022 | -0.017 (-0.032 – -0.003) | 0.460 | -0.005 (-0.018 – 0.008) |
| Prior myocardial infarction | 0.002 | -0.016 (-0.026 – -0.006) | 0.137 | -0.008 (-0.019 – 0.003) |
| Prior PCI | <0.001 | -0.016 (-0.025 – -0.007) | 0.569 | -0.032 (-0.014 – 0.008) |
| Prior CABG | 0.896 | -0.001 (-0.019 – 0.017) | 0.166 | -0.011 (-0.014 – 0.004) |
| Indication for PCI | | | | |
| Stable angina | <0.001 | -0.025 (-0.034 – -0.016) | 0.563 | -0.002 (-0.011 – 0.005) |
| STEMI | <0.001 | 0.032 (0.025 – 0.041) | 0.171 | 0.006 (-0.003 – 0.015) |
| **Vessel characteristics** | | | | |
| Lesion type | | | | |
| A | <0.001 | 0.022 (0.009 – 0.035) | 0.040 | 0.012 (0.0005 – 0.023) |
| C | 0.045 | -0.008 (-0.016 – -0.0002) | 0.172 | -0.006 (-0.014 – 0.002) |
| LAD | <0.001 | -0.070 ( -0.077 – -0.064) | <0.001 | -0.063 (-0.070 – -0.056) |
| Bifurcation | <0.001 | -0.024 (-0.036 – - 0.012) | 0.883 | 0.001 (-0.010 – 0.011) |
| Calcified | <0.001 | -0.025 (-0.033 – -0.017) | 0.409 | -0.003 (-0.011 – 0.005) |
| In-stent restenosis | 0.006 | -0.031 (-0.053 – -0.009) | 0.007 | -0.029 (-0.051 – -0.008) |
| Thrombus | <0.001 | 0.031 (0.021 – 0.042) | 0.026 | 0.012 (-0.001 – 0.023) |
| Stent thrombosis | 0.920 | 0.002 (-0.034 – 0.038) | 0.362 | 0.019 (-0.022 – 0.060) |
| Ostial | 0.181 | -0.010 (-0.024 – 0.005) | 0.165 | -0.010 (-0.024 – 0.004) |
| CTO | 0.002 | -0.034 (-0.056 – -0.013) | 0.036 | -0.027 (-0.053 – -0.002) |
| Stenosis Pre (per 10%) | <0.001 | 0.007 (0.005 – 0.009) | 0.105 | 0.004 (-0.0009 – 0.009) |
| Ref diameter Pre (mm) | <0.001 | 0.030 (0.023 – 0.037) | 0.704 | 0.002 (-0.008 – 0.011) |
| Length Pre (cm) | 0.900 | -0.00002 (-0.004 – 0.003) | 0.101 | 0.004 (0.0008 – 0.009) |
| MLD Pre (mm) | <0.001 | -0.015 (-0.022 – -0.008) | 0.638 | 0.004 (-0.014 – 0.023) |
| Predilatation | <0.001 | -0.019 (-.027 – -0.011) | 0.002 | -0.012 (-0.020 – -0.005) |
| Post dilatation | <0.001 | 0.027 (-0.035 – -0.019) | 0.015 | -0.009 (-0.016 – -0.002) |
| Stenosis Post (per 10%) | 0.077 | 0.003 (-0.0003 – 0.006) | 0.029 | 0.01 (0.0007 – 0.01) |
| Ref diameter Post (mm) | <0.001 | 0.035 (0.027 – 0.042) | 0.067 | -0.022 (-0.045 – 0.002) |
| Length Post (cm) | 0.312 | -0.002 (-0.005 – 0.001) | 0.086 | 0.001 (-0.0007 – 0.001) |
| MLD Post (mm) | <0.001 | 0.032 (0.024 – 0.040) | 0.002 | 0.039 (0.015 – 0.063) |
| No. Stent | <0.001 | -0.012 (-0.018 – -0.006) | 0.620 | -0.002 (-0.012 – 0.007) |
| Stent length (cm) | <0.001 | 0.019 (0.009 – 0.041) | 0.286 | -0.003 (-0.009 – 0.002) |
| Stent diameter (mm) | <0.001 | 0.033 (0.025 – 0.042) | 0.026 | 0.012 (0.001 – 0.022) |

Beta (β) values indicate the average in-or decrease in FFR in case of a dichotomous variable or the increment per unit increase in case of continuous variables. STEMI = ST elevated myocardial infarction; CABG = coronary artery bypass graft, LAD = left anterior descending artery, CTO = chronic total occlusion, MLD = minimal lumen diameter

## DISCUSSION

The present study is the largest report to date focusing on predictors of post PCI FFR. Based on data derived from the FFR SEARCH registry, we were able to identify several patient and procedural predictors of post PCI FFR. These predictors will help to further interpret post PCI FFR values and rightfully identify those vessels prone for future events. At first, male gender appeared to be negatively correlated to post procedural FFR. The latter finding extends the findings previous studies focusing on the impact of gender on pre PCI FFR measurement [6, 11, 15, 16]. Males are known to have a lower prevalence of microvascular dysfunction as compared to females [8, 17]. The concept of FFR is based on drug induced maximal hyperemia in order to minimize microvascular resistance. Microvascular dysfunction may hamper this vasodilator response and consequently result in a dampened flow response and elevated FFR [15]. Subsequently, males have on average a larger myocardial mass and thus, larger myocardial perfusion territories as compared to females [18, 19]. The importance of the latter can be illustrated by the second and strongest predictor of post PCI FFR in the present study, measurement of FFR in the LAD. FFR values are associated with myocardial mass and outflow territory of the measured vessel. As such, the LAD, the vessel with the largest perfusion area, has previously been correlated to lower pre and post procedural FFR values [20-22].

Stent diameters of implanted stents in the RCA are, on average larger, even though the outflow territory of the LAD is larger [23]. The discrepancy between luminal dimensions and myocardial mass might explain why optimal improvement of the FFR in the LAD is hard to achieve [23].

Third, larger stent diameters and larger post PCI MLD were associated with higher post PCI FFR, however, higher post procedural percentage stenosis was also correlated to higher post PCI FFR values. While these findings might seem contradictory, also in the DEFINE PCI study post procedural percentage stenosis was not correlated to post PCI physiology [24].

In the intravascular ultrasound sub-study of the FFR SEARCH registry van Zandvoort et al. demonstrated that clear signs of residual luminal narrowing, including focal lesions, underexpansion and malapposition, were present in a significant amount of vessels with a post PCI FFR ≤ 0.85, findings that could not linked not readily apparent on QCA [25]. Percent diameter stenosis was 20% in both the cohort of patients with a post PCI<=0.85 and >0.85 [26].

Next to the latter predictors of post PCI FFR we identified several other predictors.

A dedicated analysis on 26 CTO's recently illustrated that post procedural FFR values initially are typically low; however appeared to increase at 4 months follow-up. The initial low post PCI FFR is hypothesized to be due to microvascular dysfunction in the recently opened vessel, a phenomena

which improves after several months [27]. In-stent restenosis and pre- and post-dilatation were associated with lower post PCI values. The latter is in line with previous studies demonstrating that complex lesions in general were associated with lower post PCI FFR values [20, 21, 26, 28].

Of interest was also the impact of the clinical presentation on post PCI FFR in the study population in which the majority of patients presented with ACS. In contrast to previous studies questioning the validity of invasive hyperemic physiological indices in patients presenting with ACS, we were not able to confirm an impact of clinical presentation on post PCI FFR. The identification of thrombus however, often present after a plaque rupture in ACS patients, was associated with significantly higher FFR values. Despite the restoration of epicardial flow by the PCI, a relatively large proportion of patients with STEMI have abnormal myocardial perfusion at the end of the procedure [29]. This phenomenon is thought to be related to microvascular obstruction due to distal embolization (reperfusion injury) and tissue inflammation duo to myocyte necrosis [30, 31]. The latter might explain the significantly higher post PCI FFR values in patients presenting with thrombus containing lesions as compared to those without. Conversely, our findings also illustrate that in patients without thrombus containing lesions post PCI FFR might be a valuable diagnostic tool to identify those patients with an elevated risk for future adverse cardiac events.

## LIMITATIONS

The current study was performed with the Navvus microcatheter, a dedicated rapid-exchange microcatheter with a mean diameter of 0.022'' that proved to result in a slight but significant underestimation of FFR as compared to the conventional 0.014'' pressure wires [32]. The latter withholds us from direct extrapolation of the current findings towards wire based FFR devices [14]. Based on the study protocol, no further action was taken in case of a low post PCI FFR. The Target FFR and FFR REACT study (NCT03259815 & NTR6711) should provide more information concerning post-PCI FFR and the potential of further actions intended to improve post PCI FFR and clinical outcomes [33, 34]. The latter studies should also focus on the trade-off of potential benefits and harm when performing additional interventions in order to improve the final FFR values.

## CONCLUSION

In this substudy of the FFR SEARCH registry, the largest real world post PCI FFR registry thus far, we identified gender, LAD vessels, post procedural MLD and several other independent predictors for post procedural FFR.

### - What is known about the topic?

Fractional flow reserve (FFR) has proven to be a useful technique to address coronary physiology and the haemodynamic significance of coronary segments both pre- and post-intervention. Moreover, FFR after stenting has proven to be a strong and independent predictor of major adverse cardiac events up to 2 years. Unfortunately, at present, there is lack of data on independent predictors of post PCI FFR.

### - What does this study add?

The present study is the largest report to date focusing on predictors of post PCI FFR. Based on data derived from the FFR SEARCH registry, we were able to identify several patient and procedural predictors of post PCI FFR. The main predictors included gender, LAD vessels and post procedural lumen dimensions. The latter will help to further interpret post PCI FFR values and rightfully identify those vessels prone for future events.

## REFERENCES

1. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. Circulation. 1995;92(8):2333-42.
2. De Bruyne B, Fearon Wf Fau - Pijls NHJ, Pijls Nh Fau - Barbato E, Barbato E Fau - Tonino P, Tonino P Fau - Piroth Z, Piroth Z Fau - Jagic N, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014(1533-4406 (Electronic)).
3. Wolfrum M, Fahrni G, de Maria GL, Knapp G, Curzen N, Kharbanda RK, et al. Impact of impaired fractional flow reserve after coronary interventions on outcomes: a systematic review and meta-analysis. BMC Cardiovascular Disorders. 2016;16(1):177.
4. Rimac G, Fearon WF, De Bruyne B, Ikeno F, Matsuo H, Piroth Z, et al. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis. Am Heart J. 2017;183:1-9.
5. Kasula S, Agarwal SK, Hacioglu Y, Pothineni NK, Bhatti S, Ahmed Z, et al. Clinical and prognostic value of poststenting fractional flow reserve in acute coronary syndromes. Heart. 2016;102(24):1988-94.
6. Sareen N, Baber U, Kezbor S, Sayseng S, Aquino M, Mehran R, et al. Clinical and angiographic predictors of haemodynamically significant angiographic lesions: development and validation of a risk score to predict positive fractional flow reserve. EuroIntervention. 2017;12(18):e2228-e35.
7. Baranauskas A, Peace A, Kibarskis A, Shannon J, Abraitis V, Bajoras V, et al. FFR result post PCI is suboptimal in long diffuse coronary artery disease. EuroIntervention. 2016;12(12):1473-80.
8. Crystal GJ, Klein LW. Fractional flow reserve: physiological basis, advantages and limitations, and potential gender differences. Curr Cardiol Rev. 2015;11(3):209-19.
9. Ahmadi A, Leipsic J, Ovrehus KA, Gaur S, Bagiella E, Ko B, et al. Lesion-Specific and Vessel-Related Determinants of Fractional Flow Reserve Beyond Coronary Artery Stenosis. JACC Cardiovasc Imaging. 2018.
10. Tebaldi M, Biscaglia S, Fineschi M, Manari A, Menozzi M, Secco GG, et al. Fractional Flow Reserve Evaluation and Chronic Kidney Disease: Analysis From a Multicenter Italian Registry (the FREAK Study). Catheter Cardiovasc Interv. 2016;88(4):555-62.
11. Fineschi M, Guerrieri G, Orphal D, Palmerini E, Münzel T, Warnholtz A, et al. The impact of gender on fractional flow reserve measurements. EuroIntervention. 2013;9.
12. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB, 3rd, Loop FD, et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). Circulation. 1988;78(2):486-502.
13. Diletti R, van Mieghem NMDA, Valgimigli M, Karanasos A, Everaert BR, Daemen J, et al. Rapid exchange ultra-thin microcatheter using fibre-optic sensing technology for measurement of intracoronary fractional flow reserve. EuroIntervention. 2015;11(4):428-32.
14. Menon M, Jaffe W, Watson T, Webster M. Assessment of coronary fractional flow reserve using a monorail pressure catheter: the first-in-human ACCESS-NZ trial. EuroIntervention. 2015;11(3):257-63.
15. van de Hoef TP, Meuwissen M, Escaned J, Davies JE, Siebes M, Spaan JA, et al. Fractional flow reserve as a surrogate for inducible myocardial ischaemia. Nat Rev Cardiol. 2013;10(8):439-52.
16. Kim HS, Tonino PA, De Bruyne B, Yong AS, Tremmel JA, Pijls NH, et al. The impact of sex differences on fractional flow reserve-guided percutaneous coronary intervention: a FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) substudy. JACC Cardiovasc Interv. 2012;5(10):1037-42.
17. Reis SE, Holubkov R, Lee JS, Sharaf B, Reichek N, Rogers WJ, et al. Coronary flow velocity response to adenosine characterizes coronary microvascular function in women with chest pain and no obstruc-

tive coronary disease. Results from the pilot phase of the Women's Ischemia Syndrome Evaluation (WISE) study. J Am Coll Cardiol. 1999;33(6):1469-75.
18. Iqbal MB, Shah N, Khan M, Wallis W. Reduction in myocardial perfusion territory and its effect on the physiological severity of a coronary stenosis. Circ Cardiovasc Interv. 2010;3(1):89-90.
19. Lin FY, Devereux RB, Roman MJ, Meng J, Jow VM, Jacobs A, et al. Cardiac chamber volumes, function, and mass as determined by 64-multidetector row computed tomography: mean values among healthy adults free of hypertension and obesity. JACC Cardiovasc Imaging. 2008;1(6):782-6.
20. Nam CW, Hur SH, Cho YK, Park HS, Yoon HJ, Kim H, et al. Relation of fractional flow reserve after drug-eluting stent implantation to one-year outcomes. Am J Cardiol. 2011;107.
21. Doh JH, Nam CW, Koo BK, Lee SY, Choi H, Namgung J, et al. Clinical Relevance of Poststent Fractional Flow Reserve After Drug-Eluting Stent Implantation. J Invasive Cardiol. 2015;27.
22. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv. 2016;9(10):1022-31.
23. Kimura Y, Tanaka N, Okura H, Yoshida K, Akabane M, Takayama T, et al. Characterization of real-world patients with low fractional flow reserve immediately after drug-eluting stents implantation. Cardiovascular intervention and therapeutics. 2016;31(1):29-37.
24. Jeremias A, Davies JE, Maehara A, Matsumura M, Schneider J, Tang K, et al. Blinded Physiological Assessment of Residual Ischemia After Successful Angiographic Percutaneous Coronary Intervention: The DEFINE PCI Study. JACC: Cardiovascular Interventions. 2019;12(20):1991-2001.
25. van Zandvoort LJC, Masdjedi K, Witberg K, Ligthart JMR, Tovar Forero MN, Diletti R, et al. Explanation of Postprocedural Fractional Flow Reserve Below 0.85. Circ Cardiovasc Interv. 2019;12(2):e007030.
26. Zandvoort van LJC MK, Witberg K., Ligthart JMR., Tovar Forero M.N., Diletti R., Lemmert M., Wilschut J., Jaegere de P.T., Boersma E., Zijlstra F., Mieghem van N., Daemen J.. Explanation of post procedural fractional flow reserve below 0.85: a comprehensive ultrasound analysis of the FFR Search registry. CRT meeting. 2018.
27. Karamasis GV, Kalogeropoulos AS, Mohdnazri SR, Al-Janabi F, Jones R, Jagathesan R, et al. Serial Fractional Flow Reserve Measurements Post Coronary Chronic Total Occlusion Percutaneous Coronary Intervention. Circ Cardiovasc Interv. 2018;11(11):e006941.
28. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation. 2002;105.
29. Stone GW, Webb J, Cox DA, Brodie BR, Qureshi M, Kalynych A, et al. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. Jama. 2005;293(9):1063-72.
30. Shah NR, Al-Lamee R, Davies J. Fractional flow reserve in acute coronary syndromes: A review. Int J Cardiol Heart Vasc. 2014;5:20-5.
31. Cuculi F, De Maria GL, Meier P, Dall'Armellina E, de Caterina AR, Channon KM, et al. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2014;64(18):1894-904.
32. Pouillot C, Fournier S, Glasenapp J, Rambaud G, Bougrini K, Vi Fane R, et al. Pressure wire versus microcatheter for FFR measurement: a head-to-head comparison. EuroIntervention. 2018;13(15):e1850-e6.
33. van Zandvoort LJC, Masdjedi K, Tovar Forero MN, Lenzen MJ, Ligthart JMR, Diletti R, et al. 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. Am Heart J. 2019;213:66-72.

34. Collison D, McClure JD, Berry C, Oldroyd KG. A randomized controlled trial of a physiology-guided percutaneous coronary intervention optimization strategy: Rationale and design of the TARGET FFR study. Clin Cardiol. 2020.

# Chapter

# 9

# FFR guided PCI optimization directed by high-definition intravascular ultrasound versus standard of care: Rationale and study design of the prospective randomized FFR-REACT trial

Laurens J.C. van Zandvoort BSc, **Kaneshka Masdjedi MD**, Maria Natalia Tovar Forero MD, Mattie J. Lenzen PhD, Jurgen Ligthart RT, Roberto Diletti MD, PhD, Miguel E. Lemmert MD, PhD, Jeroen Wilschut MD, Peter P.T. de Jaegere MD, PhD, Felix Zijlstra MD, PhD, Nicolas M. van Mieghem MD, PhD, Joost Daemen MD, PhD.

**Department of cardiology, Thoraxcenter, Erasmus Medical Center**

**Journal:** American Heart Journal; 2019; 213:66-72

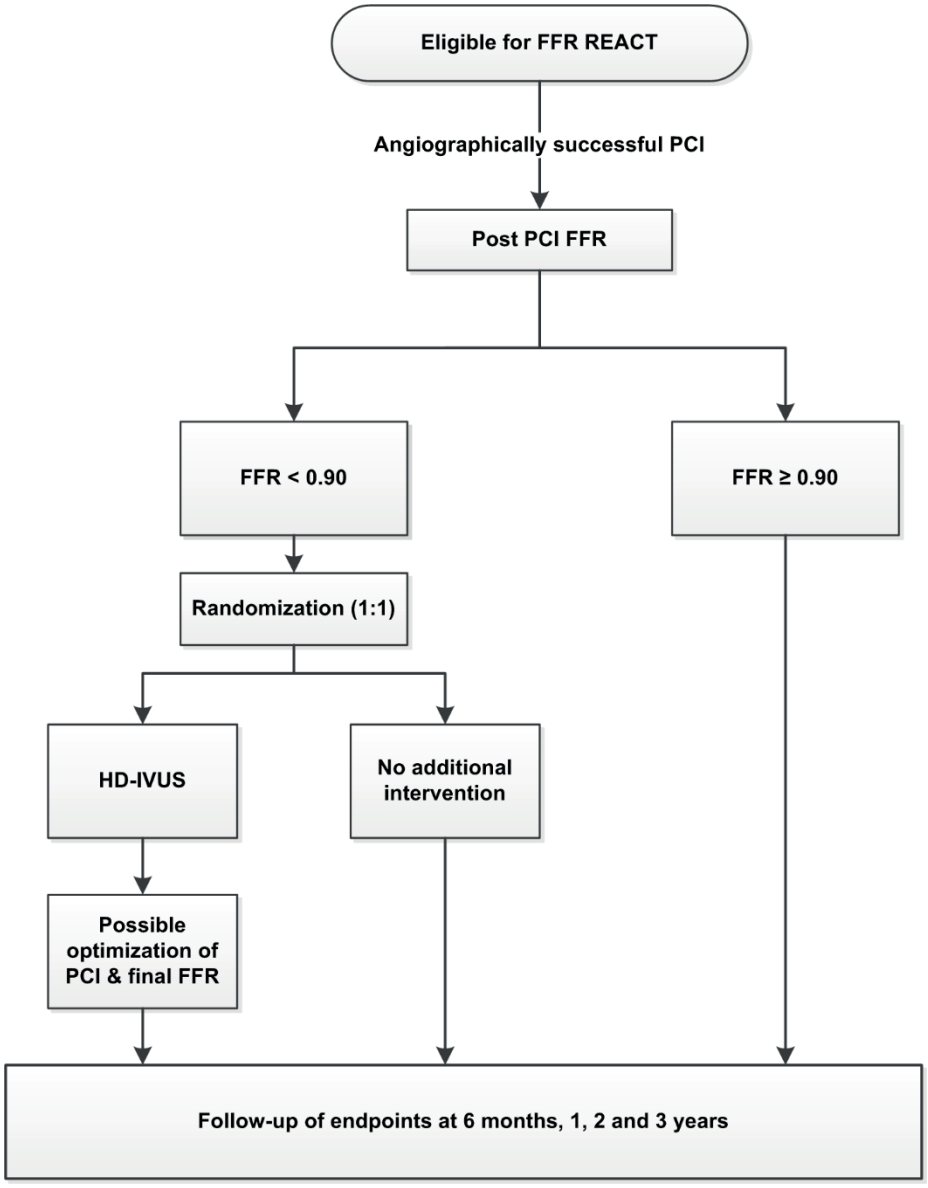
## ABSTRACT

**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 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≥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).

**Key words:** post PCI, fractional flow reserve, intravascular ultrasound, outcome




**Graphical abstract**
Study flowchart for the FFR REACT trial

## 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 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 ≥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 26$^{th}$ 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 1. 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 criteria(11)), stroke, periprocedural complications and acute kidney injury. Procedural characteristics such as contrast medium usage,

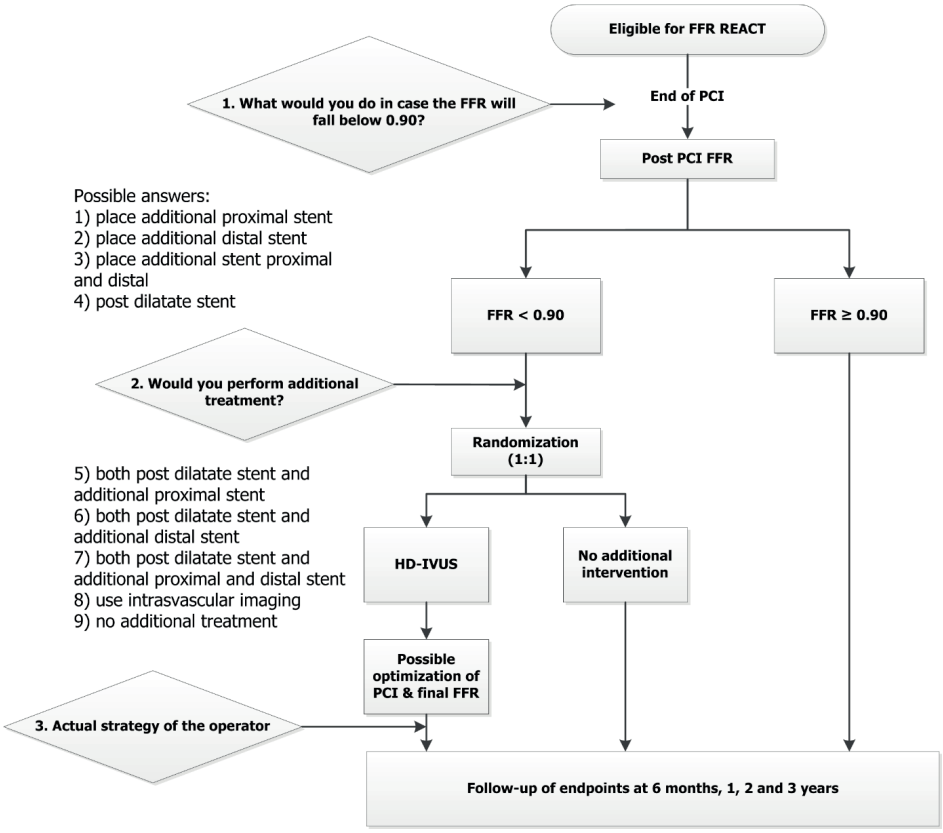



**Figure 1.** Study flow chart including the operator strategy questionnaire. The first two rhombuses contain the operator questions. The third rhombus is not asked but filled in according to the additional intervention. Nine possible answers are provided. FFR is fractional flow reserve, HD-IVUS is high definition intravascular ultrasound and PCI is percutaneous coronary intervention.

nr 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 2 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.

**Table 1.** In- and exclusion criteria

| |
|---|
| **Inclusion criteria** |
| - Age ≥18 |
| - Stable- or unstable angina or Non-ST segment elevation myocardial infarction |
| - Target lesion stenosis ≥ 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 <2.25mm |
| - 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 one year) |

* 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.

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 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, Minnesota) 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, Minnesota). Both devices are CE marked and are currently used in regular clinical practice.

**Table 2.** 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, nr 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 |
| - Rehospitalisation 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 |

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

## 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 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 µg/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.

### IVUS (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 3) 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 4 segments, a distal segment, in stent, in segment (stent ± 5mm) 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 3.

**Table 3:** stepwise protocol after high definition intravascular ultrasound (IVUS)

| |
|---|
| **Malapposition** |
| - When malapposition is present in more than 1 frame post dilatation with a balloon ≥0.25mm 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 ≥0.25mm 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 <6.0mm2. |
| - 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

### 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 intra-

vascular 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 ± 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. An 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, dyslipidaemia, 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 2.

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 (heterogenous 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 heterogenous cohort of studies with several outdated registries(4). The latter might result in a 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.

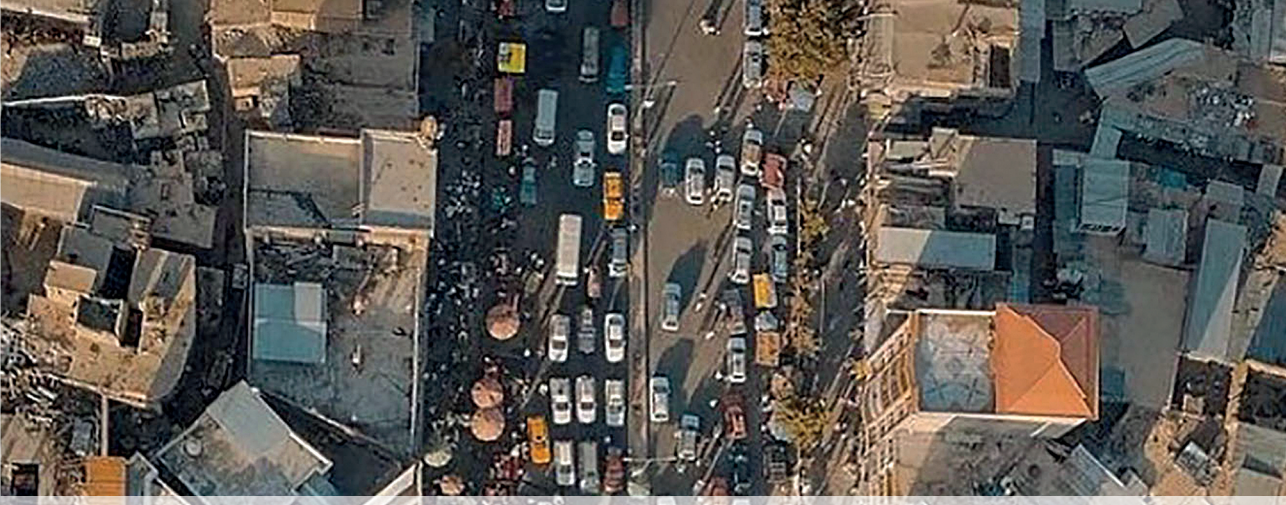
Public disclosure and publication policy

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.**.**

## REFERENCES

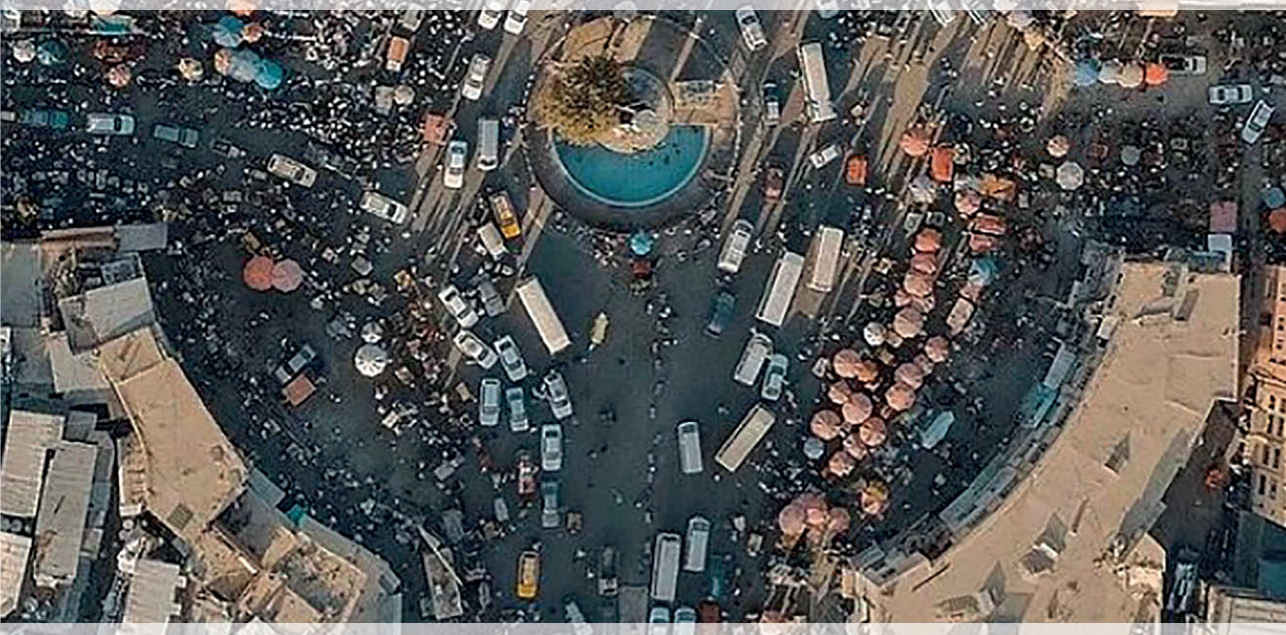
1. Cameron A, Kemp HG, Jr., Fisher LD, Gosselin A, Judkins MP, Kennedy JW, et al. Left main coronary artery stenosis: angiographic determination. Circulation. 1983;68(3):484-9.
2. Girasis C, Onuma Y, Schuurbiers JC, Morel MA, van Es GA, van Geuns RJ, et al. Validity and variability in visual assessment of stenosis severity in phantom bifurcation lesions: a survey in experts during the fifth meeting of the European Bifurcation Club. Catheter Cardiovasc Interv. 2012;79(3):361-8.
3. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.
4. Wolfrum M, Fahrni G, de Maria GL, Knapp G, Curzen N, Kharbanda RK, et al. Impact of impaired fractional flow reserve after coronary interventions on outcomes: a systematic review and meta-analysis. BMC Cardiovascular Disorders. 2016;16(1):177.
5. Rimac G, Fearon WF, De Bruyne B, Ikeno F, Matsuo H, Piroth Z, et al. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis. Am Heart J. 2017;183:1-9.
6. Tonino PA, Johnson NP. Why Is Fractional Flow Reserve After Percutaneous Coronary Intervention Not Always 1.0? JACC Cardiovasc Interv. 2016;9(10):1032-5.
7. Zandvoort van L.J.C. MK, Witberg K., Ligthart J., Tovar Forero M.N., Diletti R., Lemmert M., Wilschut J., Jaegere de P.T., Boersma E., Zijlstra F., Mieghem van N., Daemen J., . Explanation of post procedural fractional flow reserve below 0.85: a comprehensive ultrasound analysis of the FFR Search registry. CRT meeting. 2018.
8. Ahn J-M, Kang S-J, Yoon S-H, Park HW, Kang SM, Lee J-Y, et al. Meta-Analysis of Outcomes After Intravascular Ultrasound–Guided Versus Angiography-Guided Drug-Eluting Stent Implantation in 26,503 Patients Enrolled in Three Randomized Trials and 14 Observational Studies. The American Journal of Cardiology. 2014;113(8):1338-47.
9. Zhang J, Gao X, Kan J, Ge Z, Han L, Lu S, et al. Intravascular Ultrasound-Guided Versus Angiography-Guided Implantation of Drug-Eluting Stent in All-Comers: The ULTIMATE trial. J Am Coll Cardiol. 2018.
10. Diletti R, Van Bommel R, Masdjedi K, Van Zandvoort L, Lemmert ME, Wilschut J, et al. Routine Fractional Flow Reserve Measurement after Percutaneous Coronary Intervention The FFR-SEARCH Study. EuroPCR presentation. 2017.
11. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115(17):2344-51.
12. Diletti R, Van Mieghem NM, Valgimigli M, Karanasos A, Everaert BR, Daemen J, et al. Rapid exchange ultra-thin microcatheter using fibre-optic sensing technology for measurement of intracoronary fractional flow reserve. EuroIntervention. 2015;11(4):428-32.
13. Authors/Task Force m, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014.
14. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European Heart Journal. 2018:ehy394-ehy.
15. Cook Christopher M, Ahmad Y, Shun-Shin Matthew J, Nijjer S, Petraco R, Al-Lamee R, et al. Quantification of the Effect of Pressure Wire Drift on the Diagnostic Performance of Fractional Flow Reserve, Instantaneous Wave-Free Ratio, and Whole-Cycle Pd/Pa. Circulation: Cardiovascular Interventions. 2016;9(4):e002988.

16. de Jaegere P, Mudra H, Figulla H, Almagor Y, Doucet S, Penn I, et al. Intravascular ultrasound-guided optimized stent deployment. Immediate and 6 months clinical and angiographic results from the Multicenter Ultrasound Stenting in Coronaries Study (MUSIC Study). Eur Heart J. 1998;19(8):1214-23.
17. Waksman R, Legutko J, Singh J, Orlando Q, Marso S, Schloss T, et al. FIRST: Fractional Flow Reserve and Intravascular Ultrasound Relationship Study. Journal of the American College of Cardiology. 2013;61(9):917-23.
18. Ben-Dor I, Torguson R, Deksissa T, Bui AB, Xue Z, Satler LF, et al. Intravascular ultrasound lumen area parameters for assessment of physiological ischemia by fractional flow reserve in intermediate coronary artery stenosis. Cardiovasc Revasc Med. 2012;13(3):177-82.
19. Ben-Dor I, Torguson R, Gaglia MA, Jr., Gonzalez MA, Maluenda G, Bui AB, et al. Correlation between fractional flow reserve and intravascular ultrasound lumen area in intermediate coronary artery stenosis. EuroIntervention. 2011;7(2):225-33.
20. Mallidi J, Atreya AR, Cook J, Garb J, Jeremias A, Klein LW, et al. Long-term outcomes following fractional flow reserve-guided treatment of angiographically ambiguous left main coronary artery disease: A meta-analysis of prospective cohort studies. Catheter Cardiovasc Interv. 2015;86(1):12-8.
21. de la Torre Hernandez JM, Baz Alonso JA, Gomez Hospital JA, Alfonso Manterola F, Garcia Camarero T, Gimeno de Carlos F, et al. Clinical impact of intravascular ultrasound guidance in drug-eluting stent implantation for unprotected left main coronary disease: pooled analysis at the patient-level of 4 registries. JACC Cardiovasc Interv. 2014;7(3):244-54.
22. van der Sijde JN, Karanasos A, van Ditzhuijzen NS, Okamura T, van Geuns RJ, Valgimigli M, et al. Safety of optical coherence tomography in daily practice: a comparison with intravascular ultrasound. Eur Heart J Cardiovasc Imaging. 2016.
23. Pouillot C, Fournier S, Glasenapp J, Rambaud G, Bougrini K, Vi Fane R, et al. Pressure wire versus microcatheter for FFR measurement: a head-to-head comparison. EuroIntervention. 2018;13(15):e1850-e6.
24. Wijntjens GW, van de Hoef TP, Kraak RP, Beijk MA, Sjauw KD, Vis MM, et al. The IMPACT Study (Influence of Sensor-Equipped Microcatheters on Coronary Hemodynamics and the Accuracy of Physiological Indices of Functional Stenosis Severity). Circ Cardiovasc Interv. 2016;9(12).
25. Elgendy IY, Mahmoud AN, Elgendy AY, Bavry AA. Outcomes With Intravascular Ultrasound-Guided Stent Implantation: A Meta-Analysis of Randomized Trials in the Era of Drug-Eluting Stents. Circ Cardiovasc Interv. 2016;9(4):e003700.
26. Witzenbichler B, Maehara A, Weisz G, Neumann F-J, Rinaldi MJ, Metzger DC, et al. Relationship Between Intravascular Ultrasound Guidance and Clinical Outcomes After Drug-Eluting Stents The Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents (ADAPT-DES) Study. Circulation. 2014;129(4):463-70.



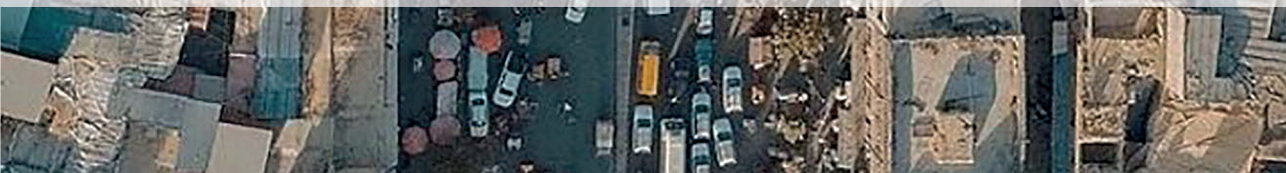
# PART III

# NOVEL NON-HYPEREMIC DIASTOLIC INDEX



"You get in life what you have the courage to ask for"

—K.S.M. Hafez



# Chapter 10

# Validation of Resting Diastolic Pressure Ratio Calculated by a Novel Algorithm and its Correlation with Distal Coronary Artery Pressure to Aortic Pressure, Instantaneous Wave-Free Ratio and Fractional Flow Reserve: The dPR Study

**Kaneshka Masdjedi, MD*;** Jurgen Ligthart, RT*; Karen Witberg, RN; Frits Mastik, BSc; Laurens van Zandvoort, BSc; Miguel E Lemmert, MD, PhD; Jeroen Wilschut, MD; Roberto Diletti, MD, PhD; Peter de Jaegere, MD, PhD; Felix Zijlstra, MD, PhD; Isabella Kardys, MD, PhD; Nicolas M Van Mieghem, MD, PhD; Joost Daemen, MD, PhD

**Department of cardiology, Thoraxcenter, Erasmus Medical Center**

* equal authorship

**Journal:** Circulation Cardiovascular Interventions; 2018;11:e006911.

## ABSTRACT

**Background:** Instantaneous wave free ratio (iFR) offers a reliable non-hyperemic assessment of coronary physiology but requires dedicated proprietary software with a fully automated algorithm. We hypothesized that diastolic pressure ratio (dPR), calculated with novel universal software, has a strong correlation with iFR, similar diagnostic accuracy relative to resting Pd/Pa and Fractional Flow Reserve (FFR).

**Methods and results:** An observational, prospective, single-center cohort study including patients who underwent iFR or FFR. Dedicated software was used to calculate the dPR from DICOM pressure waveforms. The "flat" period on the dP/dt signal was used to detect automatically the period, where the resistance is low and constant, and to calculate the dPR, which is an average over five consecutive heartbeats.

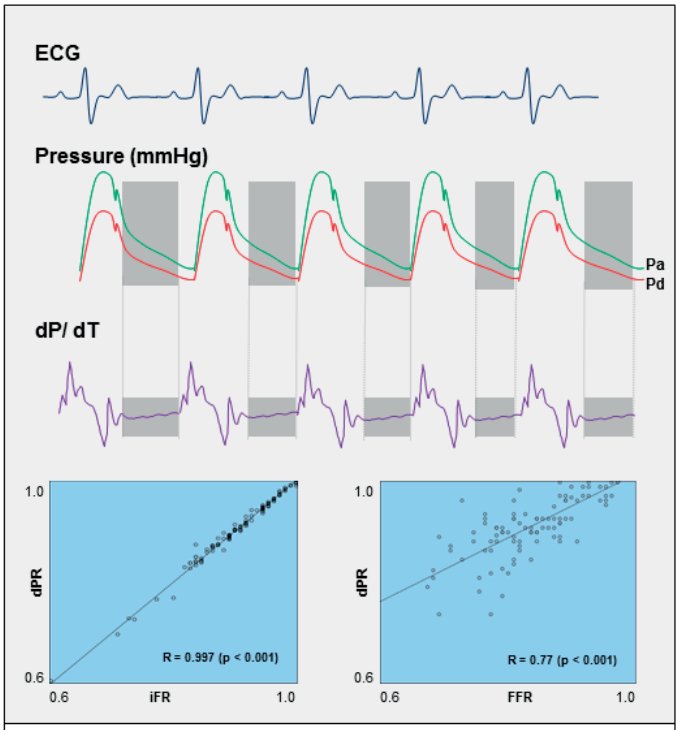
The software was validated by correlating iFR results with dPR. Software validation was done by comparing 78 iFR measurements in 44 patients who underwent iFR. Mean iFR and dPR were 0.91±0.10 and 0.92±0.10 respectively, with a significant linear correlation (R=0.997; p<0.001). Diagnostic accuracy was tested in 100 patients who underwent FFR. Mean FFR, resting Pd/Pa and dPR were 0.85±0.09; 0.94±0.05; 0.93±0.07 respectively. There was a significant linear correlation between dPR and FFR (R =0.77; p<0.001). Both Pd/Pa and dPR had good diagnostic accuracy in the identification of lesions with an FFR ≤0.80 (AUC 0.84 (95% CI: 0.76-0.92) and 0.86 (95% CI: 0.78 to 0.93) respectively).

**Conclusion:** dPR, calculated by a novel validated software tool, showed a strong linear correlation with iFR. dPR correlated well with FFR with a good diagnostic accuracy to identify positive FFR.

**Keywords:** Fractional Flow Reserve, instantaneous wave-free ratio, Pd/Pa.

### Condensed Abstract

The dPR-study is an observational, retrospective, single-center cohort study in which we demonstrated that diastolic pressure ratio (dPR), calculated with simplified software, has a strong linear correlation with instantaneous wave free ratio (iFR) (r=0.997, p<0.001). In a series of 100 patients, dPR showed to have a comparable diagnostic accuracy for the identification of lesions with an FFR ≤0.80 to Pd/Pa (AUC 0.84 (95% CI: 0.76-0.92) and 0.86 (95% CI: 0.78 to 0.93) respectively).




**CENTRAL ILLUSTRATION: Calculation of dPR based on "flat" period of aortic dP/dT curve. Correlation of dPR with iFR and FFR.**

**Central Illustration**

## INTRODUCTION

As compared to angiography guided percutaneous coronary intervention (PCI), Fractional Flow Reserve (FFR) guided PCI has been shown to significantly improve patient outcomes and cost-effectiveness and is currently considered the gold standard to identify the hemodynamic severity of coronary artery stenosis.[1-6] However, the concept of FFR which is based on maximum hyperemic conditions requiring intracoronary or intravenous hyperemic agents with potential side effects like dyspnea, chest pain and arrhythmias..[7]

In recent years, non-hyperemic pressure ratios (NHPR), such as the instantaneous wave-free ratio (iFR) and resting distal coronary artery pressure/aortic pressure (Pd/Pa), were introduced as alternative invasive indices to assess the severity of coronary artery stenosis.[8, 9] While Pd/Pa presents the ratio from the mean resting distal pressure to aortic coronary pressure during the whole cardiac cycle, iFR is based on the same ratio measured during the so-called "wave-free period", a period during diastole in which the microvascular resistance is low, and constant. As compared to FFR, the diagnostic accuracy of iFR has been assumed to be slightly better than Pd/Pa.[10]

While Pd/Pa can be calculated from any type of pressure wire or microcatheter, the algorithm of iFR belongs to the iFR core laboratory (Imperial College, London, United Kingdom) and its use is restricted to the proprietary software of a single vendor (Philips Volcano)

The aim of this study was to validate the diastolic pressure ratio (dPR), calculated using novel software applicable to any type of pressure wire or microcatheter, to assess the correlation of dPR with iFR and to assess the diagnostic accuracy of dPR as compared to FFR and resting Pd/Pa.

## METHODS

### Study design and patient population

Dedicated software was developed in the Erasmus Medical Center (Erasmus MC) (FM, JL, KW). The software was designed to calculate a dPR from DICOM pressure tracings generated by any type of pressure wire or catheter using either electrical (Piezo-Resistive) or optical sensors and from spreadsheet data (csv file), provided by the S5i console (Volcano Corporation, Rancho Cordova, California; FFR software version 2.4.1.2723) offline. The dPR study consisted of two parts: 1) validation of the dPR software with original iFR results and 2) assessment of the correlation of dPR with FFR and its diagnostic accuracy for identification of positive FFR.

For the purpose of this retrospective study patients were not subjected to study interventions, neither was any mode of behavior imposed, otherwise than as part of their regular treatment.

Therefore according to Dutch law, no formal approval was required. This study was conducted according to the privacy policy of the Erasmus MC and to the Erasmus MC regulations for the appropriate use of data in patient orientated research, which are based on international regulations, including the declaration of Helsinki. All patients consented to the use of their data for scientific research.

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

### Coronary angiography and calculation of dPR

All procedures were performed according to standard local clinical practice. Pressure measurements were performed after an intracoronary bolus of nitrates (100-200 μg), in case there was doubt regarding the hemodynamic significance of intermediate coronary artery lesions. Pd/Pa was defined as the ratio of mean distal coronary artery pressure to mean aortic pressure in the resting state during the whole cardiac cycle. FFR was defined as lowest ratio of 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 μg/kg/min through an antecubital vein. The dPR was defined by the ratio between the mean diastolic pressure distal to the stenosis and the mean diastolic aortic pressure in resting conditions. The diastolic period used to calculate the dPR was automatically delineated based on the dP/dt curve of the aortic pressure at the point at which the resistance was low, constant and stable. The dP/dt curve represents the increase and decrease of the pressure over time during the heart cycle. dP is the pressure difference between sample points and dt is the time difference between the same sample points. The “flat line” of the dP/dt tracing was used as trigger for the software to detect the “wave-free period” within the range of 60-80% of the cardiac phase as a first default. Because of this range the wave-free period detected by dP/dt tracing can be shorter than the wave-free period detected by original iFR. Both original iFR and calculated dPR values were stored in a spreadsheet, created by the dPR software and from each measurement a graphic representation was provided in PDF format (**Figure 1**), showing the pressure and dP/dt tracings together with the triggered regions and region of interest (ROI) to calculate dPR.

### Validation with iFR

A total of 78 iFR measurements from 44 patients were used for the validation step. iFR measurements were performed using the Verrata® pressure wire along with the original proprietary software (Philips Volcano). The csv spreadsheet files were imported in the software. The spreadsheet values of the reference aortic pressure and the wire pressure signals were used by the software to automatically analyze the dP/dt tracing and calculate the corresponding dPR based on 5 consecutive heart beats.

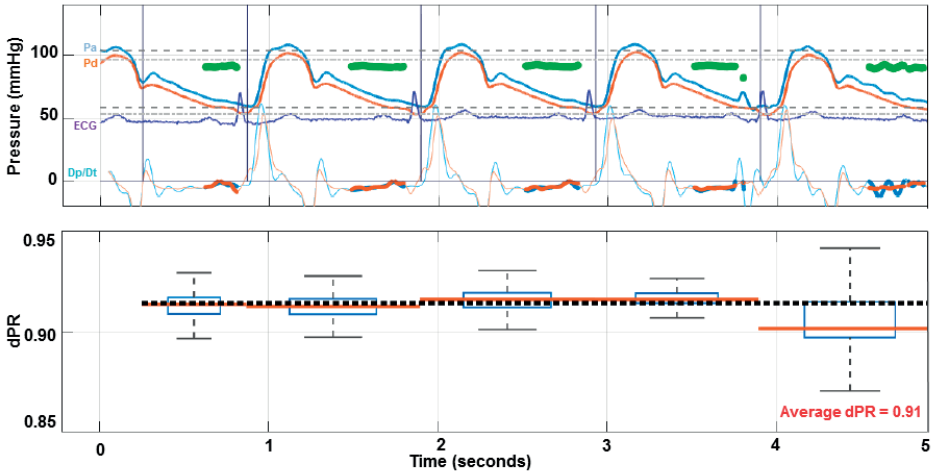



**Figure 1.** Sample tracing of the ECG, Aortic Pressure and dP/dt with the effect of different periods in the heart cycle.
Calculation of the index (dPR) during diastole by automatically indicating the "flat" period of the dP/Dt signal in 5 consecutive heartbeats.

## Validation with FFR

From April 2017 through September 2017, patients referred for coronary angiography for stable or unstable coronary artery disease and an indication to perform FFR, were included. A consecutive cohort of 100 patients with adequate pressure tracings was enrolled. DICOM recorded tracings derived from either a Pressure Wire (Pressure Wire™ X, Abbott Vascular, Santa Clara, CA,USA) or micro catheter (Navvus, ACIST Medical Systems, Eden Prairie, MN, USA) were eligible. Pressure waveforms were automatically exported to Siemens Sensis®, converted to DICOM and stored in a local hospital database.

## Statistical analysis

Continuous variables are presented as mean ±standard deviation. All continuous variables were normally distributed. Categorical variables are expressed as frequencies (n) and percentages (%). All statistical tests are 2-tailed. Pearson's correlation coefficient (R) was used to assess the relationship between the several indices. Agreement between the indices and the inter-observer variability were assessed by Bland-Altman plots with corresponding 95% limits of agreement. Receiver-operating characteristic (ROC) area under the curve (AUC) analysis was used to estimate the diagnostic accuracy of dPR as compared to FFR with a threshold of ≤0.80. Statistical analysis was carried out using the SPSS statistical package version 21 (IBM, Armonk, North Castle, New York, USA).

## RESULTS

### Validation with iFR

A total of 44 patients (age 70±10, 70% male) presenting with stable or unstable coronary artery disease underwent iFR measurements in 78 vessels (LAD n=38, LCX n=22, RCA n=18). Baseline characteristics of the iFR cohort are summarized in Table 1. Mean iFR and dPR were 0.91±0.10 and 0.92±0.10 respectively. An excellent correlation was found between both indices; (R = 0.997; p<0.001); Mean bias -0.0016±0.084), (Figure 2).

**Table 1.** Baseline characteristics iFR cohort

| | **Total (N=48)** |
|---|---|
| Age, y mean (±SD) | 70 (10) |
| Male sex, n (%) | 31 (70) |
| **Clinical indication procedure, n (%)** | |
| Stable angina | 32(67) |
| Unstable angina | 2(4) |
| Non ST segment elevation MI | 14(29) |
| **Cardiovascular risk factors, n(%)** | |
| Hypertension | 23 (52) |
| Hyperlipidemia | 17 (38) |
| Diabetes Mellitus | 14 (32) |
| Smoker | 8 (18) |
| Family history of CVD | 16 (36) |
| **Co-morbidity, mean(±SD)** | |
| Creatinine µmol/L | 111 (46) |
| Hemoglobine (mmol/L) | 8.1 (1.2) |
| BMI | 27 (4) |
| **Measured vessel Lesions, n(%)** | |
| Left anterior descending artery | 38 (49) |
| Left circumflex artery | 22 (28) |
| Right coronary artery | 18 (23) |
| **Indices, mean(±SD)** | |
| **iFR** | 0.91 (0.10) |
| **dPR** | 0.92 (0.10) |

Values are n, mean±SD of n (%); BMI =Body Mass Index; CVD =cardiovascular disease; dPR =resting diastolic pressure ratio; iFR =instantaneous wave-free ratio; MI =myocardial infarction.

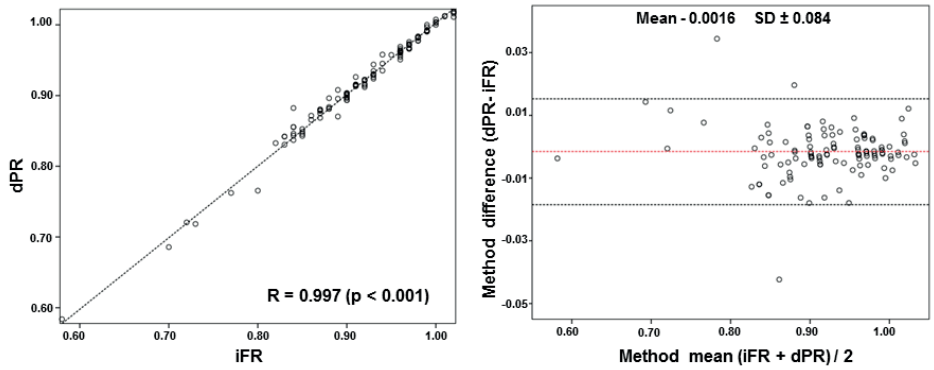



**Figure 2.** Scatter Plot showing the relationship between the iFR and dPR (left panel) and Bland- Altman plots of difference against the mean (right panel).
The mean bias is represented by the solid red line and the 95% confidence interval is represented by the dashed lines. Abbreviations as in Table 1.

## Patient demographics and procedural data of the FFR cohort

Baseline and procedural characteristics of the FFR cohort are summarized in Table 2. Mean age was 66 years and the majority of patients were male (80%). Clinical presentation was stable angina (56%), unstable angina (11%) and non ST segment elevation myocardial infarction (33%). Diabetes was present in 22% of the cases. The majority of the FFR measurements were performed in the left anterior descending artery (67%). The left circumflex artery and the right coronary artery were measured in 14% and 19% of the cases respectively.

## Relationship between dPR, Pd/Pa and FFR

Mean FFR, resting Pd/Pa and dPR were 0.85±0.09, 0.94±0.05 and 0.93±0.07 respectively (Table 2). A good linear correlation was found between dPR and FFR (R = 0.77; p<0.001) (Figure 3).The linear correlation between FFR and Pd/Pa was 0.81 (p<0.001). The correlation between FFR as measured using the Navvus system ($FFR_{MC}$) and dPR was higher as compared to pressure wire based FFR ($FFR_{PW}$) and dPR (R =0.81 vs R =0.76 respectively). dPR showed to have good diagnostic accuracy in the identification of patients with FFR values ≤0.80 (AUC of 0.86 [95% CI: 0.78-0.93]). Comparable results applies to Pd/Pa as well (AUC of 0.84 [95% CI: 0.76 – 0.92]) (Figure 4). The optimal cutoff value for an FFR ≤0.80 derived from the ROC analyses was 0.91 for dPR and 0.92 for Pd/Pa.

**Table 2.** Baseline characteristics of FFR cohort (N=100)

| | Total Cohort | $FFR_{MC}$ (N=50) | $FFR_{PW}$ (N=50) | p- value |
|---|---|---|---|---|
| Age, y mean (±SD) | 66 (11) | 67 (13) | 66 (8) | 0.94 |
| Male sex, n (%) | 80 (80) | 39 (78) | 41 (82) | 0.62 |
| **Clinical indication procedure, n (%)** | | | | |
| Stable angina | 56 (56) | 20 (40) | 36 (72) | 0.001 |
| Unstable angina | 11 (11) | 7 (14) | 4 (8) | 0.34 |
| Non ST segment elevation MI | 33 (33) | 23 (46) | 10 (20) | 0.01 |
| **Cardiovascular risk factors, n(%)** | | | | |
| Hypertension | 65 (65) | 34 (68) | 31 (62) | 0.53 |
| Hyperlipidemia | 55 (55) | 26 (52) | 29 (58) | 0.55 |
| Diabetes Mellitus | 22 (22) | 12 (24) | 10 (20) | 0.63 |
| Smoker | 18 (18) | 11 (22) | 7 (14) | 0.30 |
| Family history of CVD | 27 (27) | 17 (34) | 10 (20) | 0.12 |
| **Co-morbidity, mean(±SD)** | | | | |
| Creatinine µmol/L | 96 (46) | 96 (40) | 97 (50) | 0.94 |
| Hemoglobine (mmol/L) | 8.5 (1.1) | 8.6 (1.0) | 8.3 (1.1) | 0.27 |
| BMI | 28 (4) | 28 (5) | 27 (4) | 0.25 |
| **Measured vessel Lesions, n(%)** | | | | |
| Left anterior descending artery | 67 (67) | 34 (68) | 33 (66) | 0.83 |
| Left circumflex artery | 14 (14) | 6 (12) | 8 (16) | 0.57 |
| Right coronary artery | 19 (19) | 10 (20) | 9 (18) | 0.80 |
| **Indices, mean(±SD)** | | | | |
| Resting Pd/Pa | 0.94 (0.05) | 0.94 (0.05) | 0.94 (0.05) | 0.73 |
| FFR | 0.85 (0.09) | 0.85 (0.08) | 0.85 (0.09) | 1.00 |
| dPR | 0.93 (0.07) | 0.93 (0.06) | 0.92 (0.07) | 0.87 |

Values are n, mean ±SD of n (%); BMI= Body Mass Index; CVD =cardiovascular disease; dPR =resting diastolic pressure ratio; FFR =Fractional Flow Reserve; $FFR_{PW}$ =FFR measured by pressure wire system; $FFR_{MC}$ =FFR measured by the Acist FFR wire system; MI =myocardial infarction; Pd/Pa =resting distal to aortic coronary pressure.

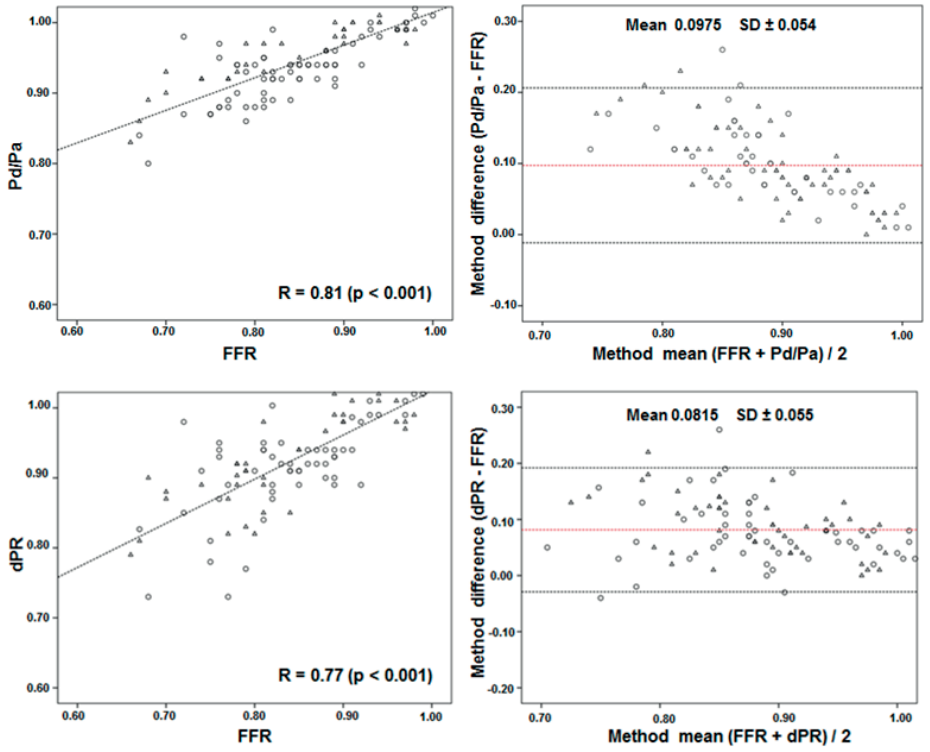



**Figure 3.** Scatter Plot showing the relationship between FFR and two different resting indices (Pa/Pa and dPR) and Bland- Altman plots of difference against the mean.
The mean bias is represented by the solid red line and the 95% confidence interval is represented by the dashed lines. Abbreviations as in Table 1 and 2. Δ represents FFR measurements as measured using the Navvus system ($FFR_{MC}$) and O represents pressure wire based FFR measurements ($FFR_{PW}$)

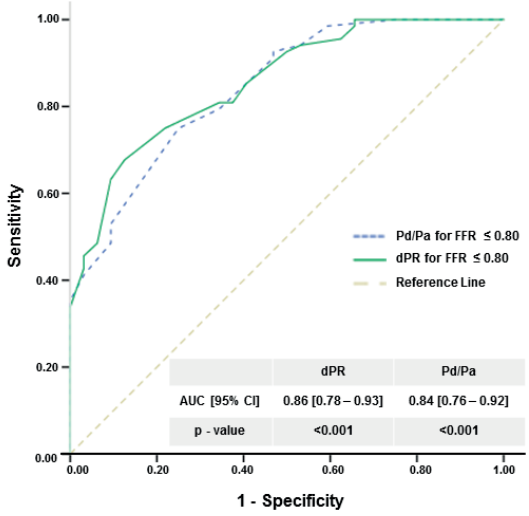



**Figure 4.** ROC Curves for dPR and Pd/Pa. Comparisons are made with an FFR at a cut point of 0.80. Abbreviations as in Table 1.

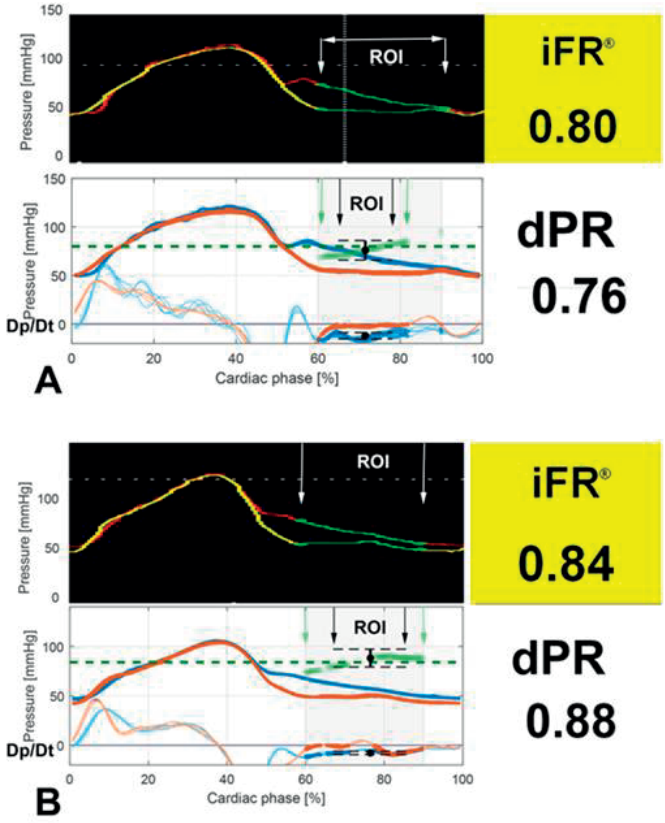



**Figure 5.** Explanation of discrepancy between iFR and dPR:
Two cases with a bias beyond the 95% confidence. Compared to iFR, dPR software triggers a shorter region of interest (ROI). Depending on the position of the ROI in the sequence this may result in a higher or lower Pd/Pa ratio compared to iFR. Case A: iFR includes a region with a "lump" in the distal pressure, dPR detected a "lump" in Dp/Dt and did not include the region beyond this "lump", positioned the ROI earlier in the sequence, resulting in a lower ratio. Case B: dPR ignored a steeper region in the Dp/Dt signal, positioned the ROI later in middle of the sequence, resulting in a higher Pd/Pa ratio compared to iFR.

## DISCUSSION

In the present study we demonstrated the feasibility of using a non-hyperemic pressure ratio, the dPR, calculated using novel software applicable to any type of pressure wire or microcatheter. dPR had an excellent linear correlation with iFR and a strong diagnostic accuracy in identifying lesions with an FFR ≤0.80.

FFR has become the gold standard to determine the severity of epicardial coronary stenoses and myocardial ischemia based on studies demonstrating significantly better outcomes with FFR-guided PCI as compared to angiography guided PCI.[5,4, 6, 11, 12] Nevertheless, despite strong

guideline recommendations and increasing evidence on its cost-effectiveness, the adoption of FFR in routine clinical practice remains low.[13-16] The latter has been linked to reimbursement issues and the need for hyperemic agents. Hyperemic agents like intravenous adenosine might provoke transient dyspnea, chest pain, vomiting, rhythm disturbances and hypotension in up to 37.5% of the cases.[8, 9] For these reasons the search for cheaper, faster and more patient-friendly methods remains relevant and several studies assessed the concept of the adenosine-independent index iFR as an alternative method to assess lesion severity. As mentioned, the concept of FFR is based on maximum hyperemic conditions necessitating the use of intravenous hyperemic agents. Nevertheless, even during hyperemia, intracoronary resistance is not static but instead fluctuates in a phasic pattern throughout the cardiac cycle with the lowest resistance during diastole due to decompression of the microvasculature and due to the lowest difference in pressure between the aorta and the coronary artery during diastole.[17] The iFR concept relies on the theory that intracoronary resistance is naturally low, constant and stable during the "wave-free" period precluding the need for hyperemic agents.[18] iFR had a high diagnostic accuracy to predict positive or negative FFR values. More recently, iFR guided PCI demonstrated to be non-inferior to FFR in reducing a composite of death from any cause, nonfatal myocardial infarction or unplanned revascularization within 12 months.[8, 9] However, in a pooled meta-analysis of this two trials, a numeric excess in the incidence of death and myocardial infarction was found in the iFR group. [19]Although no large scale randomized outcome studies are available on the efficacy of Pd/Pa as compared to FFR-guided revascularization, iFR appeared more sensitive than Pd/Pa to differentiate stenosis severity and showed a lower maximum difference in estimated major adverse cardiac event risk influenced by the measurement variability compared with resting Pd/Pa.[10] The latter supports the concept of applying the diastolic period to calculate pressure gradients when refraining from the use of hyperemic agents. At present, the use of iFR is restricted to the use of a single device and software (Philips Volcano) whereas a large variety of pressure wires and microcatheters are available to measure Pd/Pa and FFR. In the current study we demonstrated the feasibility of a fast, simple and reproducible method of measuring a dPR based on non-hyperemic DICOM pressure waveforms derived from either PW or microcatheter devices which could open up the field for a more widespread use of diastolic pressure gradients in real world clinical practice. By using a simple software tool to automatically detect the flat period in the dP/dt curve that indicates the so called "wave-free" period we found that the resultant dPR correlated nearly perfect with the original iFR output of Phillips Volcano ($r=0.997$, $p<0.001$). Subsequently, our results showed a correlation between dPR and FFR ($r=0.77$) in line with previous results from the VERIFY study demonstrating a correlation coefficient r of 0.789 between iFR and FFR.[20] Additionally, dPR showed a high diagnostic accuracy in the identification of patients with FFR values ≤0.80 (AUC of 0.86 (95% CI: 0.78-0.93)) while the AUC was 0.84 (95% CI: 0.76 – 0.92) for Pd/Pa. Also these results are in line with previous findings as published in the Resolve study in which the AUC was 0.81 and 0.82 for iFR and Pd/Pa respectively.[21] In the present study we used the flat period of the dP/dt signal to identify the "wave free period". While during this period in diastole there

is the least amount of pressure variation between aortic and distal pressures, it allowed us to develop software using the same methodology in any pressure-wire or microcatheter. It is likely that using either period during diastole to compute the dPR would result in equal results. Van 't Veer et al looked at the correlation between iFR and resting indices during different parts of the diastole by using a simple Matlab algorithm and concluded that all diastolic resting indices were identical to iFR.[22] Therefore, any diastolic resting index can be used with the same advantages and disadvantages inherent within iFR. However, in our validation cohort of 78 iFR measurements we found two cases with a bias beyond the 95% confidence interval. Analysis of these cases (Figure 5) showed that the dP/dt triggered a shorter "wave-free" period, resulting in a shorter ROI, in one case positioned earlier in the heart sequence, resulting in a lower dPR ratio compared to iFR, in the other case positioned later in the heart sequence, resulting in a higher dPR as compared to iFR. In conclusion, the length of the interval used in the present algorhythm depends on the length of the flat line on dP/dt waveform which might slightly differ per cardiac cycle. Conclusions about accuracy of iFR versus dPR and correlation to FFR cannot be drawn based on these two cases but warrant further research.

Kobayashi et al, looked at the influence of lesion location on the diagnostic accuracy of resting indices contrast FFR (cFFR), iFR and Pd/Pa and found that this three resting indices are less accurate in left main and proximal ramus descendens artery lesions as compared to other lesion locations. [23]The authors in the VERIFY 2 study, hypothesized that in comparison with FFR, revascularization decisions based on either binary cutoff values for iFR and Pd/Pa or hybrid strategies incorporating iFR or Pd/Pa will result in similar levels of disagreement. They found that binary cutoff values for iFR and Pd/Pa result in misclassification of 1 in 5 lesions. [24] We know that perfusion of the left coronary artery is predominantly diastolic while the perfusion of right coronary artery is both systolic and diastolic, due to lower pressure in the right ventricle as compared to the left ventricle.

While the diagnostic accuracy of NHPR in predicting positive FFR in general might differ between left and right sided assessments, we do not see any reason to believe that any difference might be expected in the diagnostic accuracy of dPR as compared to iFR.

Thereby, our study population is too small to analyze the differences between different lesion locations and between right (19%) vs left coronary artery (81%) (Table 2). However, we think there is no reason to believe that the dPR calculated based on dP/dt has superior diagnostic accuracy as any of the other resting indices.

Finally, small previous studies demonstrated a good correlation between $FFR_{MC}$ and $FFR_{PW}$ however also suggested an overestimation of FFR with $FFR_{MC}$ compared to $FFR_{PW}$ by approximately 1%. [25] While in the present study mean $FFR_{MC}$ and $FFR_{PW}$ were similar, the correlation between $FFR_{MC}$ and dPR was higher as compared to $FFR_{PW}$ and dPR (R=0.81, p<0.001 and R=0.76, p<0.001

respectively). We assume that the fact that the microcatheter was used merely for post-PCI FFR measurements, with subsequently lower pressure gradient, might have impacted our findings. Larger studies are needed to confirm any differences in optimal cut-off values for both devices.

## LIMITATIONS

The present results are based on a single center experience in which we restricted our analyses to those recordings with undamped pressure wave forms. The latter could have artificially influenced our results since recent core laboratory study data, assessing the prevalence of erroneous or suboptimal FFR measurements in clinical practice, demonstrated that in up to 30% of the recordings, pressure signals were inadequate. [26] In order not to be biased by measurements and results based on dampening pressure waveforms which might have biased the final FFR, iFR or Pd/Pa we scrutinized the pressure waveforms from tracings in the cases selected. In order to be able to mitigate to amount of bias caused by dampened pressure waveforms, we only selected cases in which pressure tracings and waveforms were adequate. Furthermore, Navvus microcatheter may confound the relationship with stenosis severity, which may be relevant when considering relationships between Pd/Pa and FFR. However, all included vessels in the present study were >2.5mm and that makes the comparison more reliable.

## CONCLUSION

Resting diastolic pressure ratio (dPR), calculated by a novel algorithm, had an excellent correlation with iFR, a high linear correlation to both Pd/Pa and FFR and a better diagnostic accuracy as compared to Pd/Pa.

## REFERENCES

1. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nuesch E, Juni P and Investigators FT. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med*. 2014;371:1208-17.
2. Authors/Task Force m, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W and Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35:2541-619.
3. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF and Investigators FT. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991-1001.
4. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W and de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol*. 2007;49:2105-11.
5. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF and Investigators FS. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-24.
6. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, De Bruyne B and Investigators FS. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol*. 2010;56:177-84.
7. Toth GG, Toth B, Johnson NP, De Vroey F, Di Serafino L, Pyxaras S, Rusinaru D, Di Gioia G, Pellicano M, Barbato E, Van Mieghem C, Heyndrickx GR, De Bruyne B and Wijns W. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. *Circ Cardiovasc Interv*. 2014;7:751-9.
8. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Harle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P and Escaned J. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. *N Engl J Med*. 2017;376:1824-1834.
9. Gotberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Ohagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Todt T, Venetsanos D, James SK, Karegren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Frobert O and i FRSI. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *N Engl J Med*. 2017;376:1813-1823.

10. Lee JM, Park J, Hwang D, Kim CH, Choi KH, Rhee TM, Tong Y, Park JJ, Shin ES, Nam CW, Doh JH and Koo BK. Similarity and Difference of Resting Distal to Aortic Coronary Pressure and Instantaneous Wave-Free Ratio. *J Am Coll Cardiol*. 2017;70:2114-2123.
11. Berger A, Botman KJ, MacCarthy PA, Wijns W, Bartunek J, Heyndrickx GR, Pijls NH and De Bruyne B. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *J Am Coll Cardiol*. 2005;46:438-42.
12. Sels JW, Tonino PA, Siebert U, Fearon WF, Van't Veer M, De Bruyne B and Pijls NH. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. *JACC Cardiovasc Interv*. 2011;4:1183-9.
13. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK and Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574-651.
14. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Juni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Uva MS, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A, Grupa Robocza Europejskiego Towarzystwa K, Europejskie Stowarzyszenie Chirurgii Serca i Klatki Piersiowej do spraw rewaskularyzacji miesnia s and European Association for Percutaneous Cardiovascular I. [2014 ESC/EACTS Guidelines on myocardial revascularization] Wytyczne ESC/EACTS dotyczace rewaskularyzacji miesnia sercowego w 2014 roku. *Kardiol Pol*. 2014;72:1253-379.
15. Siebert U, Arvandi M, Gothe RM, Bornschein B, Eccleston D, Walters DL, Rankin J, De Bruyne B, Fearon WF, Pijls NH and Harper R. Improving the quality of percutaneous revascularisation in patients with multivessel disease in Australia: cost-effectiveness, public health implications, and budget impact of FFR-guided PCI. *Heart Lung Circ*. 2014;23:527-33.
16. van Nunen LX, Zimmermann FM, Tonino PA, Barbato E, Baumbach A, Engstrom T, Klauss V, MacCarthy PA, Manoharan G, Oldroyd KG, Ver Lee PN, Van't Veer M, Fearon WF, De Bruyne B, Pijls NH and Investigators FS. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. *Lancet*. 2015;386:1853-60.
17. Davies JE, Whinnett ZI, Francis DP, Manisty CH, Aguado-Sierra J, Willson K, Foale RA, Malik IS, Hughes AD, Parker KH and Mayet J. Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. *Circulation*. 2006;113:1768-78.
18. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, Mayet J and Davies JE. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J Am Coll Cardiol*. 2012;59:1392-402.
19. Berry C, McClure JD and Oldroyd KG. Meta-Analysis of Death and Myocardial Infarction in the DEFINE-FLAIR and iFR-SWEDEHEART Trials. *Circulation*. 2017;136:2389-2391.
20. Berry C, van 't Veer M, Witt N, Kala P, Bocek O, Pyxaras SA, McClure JD, Fearon WF, Barbato E, Tonino PA, De Bruyne B, Pijls NH and Oldroyd KG. VERIFY (VERification of Instantaneous Wave-Free Ratio

and Fractional Flow Reserve for the Assessment of Coronary Artery Stenosis Severity in EverydaY Practice): a multicenter study in consecutive patients. *J Am Coll Cardiol*. 2013;61:1421-7.

21. Jeremias A, Maehara A, Genereux P, Asrress KN, Berry C, De Bruyne B, Davies JE, Escaned J, Fearon WF, Gould KL, Johnson NP, Kirtane AJ, Koo BK, Marques KM, Nijjer S, Oldroyd KG, Petraco R, Piek JJ, Pijls NH, Redwood S, Siebes M, Spaan JAE, van 't Veer M, Mintz GS and Stone GW. Multicenter core laboratory comparison of the instantaneous wave-free ratio and resting Pd/Pa with fractional flow reserve: the RESOLVE study. *J Am Coll Cardiol*. 2014;63:1253-1261.
22. Van't Veer M, Pijls NHJ, Hennigan B, Watkins S, Ali ZA, De Bruyne B, Zimmermann FM, van Nunen LX, Barbato E, Berry C and Oldroyd KG. Comparison of Different Diastolic Resting Indexes to iFR: Are They All Equal? *J Am Coll Cardiol*. 2017;70:3088-3096.
23. Kobayashi Y, Johnson NP, Berry C, De Bruyne B, Gould KL, Jeremias A, Oldroyd KG, Pijls NHJ, Fearon WF and Investigators CS. The Influence of Lesion Location on the Diagnostic Accuracy of Adenosine-Free Coronary Pressure Wire Measurements. *JACC Cardiovasc Interv*. 2016;9:2390-2399.
24. Hennigan B, Oldroyd KG, Berry C, Johnson N, McClure J, McCartney P, McEntegart MB, Eteiba H, Petrie MC, Rocchiccioli P, Good R, Lindsay MM, Hood S and Watkins S. Discordance Between Resting and Hyperemic Indices of Coronary Stenosis Severity: The VERIFY 2 Study (A Comparative Study of Resting Coronary Pressure Gradient, Instantaneous Wave-Free Ratio and Fractional Flow Reserve in an Unselected Population Referred for Invasive Angiography). *Circ Cardiovasc Interv*. 2016;9.
25. Menon M, Jaffe W, Watson T and Webster M. Assessment of coronary fractional flow reserve using a monorail pressure catheter: the first-in-human ACCESS-NZ trial. *EuroIntervention*. 2015;11:257-63.
26. Matsumura M, Johnson NP, Fearon WF, Mintz GS, Stone GW, Oldroyd KG, De Bruyne B, Pijls NHJ, Maehara A and Jeremias A. Accuracy of Fractional Flow Reserve Measurements in Clinical Practice: Observations From a Core Laboratory Analysis. *JACC Cardiovasc Interv*. 2017;10:1392-1401.

# Chapter 11

# Prognostic Value of Post PCI Diastolic Pressure Ratio in a real-world PCI registry

**Kaneshka Masdjedi, MD;** Laurens JC van Zandvoort, BSc; Tara Neleman, Bsc; Isabella Kardys, MD, PhD; Jurgen Ligthart, RT; Wijnand den Dekker, MD, PhD; Roberto Diletti, MD, PhD; Felix Zijlstra, MD, PhD; Nicolas M Van Mieghem, MD, PhD; Joost Daemen, MD, PhD.

**Department of cardiology, Thoraxcenter, Erasmus Medical Center**

**Journal:** Submitted

## ABSTRACT

**Aim:** To evaluate the distribution of a generic diastolic pressure ratio (dPR) after angiographically successful PCI and to assess its association with the 2-year incidence of target vessel failure (TVF), defined as a composite of cardiac mortality, target vessel revascularization, target vessel myocardial infarction and stent thrombosis.

**Methods:** The dPR SEARCH study is a post-hoc analysis of the prospective single center FFR-SEARCH registry in which physiological assessment was performed after angiographically successful PCI in a total of 1000 patients using a dedicated microcatheter. dPR was calculated offline with recently validated software in a subset of 735 patients.

**Results:** Mean post PCI dPR was 0.95±0.06. Post PCI dPR was ≤0.89 in 15.2% of the patients. The cumulative incidence of TVF at 2-years follow-up was 9.4% in patients with a final post PCI dPR≤0.89 as compared to 6.1% in patients with a post PCI dPR>0.89 (adjusted HR for dPR≤0.89; 1.53 95% CI [0.74-3.13]; p=0.249). dPR ≤0.89 was associated with significantly higher cardiac mortality at 2 years; adjusted HR 2.40 95% CI (1.01-5.68); p=0.047.

**Conclusions:** In a real world setting, despite optimal angiographic PCI results, 15.2% of the patients end up with a post PCI dPR of ≤0.89, which was associated with numerically higher rates of TVF and a significantly higher cardiac mortality rate.

## INTRODUCTION

An increasing body of evidence supports the use of either fractional flow reserve (FFR) or the non-hyperemic instantaneous wave free ratio (iFR) for the intracoronary physiological assessment with intermediate coronary artery lesions. [1-4] Recently, a series of so called non-hyperemic pressure ratios (NHPRs) have been validated and proved to have a nearly perfect correlation to iFR enhancing the adoption of general NHPRs in real world clinical practice. [5-7] At the same time, the use of post PCI physiological assessment is gaining attention. A strong and linear association has been demonstrated between post PCI FFR and the risk for both future repeat revascularization as well as hard clinical endpoints as death and myocardial infarction. [8-10] The relevance of the latter was strengthened by recent work from our group demonstrating that post PCI FFR values were ≤0.90 in up to 50% of stented vessels despite optimal angiographic results whereas 9.8% of vessels had a post PCI FFR ≤0.80. [11] With respect to post PCI NHPRs, the recently published DEFINE PCI study showed that 22.6% of treated vessels ended up with post PCI iFR ≤0.89. [12]

To date, limited data is available on the distribution of post PCI NHPRs and its prognostic value. The aim of the present study was to evaluate the distribution of a recently validated generic diastolic pressure ratio (dPR) after angiographically successful PCI in an all-comers study population and to study its association with 2-year clinical outcome.

## METHODS

### Study design and patient population

The dPR SEARCH study was a post hoc analysis of the FFR SEARCH registry (Stent Evaluated at Rotterdam Cardiology Hospital), a prospective single center registry in which routine FFR measurements were performed after angiographically successful PCI in a total of 1000 patients between March 2016 and May 2017. [11] Exclusion criteria were: 1) patients presenting with cardiogenic shock 2) “high risk” procedures defined as use of mechanical circulatory support 3) age <18 years and 4) an estimated vessel size < 2.25 mm. A total of 735 patients involving 735 vessels with available undamped pressure waveform data were selected for the present study, **Figure 1.**

The study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee of the Erasmus Medical Center. Participants were informed about the study by the physician responsible for the procedure and provided informed consent for the procedure and the use of anonymous datasets for research purposes in alignment with the Dutch Medical Research Act. JD and KM had full access to all the data in the study and take responsibility for its integrity and the data analysis.

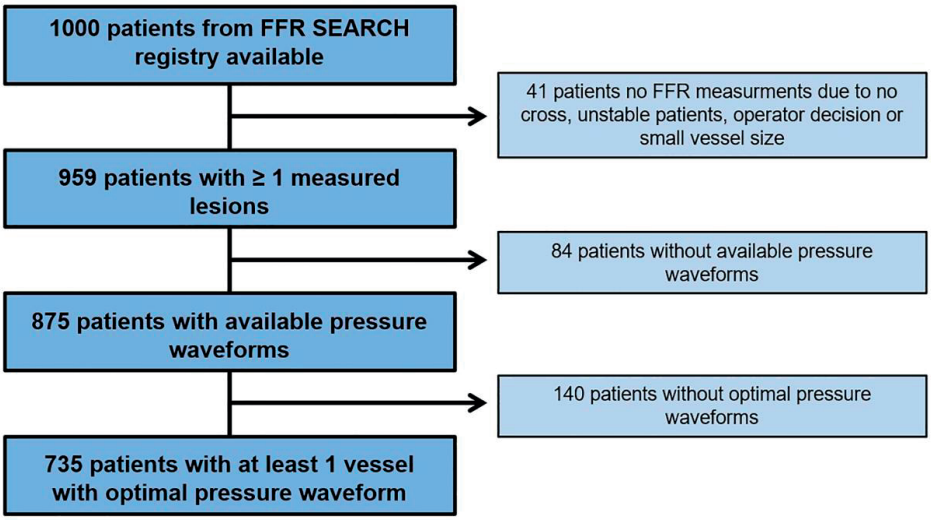



**Figure 1.** Flowchart showing all included and excluded patients.

## Coronary angiography and calculation of FFR

All procedures were performed according to standard local clinical practice with the use of intracoronary imaging and physiology at the operator's discretion. Pre procedural lesion type was defined according to the ACC/AHA guidelines.[13] All vessels, including in-stent restenosis cases, were treated with a stent. Comprehensive quantitative coronary angiography (QCA) analyses were performed pre- and post stent implantation in all treated lesions. An angiographic view with minimal foreshortening of the lesion and minimal overlap with other vessels was selected. Similar angiographic views were used pre and post stent implantation. Measurements included: pre and post procedural percent diameter stenosis; reference vessel diameter; lesion length and minimal luminal diameter (MLD). In case of a total occlusion (in patients presenting with ST elevation myocardial infarction (STEMI) or a chronic total occlusion (CTO), the MLD was considered zero and percent diameter stenosis 100%. Reference vessel diameter and lesion length were calculated from the first angiographic view with restored flow. All angiographic measurements were performed using CAAS for Windows, version 2.11.2 (Pie Medical Imaging, Maastricht, the Netherlands).

Pressure measurements were performed after an intracoronary bolus of nitrates (100-200 µg) using a dedicated rapid exchange monorail microcatheter (Navvus RXi system (ACIST Medical Systems inc., Eden Prairie, MN, USA)), with a fiber-optic-based sensor technology compatible with standard 0.014" guidewires. [14, 15] The device was inserted over the previously used coronary guidewire approximately 20mm distal to the most distal stent edge at which point Pd/Pa was measured. FFR values were subsequently recorded at 4 different positions in the coronary artery:

1) 20 mm distal from the distal stent edge 2) at the distal stent edge 3) at the proximal stent edge and 4) at the coronary ostium to verify the occurrence of drift. All analyses performed in the present study were based on values measured 20mm distal of the most distal stent edge. In patients in which dPR was assessed in multiple vessels, only the vessel with the lowest dPR was included.

### Definition and Calculation of dPR

Pd/Pa was defined as the ratio of mean distal coronary artery pressure to mean aortic pressure in the resting state during the whole cardiac cycle. FFR was defined as lowest ratio of mean distal coronary artery pressure divided by mean aortic pressure during maximal hyperemia. dPR was defined as the ratio between the mean diastolic pressure distal to the stenosis and the mean diastolic aortic pressure in resting conditions, taken over an average of 5 consecutive heartbeats. The dPR was calculated retrospectively using recently validated dedicated software developed at the Erasmus Medical Center. [5] Briefly, the diastolic period used to calculate the dPR was automatically delineated based on the dP/dt curve of the aortic pressure at the point at which the resistance was low, constant and stable. The dP/dt curve represents the increase and decrease of the pressure over time during the heart cycle. dP is the pressure difference between sample points and dt is the time difference between the same sample points.

### Endpoint definitions and clinical follow up

The primary endpoint consisted of target vessel failure (TVF), defined as a composite of cardiac mortality, target vessel revascularization (TVR), target vessel myocardial infarction (TVMI) and stent thrombosis (ST) at 2 years. Secondary endpoints included the individual components of the primary endpoint and all-cause mortality. Clinical follow-up data were obtained from electronic medical records of the hospital and general practitioner. Survival data were obtained from the municipal civil registry. In addition, all surviving patients were contacted in person or by telephone with specific queries on clinical outcome. Cardiac mortality was defined as any death due to a proximate cardiac cause, unwitnessed death or death of unknown cause. [16] Myocardial infarction was diagnosed according to the expert consensus document, defined as a rise and/or fall of troponin with at least one value above the 99$^{th}$ percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following: 1) symptoms of ischaemia 2) ECG changes indicative of new ischaemia (new ST-T changes or new LBBB) 3) development of pathological waves in the ECG and 4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. [17] [18] ST was defined as angiographically defined thrombosis within the stent or 5 mm proximal or distal to the stent with presence of a flow limiting thrombus, accompanied by acute symptoms. Event adjudication was performed by trained study personnel unaware of the final physiological assessment.

## Statistical analysis

Baseline, categorical variables are reported as either counts or percentages and reported as mean ± standard deviation. The association between dPR and clinical endpoints was analyzed by Cox proportional hazard regression analysis. Univariate predictors of outcomes were identified using Cox proportional-hazards model. Clinical relevant variables (age, male gender, diabetes mellitus and STEMI at presentation) were introduced in the multivariate Cox proportional-hazards model using the 'enter' method. Data are presented as Hazard-Ratio (HR) with a 95% confidence interval (CI 95%). All tests were two-tailed and a P value <0.05 was considered statistically significant. The Kaplan-Meier method was applied to show the cumulative incidence of the primary and secondary endpoints, whereas log-rank tests were applied to evaluate differences between the groups. Patients that were lost to follow-up were censored at the date of the last contact. Receiver- operating characteristic (ROC) curve analysis was performed to assess the optimal cutoff value of post PCI dPR for predicting clinical outcome. However, due to limited number of events, the ROC-curve was not able to identify a final post PCI dPR value to predict TVF, **supplementary figure 1.**

**Table 1.** Patients baseline characteristics (n=735)

| | Total (N=735) | dPR ≤ 0.89 (N=112) | dPR > 0.89 (N=623) | p- value |
|---|---|---|---|---|
| Age, years (mean±SD) | 64±12 | 65±11 | 64±12 | 0.381 |
| Male gender, n (%) | 552 (75) | 90 (80) | 462 (74) | 0.162 |
| **Cardiovascular risk factors, n (%)** | | | | |
| Hypertension | 373 (51) | 70 (63) | 303 (49) | 0.006 |
| Hypercholesterolemia | 329 (45) | 58 (52) | 271 (44) | 0.114 |
| Diabetes Mellitus | 140 (19) | 37 (33) | 103 (17) | <0.001 |
| Smoking history | 368 (50) | 43 (38) | 325 (52) | 0.007 |
| Peripheral art. disease | 52 (7) | 9 (8) | 43 (7) | 0.667 |
| **Cardiovascular comorbidity, n (%)** | | | | |
| Prior stroke | 51 (7) | 7 (6) | 44 (7) | 0.755 |
| Prior myocardial infarction | 144 (20) | 24 (21) | 120 (19) | 0.595 |
| Prior PCI | 192 (26) | 30 (27) | 162 (26) | 0.862 |
| Prior CABG | 42 (6) | 5 (5) | 37 (6) | 0.536 |
| Hemoglobine, mmol/L (mean±SD) | 8.7±1.0 | 8.5±1.1 | 8.70±1.0 | 0.095 |
| Creatinine, µmol/L (mean±SD) | 93±53 | 107±99 | 90±38 | 0.001 |
| **Indication, n (%)** | | | | |
| Stable angina | 231 (31) | 41 (37) | 190 (31) | 0.200 |
| NSTEMI | 263 (36) | 46 (41) | 217 (35) | 0.205 |
| STEMI | 241 (33) | 25 (22) | 216 (35) | 0.010 |

CABG= Coronary artery bypass grafting; NSTEMI= Non-ST segment elevation myocardial infarction; PCI= Percutaneous coronary intervention; SD= standard deviation; STEMI= ST segment elevation myocardial infarction.

Given the exploratory nature of the present study, we deliberately took the accepted ischemic dPR threshold of 0.89 as a cut-off value to predict clinical outcome. A predefined subgroup analysis was performed in patients presenting with stable- or unstable angina or NSTEMI. Statistical analyses were performed by using SPSS statistics for Windows, version 24.0 (SPSS, Chicago, IL, USA).

**Table 2.** Vessel and lesion characteristics (n=735)

| | Total (N=735) | dPR ≤ 0.89 (N=112) | dPR > 0.89 (N=623) | p- value |
|---|---|---|---|---|
| dPR, (mean±SD) | 0.95±0.06 | 0.86±0.04 | 0.97±0.04 | <0.001 |
| **Lesion type, n (%)** | | | | |
| A | 70 (10) | 5 (5) | 65 (10) | 0.048 |
| B1 | 156 (21) | 19 (17) | 137 (22) | 0.231 |
| B2 | 232 (31) | 46 (41) | 186 (30) | 0.019 |
| C | 277 (38) | 42 (38) | 235 (38) | 0.965 |
| **Measured vessels, n (%)** | | | | |
| Left main | 17 (2) | 4 (4) | 13 (2) | 0.336 |
| Left anterior descending artery | 383 (52) | 98 (88) | 285 (46) | <0.001 |
| Left circumflex artery | 125 (17) | 5 (5) | 120 (19) | <0.001 |
| Right coronary artery | 204 (28) | 5 (5) | 199 (32) | <0.001 |
| Vein Graft | 6 (1) | 0 (0) | 6 (1) | 0.297 |
| **Lesion characteristics, n (%)** | | | | |
| Bifurcation | 85 (12) | 20 (18) | 65 (11) | 0.024 |
| Moderate to severe calcification | 268 (37) | 55 (49) | 213 (34) | 0.003 |
| In-stent restenosis | 22 (3) | 4 (4) | 18 (3) | 0.696 |
| Thrombus | 142 (19) | 13 (12) | 129 (21) | 0.025 |
| Stent thrombosis | 9 (2) | 1 (1) | 8 (1) | 0.729 |
| Ostial | 73 (10) | 10 (9) | 63 (10) | 0.700 |
| CTO | 30 (4) | 10 (9) | 20 (3) | 0.005 |
| Predilatation | 501 (68) | 88 (79) | 413 (66) | 0.010 |
| Postdilatation | 455 (62) | 77 (69) | 378 (61) | 0.109 |
| **2D-QCA measurements, (mean±SD)** | | | | |
| Stenosis Pre, % | 65±22 | 61±22 | 65±22 | 0.052 |
| Stenosis Post, % | 4±13 | 3±15 | 4±13 | 0.585 |
| Ref diameter Pre, mm | 2.7±0.6 | 2.5±0.6 | 2.7±0.6 | <0.001 |
| Ref diameter Post, mm | 2.8±0.5 | 2.5±0.5 | 2.8±0.5 | <0.001 |
| Length Pre, mm | 21±12 | 21±11 | 21±12 | 0.983 |
| Length Post, mm | 24±14 | 25±12 | 24±14 | 0.809 |
| MLD Pre, mm | 0.94±0.6 | 0.95±0.6 | 0.94±0.6 | 0.928 |
| MLD Post, mm | 2.6±0.5 | 2.4±0.4 | 2.7±0.5 | <0.001 |

CTO =chronic total occlusion; MLD =minimum lumen diameter; QCA =Quantitative coronary angiography.

## RESULTS

### Patient demographics and procedural data

A total of 735 patients (735 vessels) were included. Patients baseline characteristics are depicted in **Table 1**. In brief, 75% of the patients were male and average age was 64±12 years. Hypertension was present in 51% of the cases and 19% were diabetic. Clinical presentation was stable angina in 31% of the cases whereas 36% and 33% of the patients presented with a NSTEMI and STEMI respectively. Vessel and lesion characteristics are presented in **Table 2.**

### Distribution of dPR and clinical outcome at 2 year follow up

Mean post PCI dPR was 0.95±0.06. Post PCI dPR was ≤0.89 in 15.2% of the cases, **Figure 2.** The cumulative incidence of TVF was 6.1% in patients with a final post PCI dPR≤0.89 as compared to 9.4% in patients with a post PCI dPR>0.89 (adjusted HR for dPR≤0.89: 1.53; 95% CI [0.74 – 3.13]; p=0.249). Cardiac mortality rates were significantly higher in patients with a final post PCI dPR≤0.89 as compared to those with a dPR>0.89 (7.4 vs 3.1%, adjusted HR 2.40, 95% CI [1.01 – 5.68]); p=0.047). **Figure 3, Table 3 and 4.**

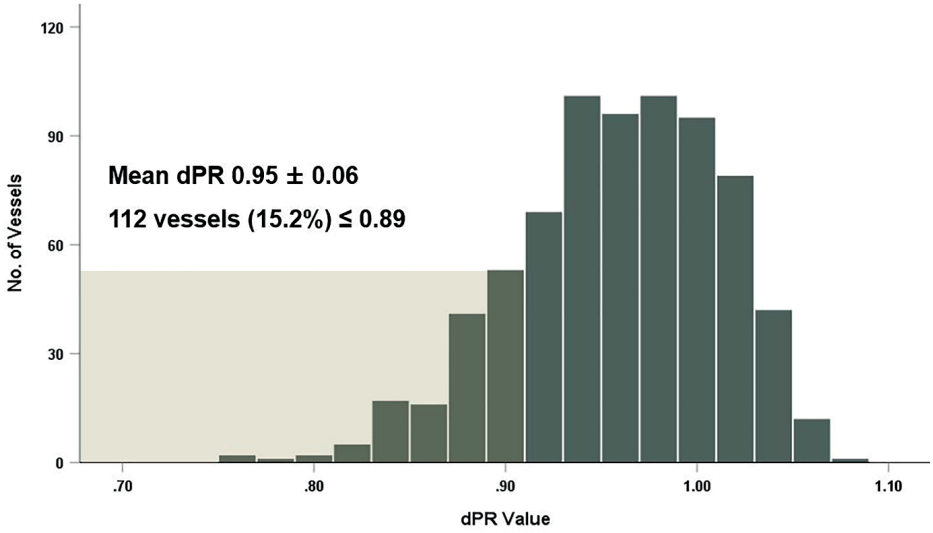



**Figure 2.** Distribution of post PCI dPR.

### *Stratified analysis in patients* presenting with stable- or unstable angina or NSTEMI

A total of 494 (patients67.2%) presented with stable- or unstable angina or NSTEMI. **.** The cumulative incidence of TVF was 11.8% in patients with a final post PCI dPR≤0.89 as compared to 6.5% in patients with a post PCI dPR>0.89 (adjusted HR for dPR≤0.89: 1.92; 95% CI [0.91 – 4.01]; p=0.0.070). **(Supplementary figure 2)**

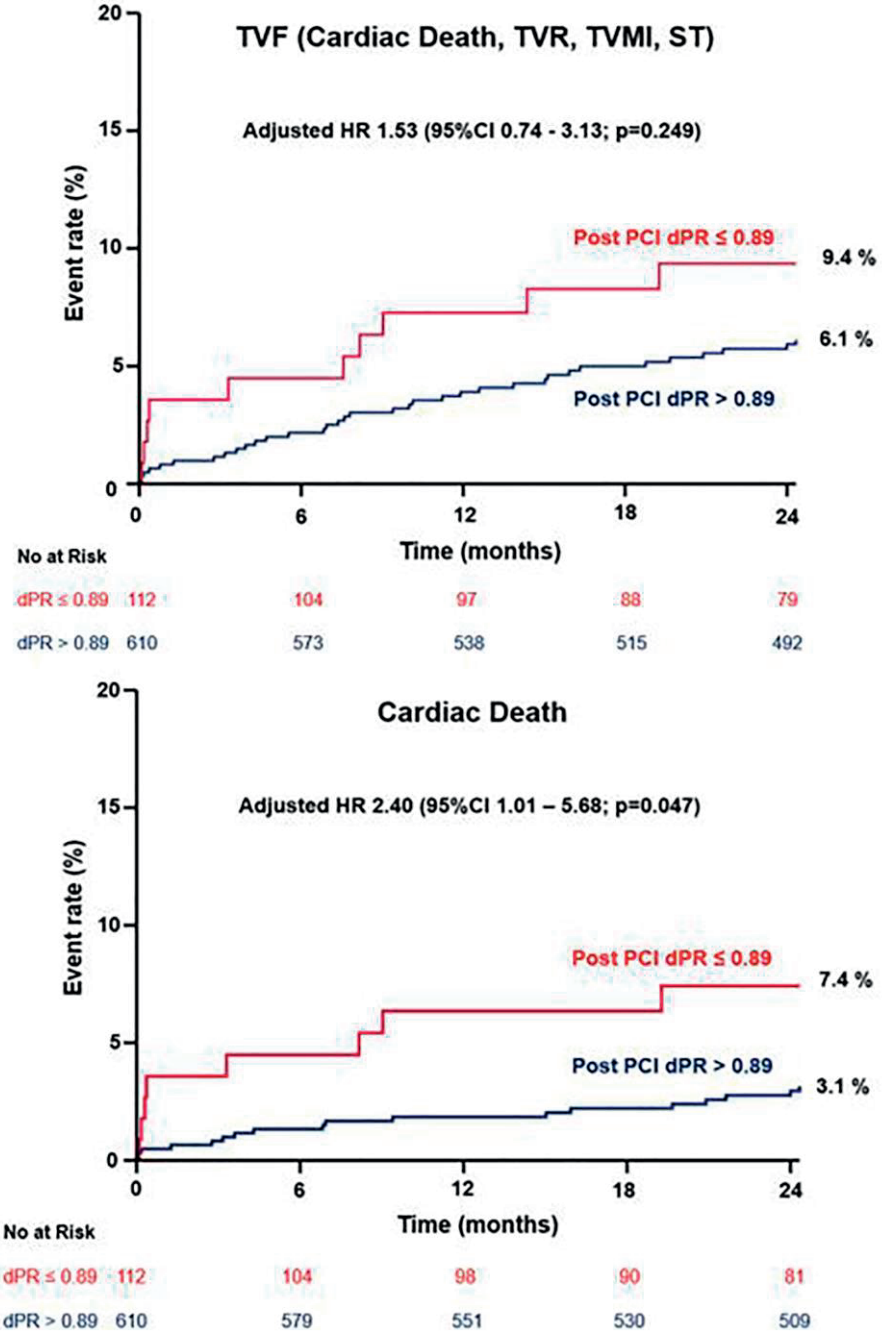



**Figure 3.** Cumulative incidence of TVF and Cardiac death at 2 years follow up.
dPR= diastolic pressure ratio; PCI= percutaneous coronary intervention; TVF= target vessel failure; TVR= target vessel revascularization; TVMI= target vessel myocardial infarction; ST= stent thrombosis.

**Table 3.** Cumulative incidence of clinical outcome at 2 year follow up.

| | Total (N=735) N (%) | dPR ≤ 0.89 (N=112) % | dPR > 0.89 (N=623) % | Log-rank P- value |
|---|---|---|---|---|
| All-cause mortality | 43 (5.9) | 10.3 | 5.2 | 0.033 |
| Cardiac mortality | 26 (3.5) | 7.4 | 3.1 | 0.023 |
| TVR | 19 (2.6) | 2.0 | 3.0 | 0.566 |
| TVMI | 16 (2.2) | 4.0 | 2.1 | 0.267 |
| ST | 10 (1.4) | 0.9 | 1.6 | 0.644 |
| TVF* | 45 (6.1) | 9.4 | 6.1 | 0.176 |

TVR= Target Vessel Revascularization; TVMI= Target Vessel Myocardial Infarction; ST= Stent Thrombosis; TVF= Target Vessel Failure.

* Cardiac mortality, TVR, TVMI and ST.

**Table 4.** Association of post PCI dPR and risk of clinical events at 2 year follow up

| | Univariable HR (95% CI) | p- value | Multivariable HR (95% CI) | p- value |
|---|---|---|---|---|
| **Target Vessel Failure (TVF)** | | | | |
| Post PCI dPR≤0.89 | 1.62 (0.80-3.26) | 0.181 | 1.53 (0.74-3.13) | 0.249 |
| Age | 1.02 (0.99-1.05) | 0.128 | 1.02 (0.99-1.05) | 0.199 |
| Male gender | 0.82 (0.43-1.56) | 0.542 | 0.87 (0.45-1.69) | 0.684 |
| Diabetes Mellitus | 1.23 (0.61-2.48) | 0.570 | 1.09 (0.53-2.24) | 0.809 |
| STEMI | 0.636 (0.32-1.29) | 0.207 | 0.70 (0.34-1.42) | 0.320 |
| **Cardiac Mortality** | | | | |
| Post PCI dPR≤0.89 | 2.53 (1.10-5.83) | 0.029 | 2.40 (1.01-5.68) | 0.047 |
| Age | 1.05 (1.01-1.08) | 0.012 | 1.05 (1.01-1.09) | 0.015 |
| Male gender | 0.90 (0.38-2.15) | 0.816 | 1.04 (0.43-2.53) | 0.936 |
| Diabetes Mellitus | 1.30 (0.52-3.23) | 0.579 | 1.14 (0.45-2.91) | 0.783 |
| STEMI | 0.826 (0.35-1.96) | 0.665 | 1.00 (0.41-2.43) | 0.996 |
| **Target Vessel Revascularization (TVR)** | | | | |
| Post PCI dPR≤0.89 | 0.65 (0.15-2.83) | 0.569 | 0.64 (0.15-2.83) | 0.560 |
| Age | 0.99 (0.96-1.03) | 0.748 | 0.99 (0.95-1.03) | 0.534 |
| Male gender | 0.72 (0.27-1.89) | 0.505 | 0.72 (0.27-1.93) | 0.516 |
| Diabetes | 0.80 (0.23-2.73) | 0.718 | 0.73 (0.21-2.53) | 0.619 |
| STEMI | 0.26 (0.06-1.14) | 0.073 | 0.24 (0.06-1.06) | 0.059 |
| **Target Vessel Myocardial Infarction (TVMI)** | | | | |
| Post PCI dPR≤0.89 | 1.88 (0.61-5.82) | 0.275 | 1.92 (0.61-6.10) | 0.268 |
| Age | 0.99 (0.95-1.03) | 0.696 | 0.98 (0.94-1.03) | 0.414 |
| Male gender | 0.56 (0.20-1.53) | 0.257 | 0.52 (0.19-1.44) | 0.206 |
| Diabetes | 0.99 (0.28-3.46) | 0.983 | 0.79 (0.22-2.83) | 0.713 |
| STEMI | 0.32 (0.07-1.39) | 0.128 | 0.31 (0.07-1.40) | 0.129 |

## DISCUSSION

In the present study focusing on the real world impact of post PCI dPR, we demonstrated that: 1) despite optimal angiographic results 15.2% of the vessels end up with a post PCI dPR of ≤0.89; 2) rates of TVF were numerically higher in patient with post PCI dPR ≤0.89 however 3) a post PCI dPR ≤0.89 was associated with higher cardiac mortality rate.

Despite the unequivocal evidence supporting the use of pre PCI physiological lesion assessment, the use of the technology in a post PCI setting is still rare. Instead, post PCI results are routinely assessed by visual angiographic assessment, a technique that has repeatedly been shown to correlate poorly with invasive functional assessment. [19-21] The importance of the latter was further illustrated by a growing body of evidence showing the strong predictive value of post PCI FFR for future adverse events. [22-25] However, little is known about the use of post-PCI dPR and its predictive value. To the best of our knowledge, the present study is the largest study on the distribution and predictive value of post PCI dPR to date and the first to assess the correlation between post PCI dPR and 2-year clinical outcome.

We were able to demonstrate that in an all-comers study population, despite satisfactory angiographic results, 15.2% of the patients had a post PCI dPR≤0.89. Our work thereby complements the findings of the DEFINE PCI study in which 22.6% of the treated vessels ended up with a post PCI iFR ≤0.89. [12] Our work however differed from the DEFINE PCI population by enrolling a larger and more real-world patient population in which patients with prior CABG, CTO treatment, ST segment myocardial infarction (STEMI) and TIMI flow <3 were not excluded. Especially the inclusion of patients presenting with STEMI and the lower number of patients with diabetes (19% vs 34% respectively) might explain the numerically lower number of cases of a post PCI dPR≤0.89 as compared to the DEFINE PCI study. [26] Despite the restoration of epicardial flow through PCI, patients with STEMI have abnormal myocardial perfusion at the end of the procedure. [27] This phenomenon is thought to be related to microvascular obstruction due to distal embolization, reperfusion injury and tissue inflammation due to myocyte necrosis. [28] In addition physiologic assessment in patients with diabetes mellitus underestimates disease severity because of diffuse coronary atherosclerosis, microvascular disease and a tendency for negative remodeling. [29] The latter resulted in the pre-defined subanalysis in patients presenting with stable- or unstable angina or NSTEMI in which an a more pronounced effect of post PCI dPR≤0.89 was seen to predict 2 year TVF rates.

In the present study pressure measurements were performed approximately 20mm distal to the distal stent edge while in the DEFINE PCI investigators reported consistently placing their pressure sensors in the distal third of the study vessel which is another potential explanation for the lower proportion of patients with dPR ≤0.89 in the present study.

Despite a growing body of evidence on the strong correlation between post PCI FFR and the risk for future adverse cardiovascular events, the present study is the first to assess the correlation between post PCI dPR and clinical outcome at 2 years. [24, 25] We found a numerically higher TVF rate in patient with post PCI dPR ≤0.89 as compared to those with a dPR >0.89. More specifically, a post PCI dPR≤0.89 proved to be associated with a 2.4 fold increased risk for cardiac mortality at 2 years when corrected for clinically relevant variables as age, gender, diabetes mellitus and STEMI at presentation (p=0.047). The latter is in line with the results of the recently presented 1 year follow up of the DEFINE PCI study which showed that post PCI iFR<0.95 was associated with lower event rates. [30]

The present study demonstrates the feasibility of post PCI physiological assessment using a dedicated monorail microcatheter without the need for hyperemic agents associated with increased time, costs and side effects. Routine physiological post PCI dPR assessment identifies a significant number of patients with suboptimal post PCI results that are at increased risk for future adverse cardiac events. The ongoing randomized FFR REACT trial will assess whether invasive imaging and PCI optimization (using additional stents and post-dilation) will improve outcomes in patients with suboptimal post-PCI physiology measurements. [31]

## LIMITATIONS

Several limitations deserve to be mentioned. First of all, post physiologic assessment was performed using the Navvus microcatheter which is an over the wire microcatheter with a profile of 0.022'' that proved to result in a slight but significant lower FFR as compared to the conventional 0.014'' pressure wires with 1 to 3%. [32]. In addition, the results are based on a single center experience in which we restricted our analyses to recordings with adequate pressure wave forms. The latter could have artificially influenced our results since previous work, assessing the prevalence of erroneous or suboptimal FFR measurements in clinical practice, demonstrated that in up to 30% of the recordings, pressure signals were inadequate. [33] Finally, the data acquisition protocol of the FFR SEARCH registry included only a pullback during maximum hyperemia precluding us from analyzing detailed post procedural dPR gradients within the treated vessel.

## CONCLUSION

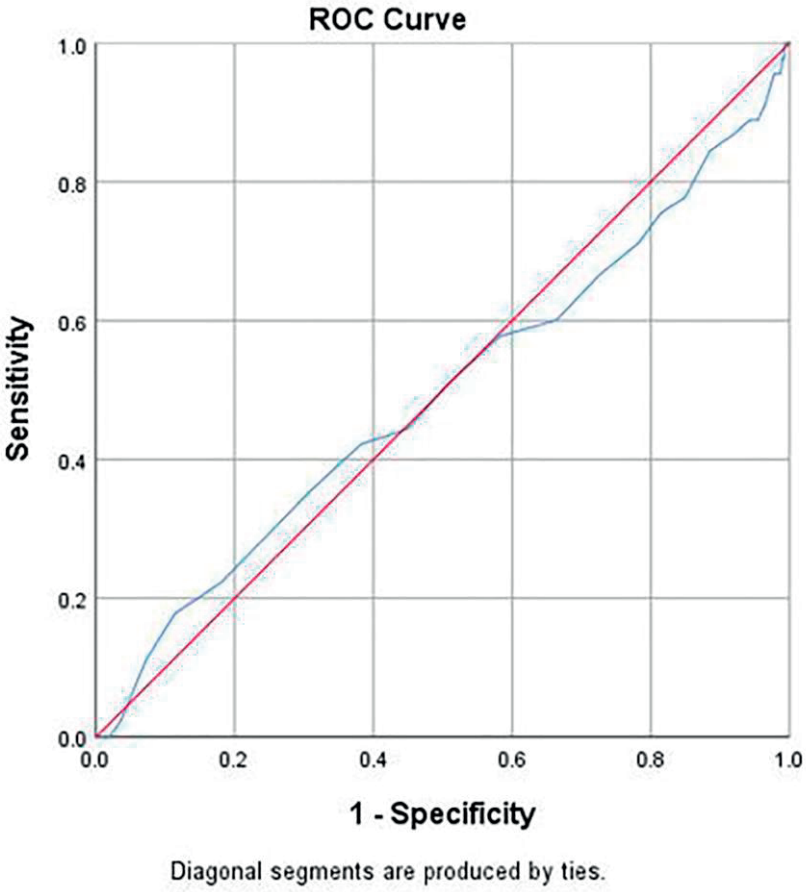
Despite optimal angiographic PCI results, 15.2% of the patients end up with a post PCI dPR of ≤0.89 which was associated with significantly higher cardiac mortality rate. TVF rate was numerically higher in patient with post PCI dPR ≤0.89.

## REFERENCES

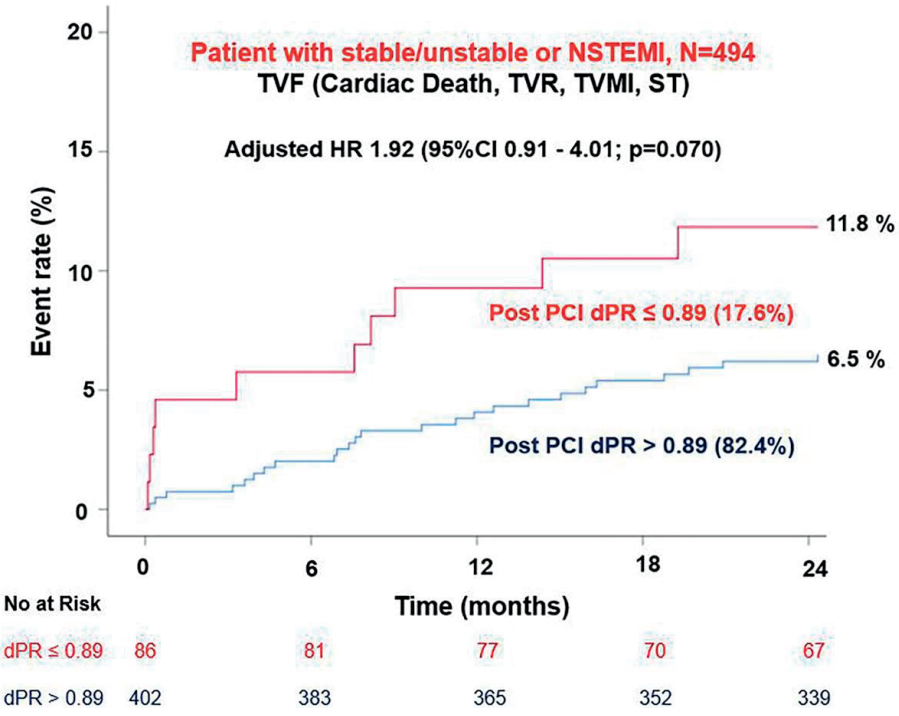
1. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J, Janssens L, Vrints CJ, Khashaba A, Laine M, Van Belle E, Krackhardt F, Bojara W, Going O, Harle T, Indolfi C, Niccoli G, Ribichini F, Tanaka N, Yokoi H, Takashima H, Kikuta Y, Erglis A, Vinhas H, Canas Silva P, Baptista SB, Alghamdi A, Hellig F, Koo BK, Nam CW, Shin ES, Doh JH, Brugaletta S, Alegria-Barrero E, Meuwissen M, Piek JJ, van Royen N, Sezer M, Di Mario C, Gerber RT, Malik IS, Sharp ASP, Talwar S, Tang K, Samady H, Altman J, Seto AH, Singh J, Jeremias A, Matsuo H, Kharbanda RK, Patel MR, Serruys P, Escaned J. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med 2017;**376**(19):1824-1834.
2. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, Jagic N, Mobius-Winckler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd K, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Limacher A, Nuesch E, Juni P, Investigators FT. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med 2014;**371**(13):1208-17.
3. Gotberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Ohagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Todt T, Venetsanos D, James SK, Karegren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson AC, Panayi G, Erlinge D, Frobert O, i FRSI. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N Engl J Med 2017;**376**(19):1813-1823.
4. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF, Investigators FS. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;**360**(3):213-24.
5. Ligthart J, Masdjedi K, Witberg K, Mastik F, van Zandvoort L, Lemmert ME, Wilschut J, Diletti R, de Jaegere P, Zijlstra F, Kardys I, Van Mieghem NM, Daemen J. Validation of Resting Diastolic Pressure Ratio Calculated by a Novel Algorithm and Its Correlation With Distal Coronary Artery Pressure to Aortic Pressure, Instantaneous Wave-Free Ratio, and Fractional Flow Reserve. Circ Cardiovasc Interv 2018;**11**(12):e006911.
6. Svanerud J, Ahn JM, Jeremias A, van 't Veer M, Gore A, Maehara A, Crowley A, Pijls NHJ, De Bruyne B, Johnson NP, Hennigan B, Watkins S, Berry C, Oldroyd KG, Park SJ, Ali ZA. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. EuroIntervention 2018.
7. Van't Veer M, Pijls NHJ, Hennigan B, Watkins S, Ali ZA, De Bruyne B, Zimmermann FM, van Nunen LX, Barbato E, Berry C, Oldroyd KG. Comparison of Different Diastolic Resting Indexes to iFR: Are They All Equal? J Am Coll Cardiol 2017;**70**(25):3088-3096.
8. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv 2016;**9**(10):1022-31.
9. Leesar MA, Satran A, Yalamanchili V, Helmy T, Abdul-Waheed M, Wongpraparut N. The impact of fractional flow reserve measurement on clinical outcomes after transradial coronary stenting. EuroIntervention 2011;**7**(8):917-23.
10. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, Escaned J, Tsurumi Y, Akasaka T, Samady H, De Bruyne B, Fractional Flow Reserve Post-Stent Registry I. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation 2002;**105**(25):2950-4.
11. van Bommel RJ, Masdjedi K, Diletti R, Lemmert ME, van Zandvoort L, Wilschut J, Zijlstra F, de Jaegere P, Daemen J, van Mieghem NM. Routine Fractional Flow Reserve Measurement After Percutaneous Coronary Intervention. Circ Cardiovasc Interv 2019;**12**(5):e007428.

12. Jeremias A, Davies JE, Maehara A, Matsumura M, Schneider J, Tang K, Talwar S, Marques K, Shammas NW, Gruberg L, Seto A, Samady H, Sharp A, Ali ZA, Mintz G, Patel M, Stone GW. Blinded Physiological Assessment of Residual Ischemia After Successful Angiographic Percutaneous Coronary Intervention: The DEFINE PCI Study. JACC Cardiovasc Interv 2019;**12**(20):1991-2001.
13. Ryan TJ, Faxon DP, Gunnar RM, Kennedy JW, King SB, 3rd, Loop FD, Peterson KL, Reeves TJ, Williams DO, Winters WL, Jr., et al. Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). Circulation 1988;**78**(2):486-502.
14. Diletti R, Van Mieghem NM, Valgimigli M, Karanasos A, Everaert BR, Daemen J, van Geuns RJ, de Jaegere PP, Zijlstra F, Regar E. Rapid exchange ultra-thin microcatheter using fibre-optic sensing technology for measurement of intracoronary fractional flow reserve. EuroIntervention 2015;**11**(4):428-32.
15. Menon M, Jaffe W, Watson T, Webster M. Assessment of coronary fractional flow reserve using a monorail pressure catheter: the first-in-human ACCESS-NZ trial. EuroIntervention 2015;**11**(3):257-63.
16. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW, Academic Research C. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;**115**(17):2344-51.
17. Thygesen K. 'Ten Commandments' for the Fourth Universal Definition of Myocardial Infarction 2018. Eur Heart J 2019;**40**(3):226.
18. Thygesen K. What's new in the Fourth Universal Definition of Myocardial infarction? Eur Heart J 2018;**39**(42):3757-3758.
19. Nakamura M, Yamagishi M, Ueno T, Hara K, Ishiwata S, Itoh T, Hamanaka I, Wakatsuki T, Sugano T, Kawai K, Akasaka T, Tanaka N, Kimura T. Prevalence of visual-functional mismatch regarding coronary artery stenosis in the CVIT-DEFER registry. Cardiovasc Interv Ther 2014;**29**(4):300-8.
20. Park SJ, Kang SJ, Ahn JM, Shim EB, Kim YT, Yun SC, Song H, Lee JY, Kim WJ, Park DW, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW. Visual-functional mismatch between coronary angiography and fractional flow reserve. JACC Cardiovasc Interv 2012;**5**(10):1029-36.
21. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 2010;**55**(25):2816-21.
22. Agarwal SK, Kasula S, Almomani A, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Clinical and angiographic predictors of persistently ischemic fractional flow reserve after percutaneous revascularization. Am Heart J 2017;**184**:10-16.
23. Ishii H, Kataoka T, Kobayashi Y, Tsumori T, Takeshita H, Matsumoto R, Shirai N, Nishioka H, Hasegawa T, Nakata S, Shimada Y, Ehara S, Muro T, Yoshiyama M. Utility of myocardial fractional flow reserve for prediction of restenosis following sirolimus-eluting stent implantation. Heart Vessels 2011;**26**(6):572-81.
24. Johnson NP, Toth GG, Lai D, Zhu H, Acar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen SL, Di Serafino L, Dominguez-Franco AJ, Dupouy P, Esen AM, Esen OB, Hamilos M, Iwasaki K, Jensen LO, Jimenez-Navarro MF, Katritsis DG, Kocaman SA, Koo BK, Lopez-Palop R, Lorin JD, Miller LH, Muller O, Nam CW, Oud N, Puymirat E, Rieber J, Rioufol G, Rodes-Cabau J, Sedlis SP, Takeishi Y, Tonino PA, Van Belle E, Verna E, Werner GS, Fearon WF, Pijls NH, De Bruyne B, Gould KL. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. J Am Coll Cardiol 2014;**64**(16):1641-54.

25. Nam CW, Hur SH, Cho YK, Park HS, Yoon HJ, Kim H, Chung IS, Kim YN, Kim KB, Doh JH, Koo BK, Tahk SJ, Fearon WF. Relation of fractional flow reserve after drug-eluting stent implantation to one-year outcomes. Am J Cardiol 2011;**107**(12):1763-7.
26. Allen Jeremias M, Msc, Justin Davis, manesh Patel, Gregg Stone, the DEFINE PCI Investigators. Blinded Physiological Assessment of Residual Ischemia after Successful Angiographic PCI. Oral presentation at ACC 2019.
27. Stone GW, Webb J, Cox DA, Brodie BR, Qureshi M, Kalynych A, Turco M, Schultheiss HP, Dulas D, Rutherford BD, Antoniucci D, Krucoff MW, Gibbons RJ, Jones D, Lansky AJ, Mehran R, Enhanced Myocardial E, Recovery by Aspiration of Liberated Debris I. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. JAMA 2005;**293**(9):1063-72.
28. Shah NR, Al-Lamee R, Davies J. Fractional flow reserve in acute coronary syndromes: A review. Int J Cardiol Heart Vasc 2014;**5**:20-25.
29. Bishop AH, Samady H. Fractional flow reserve: critical review of an important physiologic adjunct to angiography. Am Heart J 2004;**147**(5):792-802.
30. Manesh Patel AJ, Justin Davies, Akiko Maehara, Mitsuaki Matsumura, Arnold Seto, Habib Samady, Andrew Sharp, Joel Schneider, Kare Tang, Ziad Ali, Suneel Talwar, Gregg W. Stone on, Investigators botDP. 1-Year Outcomes of Patients with Residual Physiologic Ischemia After Percutaneous Coronary Intervention: The DEFINE PCI Trial. TCT 2020 (Presentation) 2020.
31. van Zandvoort LJC, Masdjedi K, Tovar Forero MN, Lenzen MJ, Ligthart J, Diletti R, Lemmert ME, Wilschut J, de Jaegere PPT, Zijlstra F, van Mieghem NM, Daemen J. 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. Am Heart J 2019;**213**:66-72.
32. Pouillot C, Fournier S, Glasenapp J, Rambaud G, Bougrini K, Vi Fane R, Geyer C, Adjedj J. Pressure wire versus microcatheter for FFR measurement: a head-to-head comparison. EuroIntervention 2018;**13**(15):e1850-e1856.
33. Matsumura M, Johnson NP, Fearon WF, Mintz GS, Stone GW, Oldroyd KG, De Bruyne B, Pijls NHJ, Maehara A, Jeremias A. Accuracy of Fractional Flow Reserve Measurements in Clinical Practice: Observations From a Core Laboratory Analysis. JACC Cardiovasc Interv 2017;**10**(14):1392-1401.




**Supplementary Figure 1.**
**AUC= 0.506**




**Supplementary Figure 2.** TVF in patient presenting with stable, unstable angina or NSTEMI.

# PART IV
## ADVENT OF 3D-QCA BASED FFR

"I have built a high palace that will never disappear.
No rain, no wind will destroy it"
—A.Q. Ferdowsi

# Chapter 12

# Angiography-Based FFR: Reevaluating the Role of the Pressure Wire: Reviewing the nuances of coronary angiography–based FFR and results of initial validation studies

**K. Masdjedi, MD;** J. Daemen, MD, PhD

**Department of Cardiology, Thoraxcenter, Erasmus Medical Center**

**Journal:** Cardiac Interventions Today; May/June 2019 Vol. 13, No.3

Assessment of coronary stenosis severity by a visual estimate of the coronary angiogram has traditionally served as the cornerstone for the diagnosis of patients with known or suspected coronary artery disease (CAD). In contrast to visual assessment, quantitative coronary angiography (QCA) allows for a more accurate estimation of both the diameter stenosis and length of a coronary lesion, parameters that proved to contribute to resistance to blood flow. As such, QCA-based percentage diameter stenosis is commonly used to detect the presence of obstructive CAD.1 Yet, in the current era, the use of coronary physiology to assess the coronary stenosis severity is gaining importance and is recommended by international revascularization guidelines to guide revascularization strategies.2,3

## FRACTIONAL FLOW RESERVE

In the past decade, a wealth of data have become available demonstrating pitfalls of angiographic lesion assessment. To overcome these limitations, fractional flow reserve (FFR) has emerged as the mainstay of functional hemodynamic assessment of coronary artery lesions and is presently regarded as the gold standard for identifying stenoses that cause myocardial ischemia.4-7 Several reports have described the discordance between anatomic and functional assessment of coronary lesions, showing that mismatch (ie, anatomically significant but hemodynamically non-significant lesions) and reverse mismatch (ie, anatomically non-significant but hemodynamically significant lesions) were far from rare.8-10 As such, angiographic-FFR mismatch was found in 43.4% of lesions, whereas reverse angiographic mismatch was found in 23.2%. With subsequent clinical validation studies demonstrating significantly better short- and long-term outcomes with FFR-guided percutaneous coronary intervention (PCI) as compared with angiography-guided PCI, FFR has become an established modality in the evidence-based management of patients with CAD.7,11-14 Unfortunately, even 25 years after the introduction of FFR and despite indisputable evidence supporting the benefit of FFR to guide clinical decision-making, adoption into daily practice has been limited. This has been hypothesized to be due to the need for pressure wires or microcatheters, time consuming FFR procedures, and (in some countries) expensive hyperemic agents with known adverse events, such as dyspnea and arrhythmias and/or intolerance due to pulmonary disease.15 However, the majority of these arguments were refused in clinical trials in which the use of FFR was not associated with longer procedure times and/or higher costs.7,11-14

## NONHYPEREMIC PRESSURE RATIOS

In recent years, the instantaneous wave-free ratio (iFR) and resting distal coronary artery pressure/aortic pressure (Pd/Pa) were introduced as alternative invasive indices to assess the severity of coronary artery stenosis without the need for hyperemic agents. Although Pd/ Pa represents

the ratio from the mean resting distal pressure to aortic coronary pressure during the whole cardiac cycle, iFR is based on the same ratio measured during the so-called "wave-free period," the period dur- ing diastole in which the microvascular resistance is low and constant.16,17

Because the proprietary algorithm of iFR is linked to a single vendor, several validation studies were recently performed to find more generic options to calculate so- called non-hyperemic pressure ratios (NHPRs). As such, a good correlation was found between iFR and several NHPRs, including the diastolic pressure ratio and resting full-cycle ratio, among others.18,19 Although NHPRs have emerged as adenosine-free, faster, and easier methods to achieve physiologic assessment, the need for a costly pressure wire or microcatheter remains a fact.18,19 For these reasons, the search for cheaper, faster, and more patient-friendly methods to assess coronary physiology remains imperative to increase its use in routine daily practice. Therefore, a modality combining functional and anatomic evaluation of epicardial coronary artery lesions in a single noninvasive test would help increase the use of coronary physiology in catheterization laboratories worldwide.

## COMPUTATIONAL FLUID DYNAMICS AND FFRCT

There has been a growing interest in noninvasive FFR derived from coronary CTA (FFRCT) using the concepts of computational fluid dynamics (CFD).20-22 CFD is a well-known and widely used method in mechanical engineering to solve complex problems by analyzing behaviors including fluid flow, heat transfer, and associated phenomena using computer simulations. The governing equations of fluid dynamics, the so-called Navier-Stokes equations, can be calculated to obtain coronary flow and pressure. To simulate realistic coronary blood flow, a domain of interest must be defined and boundary conditions must be specified. The isolation and generation of boundary conditions are challenging steps in integrating CFD to assess the physiologic significance of CAD.23

The prospective, multicenter DISCOVER-FLOW trial demonstrated a diagnostic accuracy, sensitivity, speci- ficity, positive predictive value, and negative predictive value of 84.3%, 87.9%, 82.2%, 73.9%, 92.2%, respectively, for FFRCT, and 58.5%, 91.4%, 39.6%, 46.5%, 88.9%, respectively, for coronary CTA to identify a positive FFR as assessed using conventional pressure wires.21 In the PLATFORM study, the use of FFRCT was associated with a reduction of unnecessary coronary angiographic procedures, while maintaining the same number of patients who underwent PCI.24 Therefore, FFRCT proved to be a reliable gatekeeper to invasive coronary angiography and revascularization, which may have significant health and economic implications. However, as FFRCT is based on the reconstruction of an accurate anatomic model of the epicardial coronary arteries derived from coronary CT scan data, any artifacts that significantly compromise image quality can impact assessment of the lumen and limit diagnostic accuracy of FFRCT. Although the technology

is quickly gaining momentum in patient screening and even more comprehensive procedural planning, the technology is still hampered by long computation times and, at present, a lack of reimbursement in the majority of countries.21

## CORONARY ANGIOGRAPHY (3D-QCA)–BASED FFR

Despite excellent results of FFRCT studies, there is an ongoing search for tools that allow online physiologic lesion assessment with the potential to be integrated into daily clinical practice. In 2000, the ANGUS study demonstrated that three-dimensional (3D) reconstruction of coronary arteries can be successfully performed by combining orthogonal angiographic projections of the coronary along with intravascular ultrasound images.25 Schuurbiers et al demonstrated that the CAAS Workstation QCA-3D system (Pie Medical Imaging) allows 3D reconstruction of human coronary arteries based on biplane angiographic projections.26 Validation of the CAAS QCA-3D system against the ANGUS system showed that both the 3D geometry and lumen areas were highly correlated and set the stage for more comprehensive CFD.

Within the last few years, the CAAS Workstation software (Pie Medical Imaging) has been modified to integrate a simplified method for calculating 3D-QCA–based FFR. The software allows instantaneous calculation of pressure drops by applying physical laws including viscous resistance and turbulent effects of coronary flow, as described by Gould et al and Kirkeeide.27,28 Within these physical laws, both Gould et al and Kirkeeide incorporated viscous and separation loss effects into coronary flow behavior. The methods proposed by Gould et al and Kirkeeide are based on a single angiographic x-ray projection. Within the CAAS Workstation, the geometry of the coronary artery is derived from well-validated 3D coronary reconstruction technique,26,29 which reduces the effects of foreshortening, out-of-plane magnification, and nonsymmetric coronary lesions during the pressure drop calculations. One of the first studies validating the software with more extensive CFD was performed by Papafaklis et al in which a method for fast virtual functional assessment of intermediate coronary lesions using routine x-ray angiography (ie, virtual Functional Assessment Index [vFAI]) was described.30 To compute the vFAI, the $f_v$ and $f_s$ parameters were derived from the artery- specific quadratic equation $\Delta P = f_vQ + f_sQ2$ by performing two separate CFD simulations using the geometry resulting from 3D-QCA. After solving $f_v$ and $f_s$, the vFAI was calculated as the ratio of the area under the curve ($Pd/Pa = 1-f_v\, Q/Pa-f_s\, Q2/Pa$) for a flow ranging from 0 to 4 mL/sec. The authors concluded that vFAI showed a high diagnostic performance and incremental value to QCA for predicting FFR.

### Validation Studies of Coronary Angiography–Based FFR

The software and algorithms of (at present) three different vendors matured over time applying several assumptions, such as using steady flow instead of transient flow, which proved to have

only limited impact on the average pressure distribution over the cardiac cycle, significantly reducing computation times from hours to seconds. Table 1 summarizes the currently commercially available software packages to calculate angiography-based FFR.31-36

**Table 1.** Available software for coronary angiography–based ffr calculation

| Company | Product Name | Acronym Index | Validation Study | Correlation With Pressure Wire FFR | Bias Mean ± SD | AUC CI (95% CI) | Interobserver Variability |
|---|---|---|---|---|---|---|---|
| Medis Medical Imaging Systems, BV | QAngio XA | QFR | FAVOR Pilot Study31<br>FAVOR II China32<br>FAVOR II Europe-Japan36 | 0.77<br>0.86<br>0.83 | 0.001 ± 0.06<br>0.01 ± 0.06<br>0.01 ± 0.06 | 0.92 (0.85–0.97)<br>0.96 (0.94–0.98)<br>0.92 (0.89–0.96) | N/A |
| CathWorks | FFRangio system | FFRangio | Pellicano et al33<br>FAST-FFR study34 | 0.88<br>0.80 | 0.007 ± 0.05<br>-0.14 ± 0.12 | N/A<br>0.94 (0.92–0.97) | R = 0.92<br>N/A |
| Pie Medical Imaging | CAAS 3D-QCA | vFFR | FAST study35<br>FAST II study* | 0.89<br>* | 0.01 ± 0.04<br>* | 0.93 (0.88–0.97)<br>* | R = 0.95<br>* |

Abbreviations: 3D, three-dimensional; AUC, area under the curve; CI, confidence interval; FFR, fractional flow reserve; N/A, not available; QCA, quantitative coronary angiograpy; QFR, quantitative flow reserve; SD, standard deviation; vFFR, vessel FFR.
*Multicenter, international, prospective, observational validation study of vFFR, ongoing (NCT03791320).

*QAngio XA.* The FAVOR pilot study assessed the diagnostic accuracy of quantitative flow ratio (QFR) as measured offline in three ways based on the different mean hyperemic flow velocities31: (1) fixed empiric hyperemic flow velocity (fQFR), (2) modeled hyper- emic flow velocity derived from angiography without drug-induced hyperemia (cQFR), and (3) measured hyperemic flow velocity derived from angiography during adenosine-induced hyperemia (aQFR). The authors observed a good agreement with FFR for all three QFR values with mean differences of 0.003 ± 0.068; 0.001 ± 0.059; and 0.001 ± 0.065 for fQFR, cQFR, and aQFR, respectively. The diagnostic accuracy for identifying a positive FFR (FFR < 0.80) was 80%, 85%, and 87% for fQFR, cQFR, and aQFR, respectively. In the prospective, multicenter FAVOR II China study, a contrast flow model used a frame count method to derive contrast flow velocity from coronary angiography calculated offline QFR (QAngio XA, Medis Medical Imaging BV).32 On a vessel and patient level, the diagnostic accuracy of QFR in identifying hemodynamically significant coronary stenosis was 97.7% and 92.4%, respectively. The FAVOR II Europe-Japan trial demonstrated the superiority of online computation of QFR in a multi- center setting as compared with two-dimensional QCA in terms of sensitivity and specificity with pressure wire–based FFR as the gold standard (86.5% vs 44.2% [*P* < .001] and 86.9% vs 76.5% [*P* = .002], respectively).36 However, both FAVOR studies only enrolled selected patients, excluding bifurcation lesions and diameter stenosis < 30% or > 90%, and no interobserver variability was assessed. At present, both the FAVOR III China (NCT03656848) and

FAVOR III Europe Japan (NCT03729739) are enrolling patients. FAVOR III China is a prospective, multicenter, blinded, randomized superiority trial comparing the clinical outcome and cost- effectiveness of QFR-guided PCI versus angiography- guided PCI. The FAVOR III Europe Japan study aims to assess if a QFR-based diagnostic strategy yields noninferior 12-month clinical outcome as compared with a pressure wire–based FFR strategy in 2,000 patients with stable angina or stabilized non–ST-segment myocardial infarction and intermediate coronary stenosis in up to 40 international sites.

*FFRangio System. Another technology that provides functional angiographic mapping of the entire coronary tree is the FFRangio system (CathWorks). FFRangio is*
a computational method based on rapid flow analysis for the assessment of FFR. FFRangio uses the patient's hemodynamic data and routine angiograms to generate a complete 3D coronary tree with color-coded FFR values at any epicardial location. Hyperemic flow ratio is derived from an automatic resistance-based lumped model of the entire coronary tree using allometric scaling laws. Pellicano et al demonstrated a high concordance between off-site measured FFRangio and pressure wire–based FFR.33 FFRangio was recently validated in the FAST-FFR study, a prospective multicenter trial that compared the accuracy of on-site FFRangio with pressure wire–based FFR. The study demonstrated a high sensitivity (94%), specificity (91%), and accuracy (92%).34 The limitation of this study included the lack of information regarding the total time needed to calculate FFRangio. At present, also for FFRangio, no inter- or intraobserver variability has been reported.

*CAAS 3D-QCA.* The CAAS 3D-QCA software evolved by applying simplified methods for computation of 3D-QCA–based vessel FFR (vFFR; Figure 1) within CAAS Workstation 8.0. Based on well-validated 3D coronary reconstructions,26,29 the pressure drop is calculated instantaneously by applying physical laws as described by Gould et al.27 Within these physical laws, patient-specific aortic rest pressure is incorporated, as measured during the catheterization procedure. The FAST study, which was a single-center observational study, aimed to validate the software to calculate vFFR offline to assess the correlation as compared with pres- sure wire–based FFR and study interobserver variability. The study demonstrated a high diagnostic accuracy of vFFR in identifying significant pressure wire–based FFR (area under the curve, 0.93; 95% confidence interval, 0.88–0.97) with low interobserver variability (R = 0.95; $P < .001$).35 However, FAST was a single-center experience and the analyses were restricted to those recordings with optimal pressure wave forms. Previous work showed the high prevalence of suboptimal FFR curves in clinical practice (up to 30%), suggesting an additional benefit when using techniques based on angiography and simplified flow models.37 A larger international, prospective, multicenter trial (FAST II) is currently ongoing to assess the diagnostic accuracy of both online and core lab–assessed vFFR as compared with conventional pressure wire–based FFR for intermediate coronary artery lesions in patients with stable and unstable CAD (NCT03791320).

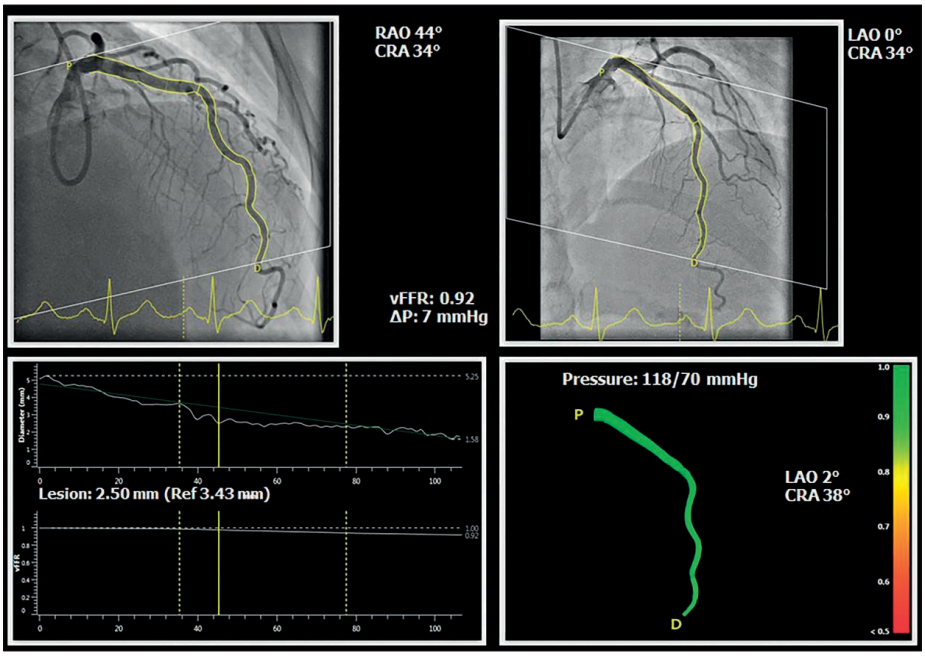



**Figure 1.** Example of vFFR analysis using CAAS Workstation software. 3D reconstruction of a coronary artery and computation of vFFR using two angiographic projections (with at least 30° apart) and invasively measured aortic root pressure. Abbreviations: CRA, cranial; LAO, left anterior oblique; RAO, right anterior oblique.

## POST STENTING ANGIOGRAPHY-BASED FFR

FFR has been used predominantly to assess coronary stenosis severity prior to PCI. However, there is increasing interest in the use of post-PCI physiologic assessment considering that several studies have shown that post-PCI FFR is a strong and independent predictor of clinical outcome.38-41 Previous work from our group has provided more insights of the potential for a post-PCI FFR < 0.85 using high-definition intravascular ultrasound.42 Stent underexpansion was the most frequently identified cause, found in 74% of the cases, followed by clear focal signs of luminal narrowing (54%), focal lesions distal to the stent (30%), residual lesions proximal to the stent (29%), and stent malapposition (22%). The latter results further support the hypothesis that post-PCI FFR increases the likelihood of identifying residual disease that might warrant additional treatment and optimize long-term results.

However, at present, post-PCI FFR is rarely performed due to a number of reasons, including pressure wires that were used pre-PCI and are damaged, additional time needed to repeat the FFR assessment, expense and side effects of hyperemic agents, and because the majority of interventionalists still strongly believe in their ability to achieve a satisfactory PCI result based

on angiography alone. A 3D-QCA–based physiologic lesion assessment after PCI could therefore drastically change the way we adjudicate our results in daily practice. The FAST POST study demonstrated good correlation between conventional invasive post-PCI FFR and 3D-QCA–based FFR and had a high diagnostic accuracy to identify a conventional post-PCI FFR < 0.90.43

## ADVANTAGES AND LIMITATIONS OF ANGIOGRAPHY-BASED FFR

Coronary angiography–based FFR has several potential advantages as compared with conventional pressure wire–based FFR. The computations of angiography-based FFR are fast and have the potential to provide wireless FFR stenosis assessment for almost all angiographic procedures, either pre-, periprocedural, and post-PCI. Second, although pressure wire–based complications are unlikely, this risk would be eliminated with angiography-based FFR. Pressure wire–based FFR requires the use of intracoronary or intravenous drugs to achieve a hyperemic condition and has potential side effects; these drugs would not be required and thus FFR assessment would be more patient-friendly.

Recent research concluded that even in dedicated multicenter trials, a significant amount of drift might occur with pressure wire–based FFR, in addition to an up to 30% likelihood that FFR values are based on dampened pressure waveforms due to inadequate position of the guiding catheter or suboptimal flush.37

Coronary angiography–based FFR is still in an early stage of development, and no outcome studies have been performed confirming the applicability of the technique in routine clinical practice. As previously mentioned, none of the currently available software solutions have been tested to guide clinical decision- making in routine practice. In all studies, the calculation of angiography-based FFR was performed by highly trained individuals, which might have influenced the study results in a positive way. Second, as with any new technology introduced into clinical practice, there is a learning curve on how and how not to use the technology. At present, accurate performance is only possible if dedicated online image exports are made. The images subsequently need to be assessed by adequately trained staff familiar with the concepts of QCA. Optimal angulations, avoidance of overlap, and accurate contour correction proved to be key to achieve optimal results, and more specifically, all of these can only work after acquiring decent-quality angiograms. Although this might sound trivial, previous studies showed that up to 65% of routine angiograms are of insufficient quality to be used in 3D-QCA–based FFR software due to insufficient luminal contrast opacification, overlap, or lack of adequate orthogonal projections.

The accuracy of the software in complex vessels (eg, bifurcations, left main disease, heavily calcified vessels, diffusely diseased vessels) remains to be determined in larger patient cohorts.

Furthermore, the image acquisition requirements and the user interface of an angiography-based FFR system should be seamlessly incorporated into the standard work of the catheterization laboratory. Additionally, the CFD equations require several assumptions from a population model regarding myocardial blood flow rates as a function of the myocardial arterial branches and the resistance of the myocardium. Because coronary flow velocity is a highly sensitive variable, which is influenced by clinical and hemodynamic parameters (including heart rate, blood pressure, left ventricular end-diastolic pressure, left and/or right ventricular hypertrophy, and systemic diseases such as diabetes mellitus and large vessel disease), there will probably be patient-specific errors related to abnormal coronary physiology, which may account for outliers in the correlation between angiography-based FFR and pressure wire–based FFR.

## CONCLUSION

There is a clear need to simplify the use of coronary physiology to increase its uptake in daily clinical practice. The advent of coronary angiography–based FFR looks promising, and the first clinical validation studies of at least three different vendors showed results that are almost too good to be true. Once the technology becomes more widely available, it might fundamentally change the way both diagnostic coronary angiography and PCI will be performed. For the time being, the results of planned and ongoing clinical outcome studies are eagerly awaited to determine the value of angio-based FFR in daily clinical practice.

## REFERENCES

1. Uren NG, Melin JA, De Bruyne B, et al. Relation between myocardial blood flow and the severity of coronary- artery stenosis. N Engl J Med. 1994;330:1782-1788.
2. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary interven- tion: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions [published erratum appears in Circulation. 2012;125:e412]. Circulation. 2011;124:e574-651.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur Heart J. 2019;40:87-165.
4. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutane- ous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35:2541-2619.
5. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med. 2012;367:991-1001.
6. Pijls NH, van Schaardenburgh P, Manoharan G, et al. Percutaneous coronary intervention of functionally nonsig- nificant stenosis: 5-year follow-up of the DEFER study. J Am Coll Cardiol. 2007;49:2105-2111.
7. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360:213-224.
8. Nakamura M, Yamagishi M, Ueno T, et al. Prevalence of visual-functional mismatch regarding coronary artery stenosis in the CVIT-DEFER registry. Cardiovasc Interv Ther. 2014;29:300-308.
9. Park SJ, Kang SJ, Ahn JM, et al. Visual-functional mismatch between coronary angiography and fractional flow reserve. JACC Cardiovasc Interv. 2012;5:1029-1036.
10. Tonino PA, Fearon WF, De Bruyne B, et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol. 2010;55:2816-2821.
11. De Bruyne B, Bartunek J, Sys SU, et al. Simultaneous coronary pressure and flow velocity measurements in humans. Feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. Circulation. 1996;94:1842-1849.
12. De Bruyne B, Fearon WF, Pijls NH, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014;371:1208-1217.
13. Pijls NH, de Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. N Engl J Med. 1996;334:1703-1708.
14. Pijls NH, Van Gelder B, Van der Voort P, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation. 1995;92:3183-3193.
15. Toth GG, Toth B, Johnson NP, et al. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. Circ Cardiovasc Interv. 2014;7:751-759.
16. Escaned J, Echavarria-Pinto M, Garcia-Garcia HM, et al. Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis relevance: results of ADVISE

II international, multicenter study (ADenosine Vasodilator Independent Stenosis Evaluation II). JACC Cardiovasc Interv. 2015;8:824-833.

17. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol. 2012;59:1392-1402.
18. Ligthart J, Masdjedi K, Witberg K, et al. Validation of resting diastolic pressure ratio calculated by a novel algorithm and its correlation with distal coronary artery pressure to aortic pressure, instantaneous wave-free ratio, and fractional flow reserve. Circ Cardiovasc Interv. 2018;11:e006911.
19. Svanerud J, Ahn JM, Jeremias A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. EuroIntervention. 2018;14:806-814.
20. Taylor CA, Fonte TA, Min JK. Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. J Am Coll Cardiol. 2013;61:2233-2241.
21. Koo BK, Erglis A, Doh JH, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol. 2011;58:1989-1997.
22. Min JK, Berman DS, Budoff MJ, et al. Rationale and design of the DeFACTO (Determination of Fractional Flow Reserve by Anatomic Computed Tomographic AngiOgraphy) study. J Cardiovasc Comput Tomogr. 2011;5:301-309.
23. Lee BK, Kwon HM, Kim D, et al. Computed numerical analysis of the biomechanical effects on coronary athero- genesis using human hemodynamic and dimensional variables. Yonsei Med J. 1998;39:166-174.
24. Douglas PS, De Bruyne B, Pontone G, et al. 1-year outcomes of FFRCT-guided care in patients with suspected coronary disease: the PLATFORM study. J Am Coll Cardiol. 2016;68:435-445.
25. Slager CJ, Wentzel JJ, Schuurbiers JC, et al. True 3-dimensional reconstruction of coronary arteries in patients by fusion of angiography and IVUS (ANGUS) and its quantitative validation. Circulation. 2000;102:511-516.
26. Schuurbiers JC, Lopez NG, Ligthart J, et al. In vivo validation of CAAS QCA-3D coronary reconstruction using fusion of angiography and intravascular ultrasound (ANGUS). Catheter Cardiovasc Interv. 2009;73:620-626.
27. Gould KL, Kelley KO, Bolson EL. Experimental validation of quantitative coronary arteriography for determining pressure-flow characteristics of coronary stenosis. Circulation. 1982;66:930-937.
28. Kirkeeide RL. Coronary obstructions, morphology and physiologic significance. In: Reiber JHC, Serruys PW, eds. Quantitative Coronary Arteriography. Dordrecht, the Netherlands: Kluwer Academic Publishers; 1991:229-244.
29. Girasis C, Schuurbiers JC, Muramatsu T, et al. Advanced three-dimensional quantitative coronary angiographic assessment of bifurcation lesions: methodology and phantom validation. EuroIntervention. 2013;8:1451-1460.
30. Papafaklis MI, Muramatsu T, Ishibashi Y, et al. Fast virtual functional assessment of intermediate coronary lesions using routine angiographic data and blood flow simulation in humans: comparison with pressure wire - fractional flow reserve. EuroIntervention. 2014;10:574-583.
31. Tu S, Westra J, Yang J, et al. Diagnostic accuracy of fast computational approaches to derive fractional flow reserve from diagnostic coronary angiography: the international multicenter FAVOR Pilot Study. JACC Cardiovasc Interv. 2016;9:2024-2035.

32. Xu B, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. J Am Coll Cardiol. 2017;70:3077-3087.
33. Pellicano M, Lavi I, de Bruyne B, et al. Validation study of image-based fractional flow reserve during coronary angiography. Circ Cardiovasc Interv. 2017;10:e005259.
34. Fearon WF, Achenbach S, Assali TEA, et al. Accuracy of fractional flow reserve derived from coronary angiogra- phy. Circulation. 2019;139:477-484.
35. Masdjedi KM, van Zandvoort LJ, Balbi MM, et al. Validation of 3-dimensional quantitative coronary angiogra- phy based software to calculate vessel fractional flow reserve: Fast Assessment of STenosis severity (FAST) study [published online May 14, 2019]. EuroIntervention.
36. Westra J, Andersen BK, Campo G, et al. Diagnostic performance of in-procedure angiography-derived quantita- tive flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. J Am Heart Assoc. 2018;7:e009603.
37. Matsumura M, Johnson NP, Fearon WF, et al. Accuracy of fractional flow reserve measurements in clinical practice: observations from a core laboratory analysis. JACC Cardiovasc Interv. 2017;10:1392-1401.
38. Agarwal SK, Kasula S, Hacioglu Y, et al. Utilizing post-intervention fractional flow reserve to optimize acute results and the relationship to long-term outcomes. JACC Cardiovasc Interv. 2016;9:1022-1031.
39. Leesar MA, Satran A, Yalamanchili V, et al. The impact of fractional flow reserve measurement on clinical outcomes after transradial coronary stenting. EuroIntervention. 2011;7:917-923.
40. Pijls NH, Klauss V, Siebert U, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation. 2002;105:2950-2954.
41. Kasula S, Agarwal SK, Hacioglu Y, et al. Clinical and prognostic value of poststenting fractional flow reserve in acute coronary syndromes. Heart. 2016;102:1988-1994.
42. Daemen J, van Zandvoort L, van Bommel R, et al. CRT-30.03: Explanation of post procedural fractional flow reserve below 0.85: a comprehensive ultrasound analysis of the FFR Search registry [abstract]. JACC Cardiovasc Interv. 2018;11(suppl):S36.
43. Masdjedi KM, Van Zandvoort LJC B, Balbi MM, et al. Validation of novel 3-dimensional quantitative coronary angiography based software to calculate vessel fractional flow reserve (vFFR) post stenting: Fast Assessment of STenosis severity POST stenting, The FAST POST-study. Presented at Trancatheter Cardiovascular Therapeutics (TCT) 2018; September 25, 2018; San Diego, California.

# Chapter 13

# Validation of 3-Dimensional Quantitative Coronary Angiography based software to calculate Fractional Flow Reserve: Fast Assessment of STenosis severity (FAST)-study

**Kaneshka Masdjedi**[1], MD; Laurens JC van Zandvoort[1], BSc; Matthew M Balbi[1], MD; Frank JH Gijsen[1], PhD; Jurgen MR Ligthart[1], RT; Marcel CM Rutten[2], ir. PhD; Miguel E Lemmert[1], MD, PhD; Jeroen Wilschut[1], MD; Roberto Diletti[1], MD, PhD; Peter de Jaegere[1], MD, PhD; Felix Zijlstra[1], MD, PhD; Nicolas M Van Mieghem[1], MD, PhD; Joost Daemen[1], MD, PhD

**[1] Department of Cardiology, Thoraxcenter, Erasmus Medical Center**

**[2] Department of Cardiovascular Biomechanics, Technical University of Eindhoven**

**Journal:** EuroIntervention; 2020;16:591-599.

## ABSTRACT

**Aim:** The aim of this study was to validate novel software to calculate vessel Fractional Flow Reserve (vFFR) based on 3D-QCA and to assess inter-observer variability in patients who underwent routine pre procedural FFR assessment for intermediate coronary artery stenosis.

**Methods and results:** In-vitro validation was performed in an experimental model. Clinical validation was performed in an observational, retrospective, single-center cohort study. A total of 100 patients presenting with stable angina or non-ST segment elevation myocardial infarction and an indication to perform FFR between Jan 2016 and Oct 2016 were included. vFFR was calculated based on the aortic root pressure along with two angiographic projections and validated against pressure wire-derived FFR.

Mean FFR and vFFR were 0.82±0.08 and 0.84±0.07 respectively. A good linear correlation was found between FFR and vFFR ($r=0.89$; $p<0.001$). Assessment of vFFR had a low inter-observer variability ($r=0.95$; $p<0.001$). The diagnostic accuracy of vFFR in identifying lesions with an FFR≤0.80 was higher as compared with 3D-QCA: AUC 0.93 (95% CI: 0.88-0.97) vs. 0.66 (95% CI: 0.55-0.77) respectively.

**Conclusions:** The 3D-QCA derived vFFR has a high linear correlation to invasively measured FFR, a high diagnostic accuracy to detect FFR ≤ 0.80 and a low inter-observer variability.

**Keywords:** Fractional Flow Reserve, Coronary Physiology, 3D-QCA, Coronary artery stenosis, Percutaneous coronary intervention.

## INTRODUCTION

Invasive coronary angiography has served as the cornerstone for the diagnosis of patients with known or suspected coronary artery disease (CAD). Unfortunately, the technique is limited in its ability to assess the hemodynamic impact of intermediate coronary artery stenosis resulting in under- or overestimation of disease severity [1]. In order to overcome this limitation, Fractional Flow Reserve (FFR) has emerged as the mainstay of functional hemodynamic lesion assessment and is presently regarded as the gold standard for identifying stenoses that cause myocardial ischemia [2-5]. Despite indisputable evidence supporting the benefit of FFR to guide clinical decision making, adoption into daily practice has been limited. FFR assessment requires the use of a (costly) pressure wire or microcatheter along with the administration of a hyperemic agent associated with temporary patient discomfort [6]. Although non-hyperemic pressure ratios (NHPR) such as instantaneous wave-free ratio (iFR), resting full-cycle ratio (RFR) and diastolic pressure ratio (dPR) have emerged as adenosine-free faster and easier methods to achieve physiologic assessment, the need for a costly pressure wire remains a fact [7-9].

The Fast Assessment of STenosis severity (FAST) study aimed to validate a new 3D-QCA-based software to calculate vessel-FFR (vFFR) using phantom models. In addition we correlated this index with pressure wire derived FFR in a consecutive series of patients and studied inter-observer variability.

## METHODS

### In vitro experimental model

An in vitro experimental model was developed for technical validation of the calculation method performed by the CAAS workstation in phantoms. The experimental set-up consists of a chamber, a water-driven systemic and coronary circulation [10]. The chamber mimics the left ventricle and artificial valves mimic the mitral- and aortic valve of the heart (**Figure 1**). The piston is powered by a computer-controlled linear motor (ETB32, Parker) creating pulsatile flow at 75 beats per minute. For non-pulsatile flow, a constant flow pump (2035, Verder) fills a higher placed reservoir, with overflow function, the output of the reservoir connects to the mitral valve. A polyurethane tube models the aorta, and input impedance characterizes the systemic circulation behaviour. Flow through the aorta was set at approximately 5 l/min and measured using an ultrasound flow probe (Transonic 28PAU, with TS 410 flowmeter). The distal systemic compliance is modelled using a Windkessel, resulting in physiological pressure conditions.

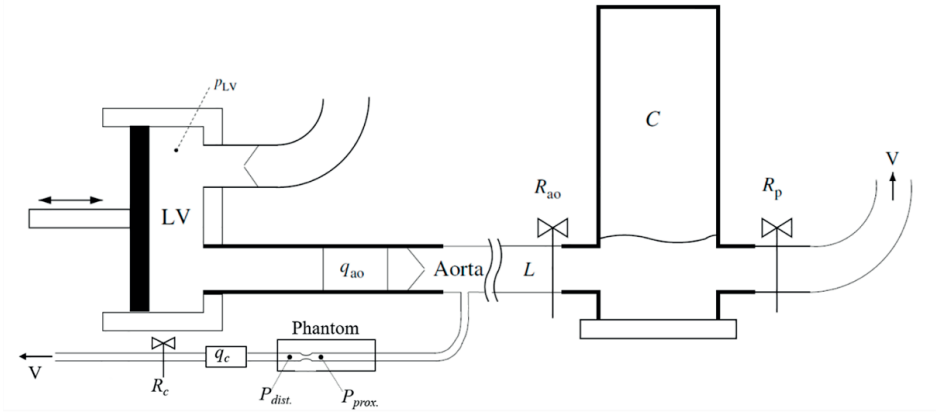



**Figure 1.** Schematic of the in vitro experimental model. The LV-chamber pumps water through the aorta flow prove (qao) and the artificial valve into the aorta and from the aorta into the systemic Windkesssel components ($R_{ao}$, L, C and $R_p$). A tube, representing the coronary artery, branches off the aorta, passes the phantom, the coronary flow probe ($q_c$) towards a venous outlet (V). The pressure sensors are positioned proximal ($P_{prox.}$) and distal ($P_{dist.}$) to the lesion in the phantom, the flow ($q_c$) is measured at the outflow tract of the phantom. The flow through the phantom is controlled by the resistance ($R_c$) in the outflow tract.

### *Coronary circulation*

The in vitro coronary circulation comprised a tube (8mm diameter) connected to the ostium of the aorta with a phantom attached at the end of this tube. The phantom consisted of an 8mm tube with a 75% sinusoidal diameter stenosis (Model: QA-STV, Simutec). A resistance was placed at the outflow tract of the phantom to control the amount of flow through the phantom. The diameter of the tubes in the phantom are relatively large compared to human coronary artery dimensions. [11] To simulate significant pressure drop along the lesion, the average flow through the phantom was set higher as compared to physiological coronary flow, and was set to an average of 100, 200, 300 and 400 ml/min for both pulsatile flow and constant flow[12] with Reynolds numbers of 1061, 2122, 3183 and 4244 for the stenotic segments and 265, 531, 796 and 1061 for healthy segments respectively. The proximal and distal pressures to the lesion were measured simultaneously with two pressure wires (Certus12006, Radi). The flow rate through the phantom was registered by an electromagnetic flow probe. The pressure drop was based on the difference between the measured pressures distal and proximal to the lesion. Measurements were averaged over four cycles during pulsatile flow, and the same period was used for averaging during constant flow.

### *Pressure drop computation methods*

The pressure drop over the phantom lesions was computed using two different approaches: 1) Computational Fluid Dynamics (CFD) being considered a reference standard in blood flow simulations [13] and 2) by using CAAS Workstation 8.0 (Pie Medical Imaging, Maastricht, the Netherlands). A 3D surface mesh, corresponding to the geometry between the locations of the two pressure wires, was used for calculating the pressure drop by both approaches. Viscosity differences of

water against blood were taken into consideration. The CFD approach uses a tetrahedron mesh with a mesh resolution adapted to specific vessel geometry and wall irregularities resulting in tetrahedron edge lengths varying between 0.05 and 0.8mm. Furthermore, three boundary layers were introduced to capture the blood flow close to the wall. Thickness of the boundary layers was calculated based on flow, viscosity, density and Reynolds number. Using the mesh, the CFD approach modeled flow using Navier-Stokes equations (Kratos, Multi-Physics 5, version 20). The following boundary conditions were applied: a constant parabolic flow profile at the inlet and a stress free outlet (zero pressure). [14] Further, rigid-wall, non-slip conditions, and a Newtonian fluid approximation were used.

The CAAS Workstation 8.0 used for the experimental model was adapted to allow importing a 3D geometry of the phantom. A single flow as applied (fixed flow value over time) to both computational approaches, to eliminate time-variation in flow profile and pressure drop. In total four experiments with different flow values were performed. The experiment learned that the average pressure drop using pulsatile flow cycle provides similar results as when using constant flow (that equals the average of the pulsatile flow cycle). This observation justified the application of a single flow value for the computation approaches**.** The pressure drop obtained by both pulsatile and constant flow for the different flow values were compared to the computed pressure drop values of both the CFD approach and CAAS Workstation vFFR **(Figure 2)**.

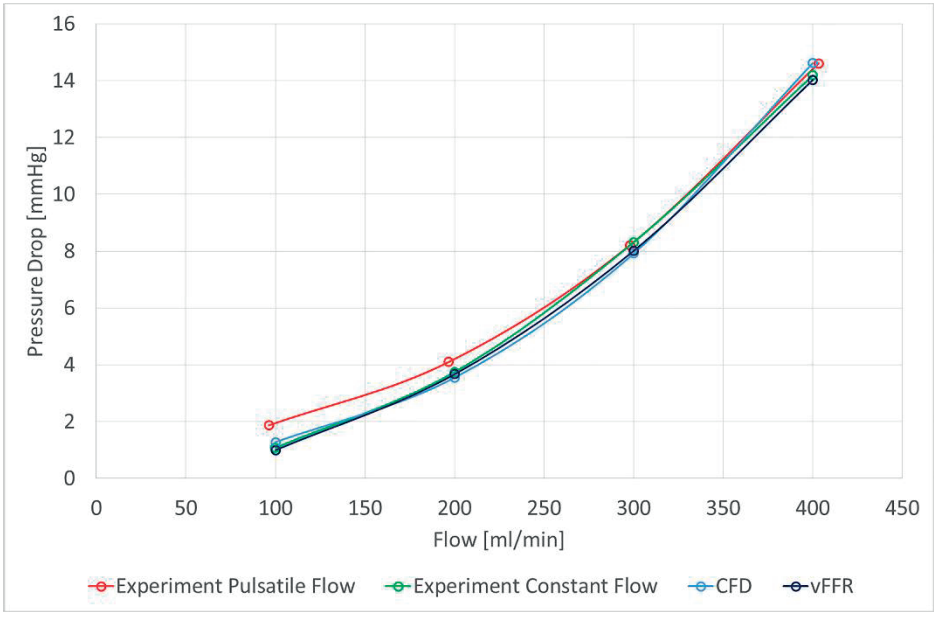



**Figure 2.** Pressure drop resulting from pressure measurements during pulsatile flow (red line) and constant flow (green line) as well as the computed pressure drop by the Computational Fluid Dynamics (CFD) (light blue) and CAAS Workstation vFFR (dark blue).

## Clinical validation study

*Study design and patient population*

The FAST (Fast Assessment of STenosis severity) study is an observational, retrospective, single-center cohort study in which offline computation of vFFR as compared with conventional invasive FFR (St. Jude Aeris, Abbott Vasuclar, St Paul, MA, USA) was studied. From January 2016 through October 2016, patients ≥18 years of age presenting with stable coronary artery disease or non-ST elevation acute coronary syndrome who underwent pre-PCI FFR assessment were eligible. Angiographic inclusion criteria were: at least one intermediate stenosis in one of the epicardial coronary arteries (diameter stenosis of 30-70% by visual assessment). Exclusion criteria were FFR measurements with damped pressure curves, patients with ST-elevation myocardial infarction (STEMI) or lesions containing thrombus, left main lesions, grafts, arteries with collaterals, cardiogenic shock or severe hemodynamic instability and adenosine intolerance.

*Procedure protocol*

Procedures were performed according to standard local clinical practice. Angiographic lesion severity was assessed by two monoplane angiographic projections (at least 30 degrees apart, preferably orthogonal) after a bolus of 200mcg nitroglycine. Hyperemia during FFR measurement was achieved by continuous infusion of adenosine at a rate of 140 µg/kg/min through an antecubital vein for at least 2 minutes. Angiograms and pressure waveforms were stored as DICOM images for offline analyses. Aortic root pressure was constantly recorded. The last blood pressure measurement taken before the start of the FFR measurement was used as input in the CAAS/vFFR software.

*Patient selection, 3D-coronary reconstruction and computation of vFFR*

**Figure 3** represents a flowchart showing all included and excluded patients.

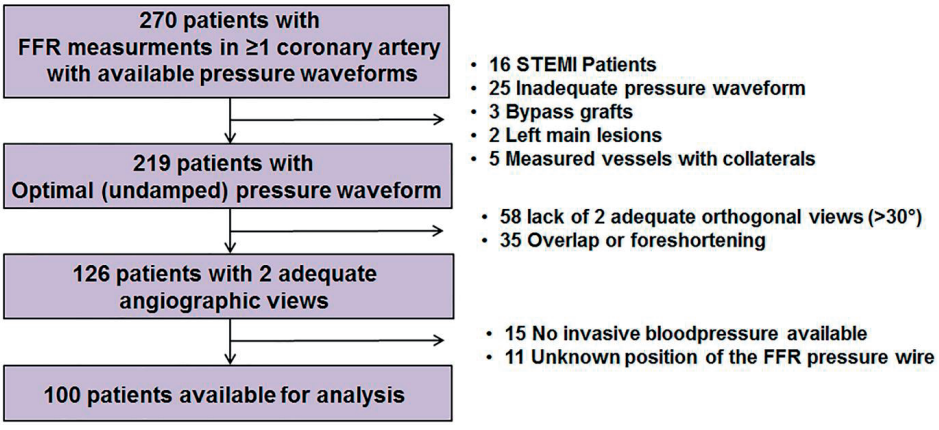



**Figure 3.** Flowchart of all included and excluded patients.

Computation of vFFR was performed offline and assessed blinded by 2 independent observers to assess inter-observer variability (KM, MB). A total of 3 two-dimensional images, were exported to the CAAS workstation 8.0 (Pie Medical Imaging, Maastricht, the Netherlands): two views with at least 30 degrees differences in rotation/angulation to create a 3D reconstruction of the coronary artery and one view to ascertain the position of the FFR pressurewire. Angiograms were recorded visualizing the entire vessel, taking into account overlapping and foreshortening to create a 3D reconstruction of the coronary artery as accurate as possible. The two independent observers used the same cine-images for the calculation of vFFR. Although temporal alignment of the cardiac cycle between the two angiograms was performed automatically by ECG triggering, manual frame selection was allowed. Contour detecting was performed semi-automatically, delineating the vessel contour from the ostium to the position at which the pressure wire sensor was positioned (3cm from the tip). As such both final frame selection and contour corrections were left to the discretion of the observer. The percent diameter stenosis, minimal lumen diameter, reference lumen diameter, minimal lumen area and lesion length were measured from the same 3D model as on which the vFFR was determined. The lesion segment was defined as proximal, mid or distal. vFFR was calculated automatically incorporating the invasively measured aortic root pressure and automatically generated 3D QCA values and vFFR along entire vessel instantaneously (**Figure 4**).

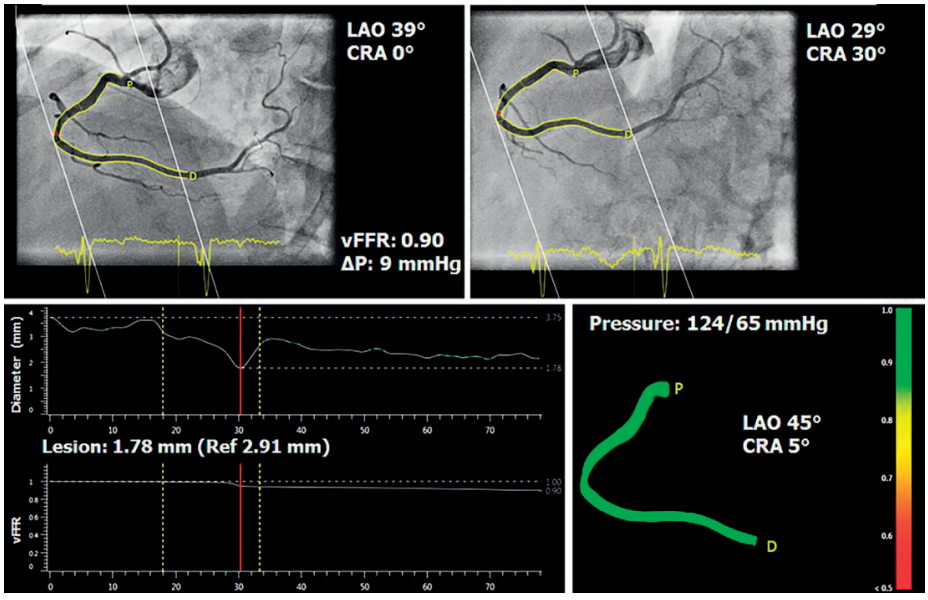



**Figure 4.** Three-dimensional reconstruction of coronary artery and computation of vessel-FFR, using 2 angiographic projections with at least 30 degrees apart and invasively measured aortic root pressure.

Within CAAS Workstation vFFR the pressure drop is calculated instantaneously by applying physical laws including viscous resistance and separation loss effects present in coronary flow behavior, as described by Gould and Kirkeeide. [15, 16]. The methods however are based on a single angiographic projection. Within CAAS vFFR, the geometry of the coronary artery is derived from well-validated 3D reconstructions [17, 18] which reduces the effects of foreshortening, out of plane magnification and non-symmetric coronary lesions. Furthermore, the pressure drop calculation by CAAS vFFR includes patient specific aortic pressure, as measured during the catheterization procedure. Maximum hyperemic blood flow was empirically determined from clinical data and we assumed that proximal coronary velocity is preserved along the coronary of interest which is adapted based on the patient specific aortic rest pressure and the 3D geometry of the coronary artery.

## STATISTICAL ANALYSIS

Continuous variables are presented as mean ±standard deviation. All continuous variables were normally distributed. Categorical variables are expressed as counts and percentages. All statistical tests are 2-tailed. Pearson's correlation coefficient (r) was used to assess the relationship between FFR and vFFR and to assess inter-observer variability. Agreement between the indices and the inter-observer reliability were assessed by Bland-Altman plots with corresponding 95% limits of agreement. Receiver-operating characteristic (ROC) area under the curve (AUC) analysis was used to estimate the diagnostic performance of vFFR as compared to the wire-based FFR threshold of ≤0.80. Statistical analysis was carried out using the SPSS statistical package version 24 (IBM, Armonk, North Castle, New York, USA).

## RESULTS

### Pre clinical data

Pulsatile flow based pressure measurements corresponded well with pressure drops obtained by constant flow (0.36±0.37 mmHg, r>0.99; p=0.002), (**Figure 2)**. This supported the assumption to apply a single flow value for the computational approaches. The CFD pressure drop results showed excellent agreement with the experimental pulsatile and constant flow (-0.36±0.28 mmHg and 0.01±0.38 mmHg respectively, r>0.99; p<0.002), as well as the CAAS Workstation vFFR pressure drop results (0.52 ±0.28 mmHg and -0.16±0.11 mmHg respectively, r>0.99; p<0.002). The difference between CFD and vFFR was -0.17±0.34 mmHg with excellent agreement (r>0.99; p<0.002).

**Table 1.** Baseline characteristics.

| | Total N = 100 |
|---|---|
| Age, y, mean±SD | 64±11 |
| Male gender, n (%) | 67 (67) |
| **Cardiovascular risk factors, n (%)** | |
| Hypertension | 70 (70) |
| Hyperlipidemia | 59 (59) |
| Diabetes Mellitus | 26 (26) |
| Current smoker | 25 (25) |
| Peripheral artery disease | 10 (10) |
| **Medical history and co-morbidity, mean±SD** | |
| eGFR, ml/min | 88±30 |
| Hemoglobine, (mmol/L) | 8.2±1.4 |
| BMI | 28±5 |
| **Lesions location and characteristics, n (%)** | |
| Left anterior descending artery | 60 (60) |
| Left circumflex artery | 13 (13) |
| Right coronary artery | 27 (27) |
| Tortuous vessels | 28 (28) |
| Tandem lesions | 7 (7) |
| Moderate or severe calcification | 36 (36) |
| Bifurcation lesions | 21 (21) |
| Ostial lesions | 2 (2) |
| Diffuse disease | 31 (31) |
| **Coronary angiography indication, n (%)** | |
| Stable coronary artery disease | 60 (60) |
| Unstable coronary artery disease | 14 (14) |
| NSTEMI | 26 (26) |
| **3D- Quantitative Coronary Angiography, mean±SD** | |
| Lesion length, mm | 20±13 |
| Minimal lumen diameter, mm | 1.7±0.33 |
| Minimal lumen area, $mm^2$ | 2.3±0.96 |
| Diameter stenosis, % | 37±13 |
| Reference vessel diameter, mm | 2.8±0.5 |
| **Indices, mean±SD** | |
| FFR | 0.82±0.08 |
| vFFR | 0.84±0.07 |

Values are n, mean±SD of n (%); BMI= Body Mass Index; eGFR= estimated glomerular filtration rate; FFR= Fractional Flow Reserve; NSTEMI= Non-ST-segment elevation myocardial infarction; vFFR= vessel Fractional Flow Reserve.

## Clinical data

*Patient demographics and procedural data*

One hundred patients were included. Mean age was 64±11 years, 67% were male and 26% had diabetes. The majority of the FFR measurements were performed in the left anterior descending artery (60%). The circumflex and right coronary artery were involved in 13% and 27% of the cases respectively. Mean angiographic percent diameter stenosis (DS), lesion length and minimum lumen diameter (MLD), measured from 3D-QCA, were 37±13%, 20±13 mm and 1.7±0.3 mm respectively (**Table 1**).

*Correlatino and agreement between ffr and vffr*

Mean FFR and vFFR were 0.82±0.08 and 0.84±0.07 respectively. A good linear correlation was found between FFR and vFFR (r=0.89; p<001). Sensitivity analysis of patients presenting with ACS vs. stable patients showed no differences in correlation between FFR and vFFR (r=0.89 vs 0.89 respectively). Assessment of vFFR had a low inter-observer variability (r=0.95; p<0.001) **(Figure 5)**. vFFR had a good accuracy in the identification of patients with significant FFR values ≤0.80 (AUC of 0.93 [95% CI: 0.88–0.97]) **(Figure 6)**. The diagnostic accuracy of 3D-QCA, based on percentage diameter stenosis was lower as compared to the diagnostics accuracy of vFFR (AUC of 0.66 [95% CI: 0.55–0.77]).

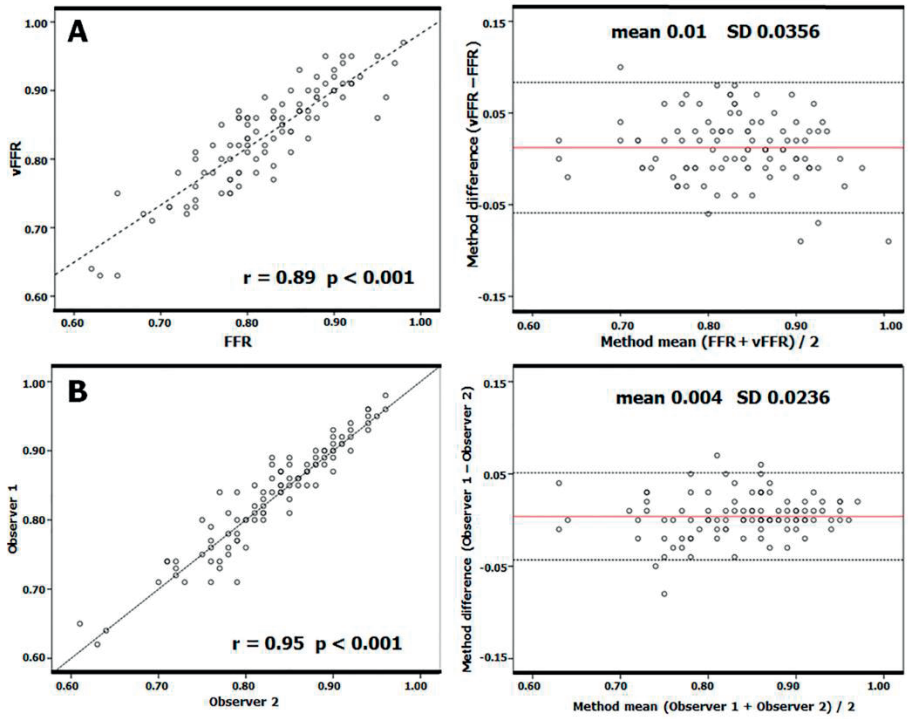



**Figure 5.** Scatter Plots showing the relationship between vFFR vs. wire-based FFR **(A)** and inter-observer variability **(B)** and Bland- Altman plots of differences against the means. The mean bias is represented by the solid red line and the 95% confidence interval is represented by the dashed lines.

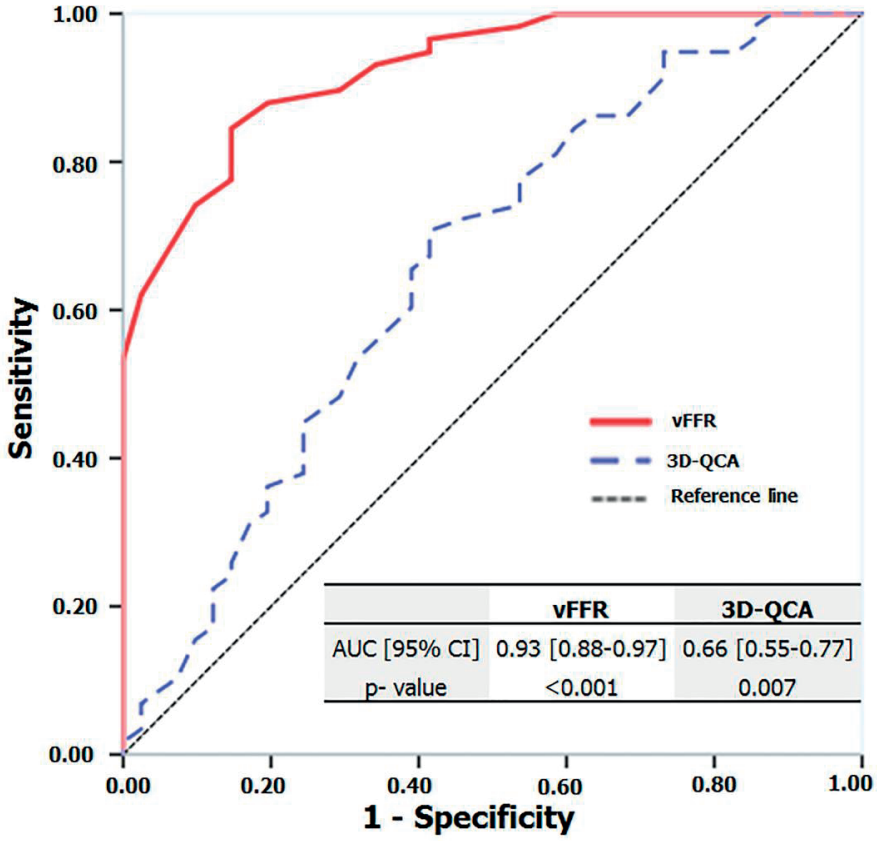



**Figure 6.** ROC Curves for vFFR and 3D-QCA. Comparison is made with a wire-based FFR at a cut point of 0.80.

## DISCUSSION

The FAST study confirmed the feasibility of novel 3D-QCA based software to calculate FFR without the use of a pressure wire or microcatheter. In the pre-clinical technical validation model vFFR proved to have a strong correlation with CFD and measured flow parameters. In our clinical validation study we confirmed a good agreement and high diagnostic accuracy of vFFR as compared to invasively measured FFR. Finally, we showed that vFFR had a low inter-observer variability.

In the past decade a wealth of data has become available demonstrating the superiority of FFR guided PCI as compared to angiography guided PCI [4, 5, 19]. FFR subsequently received strong recommendations in current revascularization guidelines [3, 20]. Even though the use of FFR proved to be contrast saving, cost effective and associated with improved quality of life, FFR is still not being performed in the vast majority of cases [3, 5, 19, 20]. The latter has been hypothesized to be due to the need for (in some countries) expensive hyperemic agents with known adverse events as dyspnea

and arrhythmias and or intolerance due to pulmonary disease and the use of a costly pressure wire [6]. More recently, the advent of adenosine-free non hyperemic pressure ratios proved to be a valuable alternative to FFR. The need for a dedicated pressure however still remains a fact. For these reasons, the search for cheaper, faster and more patient-friendly methods to assess coronary physiology remains imperative.

One of the first studies assessing the potential of angiography based functional lesion assessment was published by Papafaklis et al. in which the CAAS 3D-QCA was used to calculate a virtual Functional Assessment Index (vFAI) [21] by following the concepts as introduced by Gould et al., reporting that pressure drop was linked to flow using linear and quadratic terms ($\Delta P=fvQ + fsQ2$) [22]. In order to compute the vFAI the authors first solved the fv and fs parameters from the artery-specific quadratic equation by performing two separate CFD simulations using the geometry resulting based on 3D-QCA. In both CFD simulations, the arterial wall was considered to be rigid and no-slip conditions were applied at the vessel wall, while a reference pressure of 100 mmHg was imposed as boundary condition at the inlet and steady flow (fully developed laminar, and incompressible blood flow) was imposed at the outlet. One CFD simulation was performed with a steady flow of 1 ml/sec (corresponding to the average flow at rest) and one CFD simulation was performed with a steady flow of 3 ml/sec (corresponding to the average flow during hyperemia). After solving $f_v$ and $f_s$ parameters, the vFAI was computed as the ratio of the area under the curve ($Pd/Pa=1-f_v\ Q/Pa-f_s\ Q^2/Pa$) for a flow range from 0 to 4ml/sec. The vFAI estimates the overall behavior of the artery/stenosis-specific Pd/Pa versus flow relationship and is not identical to FFR. This approach bypasses the need to derive a patient specific blood flow within the coronary of interest. CAAS vFFR calculates the true pressure drop using patient specific aortic pressure and estimates a single patient specific coronary blood flow used for each pressure drop calculation.

Several recent studies assessed the potential value of 3D-QCA based FFR [23-25]. In the VIRTU-1 study [24], Morris et al. developed a computer model that accurately predicted virtual FFR from angiographic images alone assuming 3D reconstruction, using a Philips workstation. A good correlation (r=0.84) of virtual FFR was found with invasive FFR. The technology however used lengthy CFD analysis hampering direct clinical applicability.

More recent studies validated easier methods using contrast flow models to calculate 3D-QCA-based FFR by using frame counting [25, 26]. The FAVOR Pilot Studyassessed the diagnostic accuracy of quantitative flow ratio (QFR) as measured offline in three different ways, based on the different mean hyperemic flow velocities [26]. The authors observed a good agreement with FFR and a high diagnostic accuracy for identifying a positive FFR (FFR<0.80). Comparable results were recently found in the FAVOR II China Study in which online QFR has a high feasibility and accuracy in identifying hemodynamically significant coronary artery stenosis [25]. In both studies, QFR was performed using a prototype software package (QAngio XA 3D prototype, Medis Medical Imaging

System, Leiden, the Netherlands). The contrast flow models by QAngio however have several limitations.

Coronary flow velocity is a highly sensitive variable which is influenced by clinical and haemodynamic parameters such as heartrate, bloodpressure, left ventricular end diastolic pressure, left and/or right ventricular hypertrophy and systemic diseases as diabetes mellitus, large vessel disease etc. [27, 28] It is well known, that coronary perfusion occurs mainly during diastole. This implies that coronary velocity is not constant during the entire cardiac cycle and therefore passage of contrast agent might be different in systole and diastole. In addition, there are phasic changes in resistance. The perfusion of the left coronary artery (LCA) is predominantly diastolic while the perfusion of right coronary artery (RCA) is both systolic and diastolic, due to lower pressure in the right ventricle as compared with the left ventricle. Therefore, one could assume differences while using frame count methods to obtain pressure gradients in the left vs. the right coronary artery. Unfortunately, no inter-observer or inter-study variability was reported in both FAVOR studies. In contrast, in the present study, we demonstrated an excellent inter-observer variability ($r=0.95$; $p<0.001$).

The mean QCA-based diameter stenosis in the FAVOR II China study was 46.5% and about 34% of the measured lesions had an FFR ≤0.80. A discrepancy could be appreciated between the relatively low mean QCA based diameter stenosis (37%) and the percentage of vFFR values ≤0.80. Part of the discrepancy can be explained by the fact that the presented QCA figures and percentages diameter stenoses were based on 3D assessment which is per definition lower than the conventional 2D percentages [29]. Additionally, there have been several reports about the discordance between anatomical and functional assessment of coronary lesions is far from rare. [30-32]

Despite the relatively low % diameter stenosis in the present study, 42% of the patients had an FFR ≤0.80 which was comparable to the results of the FFRangio Accuracy versus Standard FFR (FAST-FFR) study (43% of FFR values were ≤0.80) [23]. The FAST-FFR study was a prospective, multicenter, international trial demonstrating that $FFR_{angio}$ (CathWorks, Kfar-Saba, Israel) had a high sensitivity, specificity and accuracy in providing functional angiographical mapping of the entire coronary tree as compared with the pressure wire based FFR.

The FAST study is the first validation study of CAAS vFFR with a limited sample size and offline assessment of vFFR. Clinical outcome studies should be obtained to assess the value of vFFR measured by CAAS Workstation for the hemodynamic assessment of lesion severity into daily clinical practice.

## Limitations

Our study has several limitations. First, it is a single center experience in which we restricted our analyses to those recordings with undamped pressure wave forms. Previous work showed the high prevalence of suboptimal FFR curves in clinical practice (up to 30%) suggesting an additional benefit when using techniques based on angiography and simplified flow models.[33] Second, the software's accuracy in complex vessels, e.g. bifurcations and diffusely diseased vessels, remains to be determined in larger patient cohorts. Furthermore, as mentioned in the methods section, contour detection was performed semi-automatically. Finally, although vFFR calculation was performed by two independent observers, there was no independent core-lab involved. Independent corelab adjudication of vFFR will be performed in the ongoing international multicenter FAST II study.

## Conclusion

vFFR based on 3D-QCA as determined using novel software has a high linear correlation to invasively measured FFR, a high diagnostic accuracy to detect FFR ≤ 0.80 along with a low inter-observer variability.

## Impact on daily practice

There is a clear need to simplify the use of coronary physiology in order to increase its uptake in daily clinical practice. Once vFFR technology becomes more widely available, it might fundamentally change the way both diagnostic coronary angiography and PCI are being performed.

## REFERENCES:

1. Lindstaedt M, Spiecker M, Perings C, Lawo T, Yazar A, Holland-Letz T, Muegge A, Bojara W, Germing A. How good are experienced interventional cardiologists at predicting the functional significance of intermediate or equivocal left main coronary artery stenoses? Int J Cardiol 2007;**120**(2):254-61.
2. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF, Investigators FT. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;**367**(11):991-1001.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, Group ESCSD. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2018.
4. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 2007;**49**(21):2105-11.
5. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF, Investigators FS. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;**360**(3):213-24.
6. Toth GG, Toth B, Johnson NP, De Vroey F, Di Serafino L, Pyxaras S, Rusinaru D, Di Gioia G, Pellicano M, Barbato E, Van Mieghem C, Heyndrickx GR, De Bruyne B, Wijns W. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. Circ Cardiovasc Interv 2014;**7**(6):751-9.
7. Ligthart J, Masdjedi K, Witberg K, Mastik F, van Zandvoort L, Lemmert ME, Wilschut J, Diletti R, de Jaegere P, Zijlstra F, Kardys I, Van Mieghem NM, Daemen J. Validation of Resting Diastolic Pressure Ratio Calculated by a Novel Algorithm and Its Correlation With Distal Coronary Artery Pressure to Aortic Pressure, Instantaneous Wave-Free Ratio, and Fractional Flow Reserve. Circ Cardiovasc Interv 2018;**11**(12):e006911.
8. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, Mayet J, Davies JE. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. J Am Coll Cardiol 2012;**59**(15):1392-402.
9. Svanerud J, Ahn JM, Jeremias A, van 't Veer M, Gore A, Maehara A, Crowley A, Pijls NHJ, De Bruyne B, Johnson NP, Hennigan B, Watkins S, Berry C, Oldroyd KG, Park SJ, Ali ZA. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. EuroIntervention 2018.
10. Geven MC, Bohte VN, Aarnoudse WH, van den Berg PM, Rutten MC, Pijls NH, van de Vosse FN. A physiologically representative in vitro model of the coronary circulation. Physiol Meas 2004;**25**(4):891-904.
11. Dodge JT, Jr., Brown BG, Bolson EL, Dodge HT. Lumen diameter of normal human coronary arteries. Influence of age, sex, anatomic variation, and left ventricular hypertrophy or dilation. Circulation 1992;**86**(1):232-46.
12. Li S, Chin C, Thondapu V, Poon EKW, Monty JP, Li Y, Ooi ASH, Tu S, Barlis P. Numerical and experimental investigations of the flow-pressure relation in multiple sequential stenoses coronary artery. Int J Cardiovasc Imaging 2017;**33**(7):1083-1088.

13. Morris PD, Narracott A, von Tengg-Kobligk H, Silva Soto DA, Hsiao S, Lungu A, Evans P, Bressloff NW, Lawford PV, Hose DR, Gunn JP. Computational fluid dynamics modelling in cardiovascular medicine. Heart 2016;**102**(1):18-28.
14. Wentzel JJ, Gijsen FJ, Schuurbiers JC, Krams R, Serruys PW, De Feyter PJ, Slager CJ. Geometry guided data averaging enables the interpretation of shear stress related plaque development in human coronary arteries. J Biomech 2005;**38**(7):1551-5.
15. Gould KL, Kelley KO, Bolson EL. Experimental validation of quantitative coronary arteriography for determining pressure-flow characteristics of coronary stenosis. Circulation 1982;**66**(5):930-7.
16. Kirkeeide R. Coronary obstructions, morphology and physiologic significance. 1991:229–44.
17. Girasis C, Schuurbiers JC, Muramatsu T, Aben JP, Onuma Y, Soekhradj S, Morel MA, van Geuns RJ, Wentzel JJ, Serruys PW. Advanced three-dimensional quantitative coronary angiographic assessment of bifurcation lesions: methodology and phantom validation. EuroIntervention 2013;**8**(12):1451-60.
18. Schuurbiers JC, Lopez NG, Ligthart J, Gijsen FJ, Dijkstra J, Serruys PW, Van der Steen AF, Wentzel JJ. In vivo validation of CAAS QCA-3D coronary reconstruction using fusion of angiography and intravascular ultrasound (ANGUS). Catheter Cardiovasc Interv 2009;**73**(5):620-6.
19. Siebert U, Arvandi M, Gothe RM, Bornschein B, Eccleston D, Walters DL, Rankin J, De Bruyne B, Fearon WF, Pijls NH, Harper R. Improving the quality of percutaneous revascularisation in patients with multivessel disease in Australia: cost-effectiveness, public health implications, and budget impact of FFR-guided PCI. Heart Lung Circ 2014;**23**(6):527-33.
20. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;**124**(23):e574-651.
21. Papafaklis MI, Muramatsu T, Ishibashi Y, Lakkas LS, Nakatani S, Bourantas CV, Ligthart J, Onuma Y, Echavarria-Pinto M, Tsirka G, Kotsia A, Nikas DN, Mogabgab O, van Geuns RJ, Naka KK, Fotiadis DI, Brilakis ES, Garcia-Garcia HM, Escaned J, Zijlstra F, Michalis LK, Serruys PW. Fast virtual functional assessment of intermediate coronary lesions using routine angiographic data and blood flow simulation in humans: comparison with pressure wire - fractional flow reserve. EuroIntervention 2014;**10**(5):574-83.
22. Gould KL. Pressure-flow characteristics of coronary stenoses in unsedated dogs at rest and during coronary vasodilation. Circ Res 1978;**43**(2):242-53.
23. Fearon WF, Achenbach S, Assali TEA, Jeremias RSA, Fournier S, Kirtane AJ, Kornowski R, Greenberg G, Jubeh R, Kolansky DM, McAndrew T, Dressler O, Maehara A, Matsumura M, Leon MB, Bruyne BD. Accuracy of Fractional Flow Reserve Derived From Coronary Angiography. Ciculation 2018.
24. Morris PD, Ryan D, Morton AC, Lycett R, Lawford PV, Hose DR, Gunn JP. Virtual fractional flow reserve from coronary angiography: modeling the significance of coronary lesions: results from the VIRTU-1 (VIRTUal Fractional Flow Reserve From Coronary Angiography) study. JACC Cardiovasc Interv 2013;**6**(2):149-57.
25. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, Guo L, Sun Z, Li Z, Tian F, Fang W, Chen J, Li W, Guan C, Holm NR, Wijns W, Hu S. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. J Am Coll Cardiol 2017;**70**(25):3077-3087.
26. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, Nef H, Tebaldi M, Murasato Y, Lansky A, Barbato E, van der Heijden LC, Reiber JH, Holm NR, Wijns W, Group FPTS. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. JACC Cardiovasc Interv 2016;**9**(19):2024-2035.

27. Hoffman JI. Problems of coronary flow reserve. Ann Biomed Eng 2000;**28**(8):884-96.
28. van de Hoef TP, Siebes M, Spaan JA, Piek JJ. Fundamentals in clinical coronary physiology: why coronary flow is more important than coronary pressure. Eur Heart J 2015;**36**(47):3312-9a.
29. Nishi T, Kitahara H, Fujimoto Y, Nakayama T, Sugimoto K, Takahara M, Kobayashi Y. Comparison of 3-dimensional and 2-dimensional quantitative coronary angiography and intravascular ultrasound for functional assessment of coronary lesions. J Cardiol 2017;**69**(1):280-286.
30. Nakamura M, Yamagishi M, Ueno T, Hara K, Ishiwata S, Itoh T, Hamanaka I, Wakatsuki T, Sugano T, Kawai K, Akasaka T, Tanaka N, Kimura T. Prevalence of visual-functional mismatch regarding coronary artery stenosis in the CVIT-DEFER registry. Cardiovasc Interv Ther 2014;**29**(4):300-8.
31. Park SJ, Kang SJ, Ahn JM, Shim EB, Kim YT, Yun SC, Song H, Lee JY, Kim WJ, Park DW, Lee SW, Kim YH, Lee CW, Mintz GS, Park SW. Visual-functional mismatch between coronary angiography and fractional flow reserve. JACC Cardiovasc Interv 2012;**5**(10):1029-36.
32. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leesar MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. J Am Coll Cardiol 2010;**55**(25):2816-21.
33. Matsumura M, Johnson NP, Fearon WF, Mintz GS, Stone GW, Oldroyd KG, De Bruyne B, Pijls NHJ, Maehara A, Jeremias A. Accuracy of Fractional Flow Reserve Measurements in Clinical Practice: Observations From a Core Laboratory Analysis. JACC Cardiovasc Interv 2017;**10**(14):1392-1401.

# Chapter 14

# Extended Validation of Novel 3D Quantitative Coronary Angiography-Based Software to Calculate vFFR: The FAST EXTEND study

Tara Neleman, BSc[1]; **Kaneshka Masdjedi, MD[1];** Laurens J C Van Zandvoort, BSc[1]; Mariusz Tomaniak, MD[1, 2]; Jurgen M R Ligthart, RT[1]; Karen T Witberg, CCRN[1]; Alise Vermaire, RT[1]; Eric Boersma, MSc, PhD[1]; Nicolas M Van Mieghem, MD, PhD[1]; Joost Daemen, MD, PhD[1]

**[1] Department of Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands.**
**[2] First Department of Cardiology, Medical University of Warsaw, Warsaw, Poland.**

**Journal:** JACC Cardiovascular Imaging; 2020 SSN 1936-878X

Despite a strong body of evidence underpinning the superiority of fractional flow reserve (FFR) over angiography-guided percutaneous coronary intervention, FFR adoption in routine practice remains limited. [1] Eliminating the need for a pressure wire and hyperemic agent may promote its application.

In the Fast Assessment of STenosis severity (FAST) study (n = 100), we recently validated a new software tool to derive vessel FFR (vFFR) based on threedimensional–quantitative coronary angiography (3DQCA) in vitro and in vivo. [2] vFFR proved to be strongly correlated to invasive FFR (r = 0.89), showed excellent diagnostic performance in predicting FFR ≤0.80 (area under the curve [AUC]: 0.93), and had low interobserver variability (r = 0.95). However, due to its small sample size, no conclusions could be drawn on its performance in specific lesion subsets. The aims of the FAST EXTEND study were to validate vFFR in an extended cohort of patients and to evaluate its performance in more complex disease subsets.

In this retrospective cohort study, 912 consecutive patients were screened for eligibility between January 2016 and May 2018. Details on inclusion and exclusion criteria and acquisition of diagnostic angiographic projections and FFR and vFFR measurements have been previously described.[2] Ethical approval was waived for this study by the Institutional Review Board of the Erasmus Medical Center.

A total of 294 patients met the inclusion criteria. Mean age was 66 (±10.2) years and 66% of the patients was male. Clinical indication for coronary angiography was stable angina (68%), unstable angina (12%), and non–ST-segment elevation myocardial infarction (20%).

Median FFR was 0.84 (interquartile range: 0.79 to 0.90) and median vFFR was 0.85 (interquartile range: 0.80 to 0.90). Hemodynamically significant lesions (≤0.80) by FFR and vFFR were identified in 31% and 28% of patients, respectively (p = 0.13).

A strong correlation was observed between vFFR and FFR in the overall cohort (r = 0.89), in specific lesion subsets (bifurcations [24%], r = 0.90; tortuosity [18%], r = 0.90; calcified lesions [36%], r = 0.86; tandem lesions [14%], r = 0.90; and diffuse disease [41%], r = 0.91) and in specific coronary arteries (left anterior descending [58], r = 0.87; left circumflex artery [14%], r = 0.94; right coronary artery [26%], r = 0.86; and left main [3%], r = 0.86) (Spearman correlation coefficients).

Receiver operating characteristics curve analysis revealed excellent accuracy of vFFR in predicting FFR ≤0.80 (AUC: 0.94; 95% confidence interval: 0.92 to 0.97). Using a cutoff value of ≤0.80 for vFFR, sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 75%, 94%, 84%, 89%, and 88%, respectively.

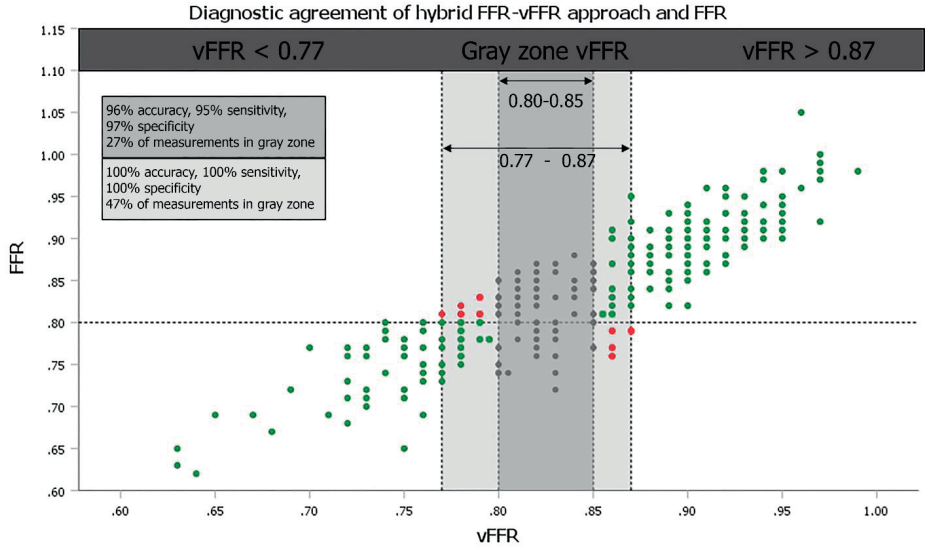



**Figure 1.** Diagnostic agreement of Hybrid FFR-vFFR approach with FFR
Two different gray zones are represented with corresponding diagnostic performance for a hybrid vFFR-FFR approach. Green dots represent agreement, red dots represent disagreement and gray dots represent measurements for the vFFR gray zone 0.80 - 0.85.
vFFR = vessel fractional flow reserve, FFR = fractional flow reserve.

vFFR cutoff values to achieve sensitivity and specificity $95% identified a vFFR "gray zone" of 0.80 to 0.85. "Gray zone" vFFR values were found in 27% of cases. Implementation of a hybrid vFFR-FFR approach with FFR evaluation in the vFFR "gray zone" resulted in 96% diagnostic accuracy, assuming that FFR is 100% accurate. A vFFR-FFR hybrid approach with 100% diagnostic accuracy resulted in a vFFR "gray zone" of 0.77 to 0.87 (47% of patients) (Figure 1).

In this extended validation study, we confirm the excellent diagnostic performance and strong correlation between vFFR and FFR, which appeared to be consistent among different vessel and anatomy subsets.

A number of alternative methods to derive FFR from coronary angiography were recently proposed and validated in a prospective manner. In FAST EXTEND a smaller gray zone for vFFR-FFR hybrid approaches (0.80 to 0.85) was found as compared with quantitative flow ratio (QAngio XA 3D, Medis,Medical Imaging System) (0.78 to 0.86) with similar diagnostic accuracy, which could be related to the influence of clinical and hemodynamic parameters on the contrast flow models used by quantitative flow ratio. [3] Alternatively, $FFR_{angio}$ (CathWorks, Ltd.) is calculated based on a reconstruction of the whole coronary tree and also has proven its diagnostic performance. [4] Yet only a limited amount of bifurcations, calcified lesions, tandem lesions, tortuosity, and no vessels with diffuse disease were included and so far no gray zone has been presented.

Limitations of our analysis include the retrospective nature of our study and the off-line vFFR assessment. Furthermore, the need to exclude 60% of patients from the analysis is also a concern and a potential limitation to the use of this technology at large scale. FAST II (NCT03791320), a prospective observational multicenter study assessing the diagnostic accuracy of vFFR calculated off-line by a blinded independent core laboratory, is addressing these limitations and is currently enrolling patients.

## REFERENCES

1. Zhang D, Lv S, Song X, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention: a meta-analysis. Heart 2015;101: 455–62.
2. Masdjedi K, van Zandvoort LJC, Balbi MM, et al. Validation of 3-dimensional quantitative coronary angiography based software to calculate fractional flow reserve: Fast Assessment of STenosis severity (FAST)-study. EuroIntervention 2019 May 14 [E-pub ahead of print].
3. Westra J, Andersen BK, Campo G, et al. Diagnostic performance of inprocedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan Study. J Am Heart Assoc 2018;7:e009603.
4. Fearon WF, Achenbach S, Engstrom T, et al. Accuracy of fractional flow reserve derived from coronary angiography. Circulation 2019;139: 477–84.

# Chapter 15

# Validation of novel 3-Dimensional Quantitative Coronary Angiography based software to calculate Fractional Flow Reserve post stenting: FAST POST-study

**Kaneshka Masdjedi, MD;** Laurens JC van Zandvoort, BSc; Matthew M Balbi, MD; Rutger-Jan Nuis, MD, PhD; Jeroen Wilschut, MD; Roberto Diletti, MD, PhD; Peter P.T. de Jaegere, MD, PhD; Felix Zijlstra, MD, PhD; Nicolas M Van Mieghem, MD, PhD; Joost Daemen, MD, PhD

**Department of cardiology, Thoraxcenter, Erasmus Medical Center**

**Journal:** Catheter Cardiovasc Interventions; 2020;1–7.

## ABSTRACT

**Objectives:** To validate novel dedicated 3D-QCA based software to calculate post PCI vessel-FFR (vFFR) in a consecutive series of patients and to assess the diagnostic accuracy and to assess inter-observer variability.

**Background:** Low post percutaneous coronary intervention (PCI) Fractional Flow Reserve (FFR) predicts future adverse cardiac events. However, FFR assessment requires the insertion of a pressure wire in combination with the use of a hyperemic agent.

**Methods**: FAST POST study is an observational, retrospective, single-center cohort study. One hundred patients presenting with stable angina or non ST- elevation myocardial infarction, who underwent post PCI FFR assessment using a dedicated microcatheter were included. Two orthogonal angiographic projections were acquired to create a 3D reconstruction of the coronary artery using CAAS workstation 8.0. vFFR was subsequently calculated using the aortic root pressure.

**Results:** Mean age was 65±12 years and 70% was male. Mean microcatheter based FFR and vFFR were 0.91±0.07 and 0.91±0.06 respectively. A good linear correlation was found between FFR and vFFR ($r = 0.88$; $p < 001$). vFFR had a higher accuracy in the identification of patients with FFR values <0.90, AUC 0.98 (95% CI: 0.96-1.00) as compared to 3D-QCA AUC 0.62 (95% CI: 0.94-0.74). Assessment of vFFR had a low inter-observer variability ($r = 0.95$; $p < 0.001$).

**Conclusion:** 3D-QCA derived post PCI vFFR correlates well with invasively measured microcatheter based FFR and has a high diagnostic accuracy to detect FFR <0.90 with low inter-observer variability.

## INTRODUCTION

In contrast to Fractional flow reserve (FFR) coronary angiography has limited ability to accurately assess the hemodynamic significance of coronary stenosis. (1-6) Furthermore, FFR post PCI is a strong and independent predictor of major adverse cardiac events (MACE) up to 2 years(7-9). However, despite unequivocal evidence supporting the use of FFR to guide clinical decision-making, adoption into routine practice has been limited and in particular FFR assessment after stenting is rarely performed. The latter illustrates the need for tools that allow simple and fast post PCI physiological assessment without the need for a pressure wire and hyperemic agent.

Vessel FFR (vFFR) as assessed by three-dimensional quantitative coronary angiography (3D-QCA) proved to have a high correlation with FFR and a high diagnostic accuracy to detect FFR ≤ 0.80 and a low inter-observer variability. (10)

The aim of the present study was to validate 3D-QCA based vFFR with microcatheter based FFR post stenting in a consecutive series of patients, assess the diagnostic accuracy to detect an FFR <0.90 and determine inter-observer variability.

## MATERIALS AND METHODS

The FAST POST (Fast Assessment of STenosis severity POST PCI) study is an observational, single-center cohort study with the aim to assess the diagnostic accuracy of offline post PCI vFFR assessment as compared to invasively measured FFR using the Acist Navvus$^{TM}$ rapid exchange FFR (ACIST Medical Systems) microcatheter.

Based on the findings of the FAST I trial (n=100), a sample of 100 patients was selected from the FFR SEARCH registry to validate post PCI vFFR. FFR SEARCH registry was a prospective registry in which FFR measurements were routinely performed after angiographically successful PCI in 1000 consecutive patients between March 2016 and May 2017. Patients referred for coronary angiography with at least one hemodynamically significant stenosis who underwent PCI with stenting were eligible. Inclusion criteria for the present study were age ≥18 years and presentation with either stable- or unstable angina or non ST-elevation myocardial infarction. Angiographic inclusion criteria study were: at least one significant stenosis in one of the epicardial coronary arteries (diameter stenosis of >70% on QCA or hemodynamically significant stenosis defined as FFR ≤0.80). Exclusion criteria were patients with ST-elevation myocardial infarction (STEMI), coronary bypass grafts (CABG), cardiogenic shock or severe hemodynamic instability and adenosine intolerance. The sample of 100 patients for the present study was derived from a consecutive cohort of the 200 most recent patients in the FFR SEARCH registry. The majority of the patients were

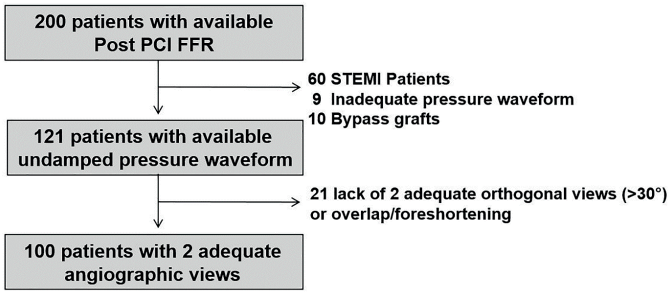



**Figure 1.** Flowchart of all included and excluded patients.

excluded due to STEMI. Furthermore, patients with inadequate pressure waveform or lack of two adequate orthogonal view to create a 3D reconstruction of the vessel, were excluded, Figure 1. The significant percentage of cases that had to be excluded due to a lack of qualifying angiograms should be put into perspective to procedures that were performed in routine practice with a lack of focus on post PCI vFFR.

All procedures were performed according to standard local routine clinical practice. FFR was 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 µg/kg/min through an antecubital vein. Post PCI FFR assessment was performed using the Acist Navvus microcatheter, 2 cm distal from the most distal stent-edge. Subsequently, two standard monoplane angiographic projections (at least 30 degrees apart, preferably orthogonal) were performed after a bolus of 200mcg nitroglycine. An additional projection was recorded with the Navvus catheter in situ to capture the position of the device. Aortic root pressure was constantly recorded, the pressure measurement taken before the start of the FFR measurement was used as input in the CAAS/vFFR software. Angiograms and pressure waveforms were stored as DICOM image format for offline analyses.

We recently reported the methodology of vFFR calculation. (10) vFFR computation was performed offline by 2 independent observers, blinded to the invasive post PCI FFR measurement, in order to assess inter-observer variability (KM, MB). A total of three 2D images, were exported to the CAAS workstation 8.0 (Pie Medical Imaging, Maastricht, the Netherlands) that used the same algorithms for vFFR computation as previously described. (10) Two views with at least 30 degrees differences in rotation/angulation to create a 3D reconstruction of the coronary arteries and one view to determine the position of the FFR pressure wire. Within CAAS Workstation vFFR the pressure drop is calculated instantaneously by applying physical laws including viscous resistance and separation loss effects present in coronary flow behavior, as described by Gould and Kirkeeide.

(11,12) The methods however are based on a single angiographic projection. Within CAAS vFFR, the geometry of the coronary artery is derived from well-validated 3D reconstructions (13,14) which reduces the effects of foreshortening, out of plane magnification and non-symmetric coronary lesions.

The two independent observers used the same cine-images for the calculation of vFFR. Although temporal alignment of the cardiac cycle between the two angiograms was performed automatically by ECG triggering, manual frame selection was allowed. Contour detecting was performed semi-automatically, delineating the vessel contour from the ostium to the most distal position of the Navvus catheter. The percent diameter stenosis, minimal lumen diameter, reference lumen diameter, minimal lumen area and lesion length were measured from the same 3D model as in which the vFFR was determined. vFFR was calculated automatically integrating the invasively measured aortic root pressure and the automatically generated 3D QCA dimensions. Based on well-validated 3D coronary reconstruction, (13,14) CAAS Workstation generated a 3D coronary reconstruction using 2 different angiographic projections. vFFR was calculated instantaneously with a proprietary algorithm which incorporates the morphology of the 3D coronary reconstruction and routinely measured real-time aortic pressure.

### Statistical analysis

Continuous variables are presented as mean ± standard deviation. All continuous variables were normally distributed. Categorical variables are expressed as counts and percentages. All statistical tests are 2-tailed. Pearson's correlation coefficient (r) was used to assess the relationship between FFR and vFFR and to assess inter-observer variability. Agreement between the indices and the inter-observer variability were assessed by Bland-Altman plots with corresponding 95% limits of agreement. Receiver-operating characteristic (ROC) area under the curve (AUC) analysis was used to estimate the diagnostic performance of both vFFR and 3D QCA-based diameter stenosis as compared to the microcatheter-based FFR with a threshold of <0.90 which has been used in previous studies as an arbitrary cut-off value to predict clinical outcome. (1,5,8) Statistical analysis was carried out using the SPSS statistical package version 24 (IBM, Armonk, North Castle, New York, USA).

## RESULTS

Baseline and procedural characteristics are summarized in **Table 1**. Mean age was 65±12 years and the majority of patients were male (70%). Diabetes was present in 21% of the cases. A prior myocardial infarction (MI) or PCI was present in 26% and 33% of the patients respectively. In 50 % of the cases, the FFR measurement was performed in the left anterior descending artery.

**Table 1.** Baseline characteristics.

| | Total N=100 |
|---|---|
| Age, y, mean±SD | 65±12 |
| Male sex, n (%) | 70 (70) |
| **Cardiovascular risk factors, n (%)** | |
| Hypertension | 59 (59) |
| Hyperlipidemia | 53 (53) |
| Diabetes Mellitus | 21 (21) |
| Current Smoker | 30 (30) |
| **Medical history and co-morbidity** | |
| Prior ACS, n (%) | 26 (26) |
| Prior PCI, n (%) | 33 (33) |
| Peripheral artery disease, n (%) | 8 (8) |
| Creatinin, µmol/L, µmol/L, Mean±SD | 99 (84) |
| Hemoglobine, (mmol/L) , Mean±SD | 8.7 (1.0) |
| BMI , Mean±SD | 24 ± 4 |
| **Measured vessel, n (%)** | |
| Left main stem | 6 (6) |
| Left anterior descending artery | 50 (50) |
| Left circumflex artery | 22 (22) |
| Right coronary artery | 22 (22) |
| **3D- Quantitative Coronary Angiography, mean±SD** | |
| Lesion length, mm | 10.5±10 |
| Minimal lumen diameter, mm | 2.7±0.7 |
| Reference vessel diameter, mm | 3.0±0.6 |
| Diameter stenosis, % | 11±15 |
| **Indices, mean±SD** | |
| Pd/Pa | 0.96 (0.04) |
| FFR | 0.91 (0.07) |
| vFFR | 0.91 (0.06) |

Values are n, mean±SD of n (%); ACS =Acute coronary syndrome; BMI= Body Mass Index; FFR= Fractional Flow Reserve; PCI = Percutaneous coronary intervention; SD = Standard deviation; vFFR= vessel Fractional Flow Reserve.

Mean 3D QCA-based diameter stenosis post PCI was 11±15% with a reference vessel diameter of 3.0±0.6 mm.

Mean distal coronary artery pressure to mean aortic pressure in the resting state during the whole cardiac cycle (Pd/Pa) was 0.96 ±0.04. Mean FFR and vFFR were 0.91±0.07 and 0.91±0.06 respectively**, Table 1**. A good linear correlation was found between FFR and vFFR (r =0.88; p<001), **Figure 2**. Assessment of vFFR had a low inter-observer variability (r =0.95; p<0.001), **Figure 3**.

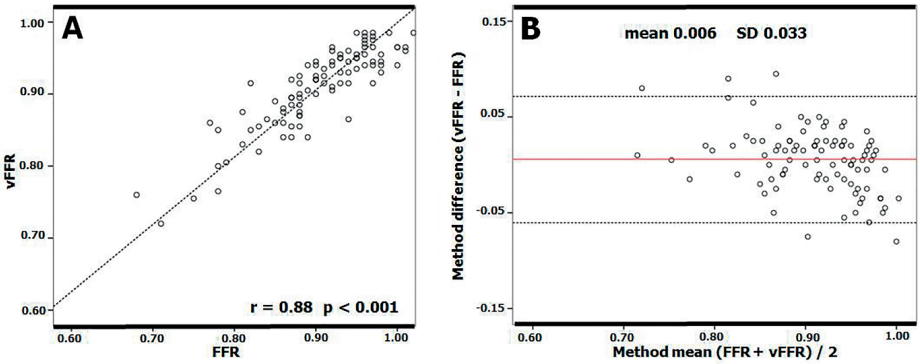



**Figure 2.** Scatter Plot showing the relationship between vessel-FFR (vFFR) and invasive measured FFR using a rapid exchange microcatheter (FFR) **(A)** and Bland- Altman plots of differences against the means **(B)**. The mean bias is represented by the solid red line and the 95% confidence interval is represented by the dashed lines.

FFR = Fractional Flow Reserve; vFFR = Vessel Fractional Flow Reserve.

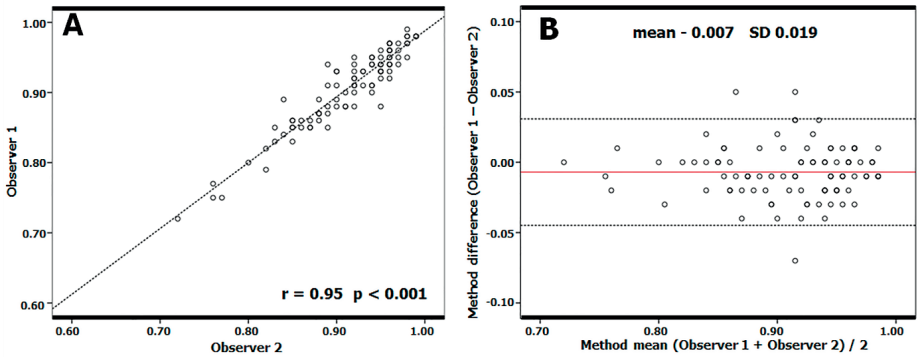



**Figure 3.** Scatter Plot **(A)** and Bland- Altman Analysis of inter-observer variability **(B)**. The mean bias is represented by the solid red line and the 95% confidence interval is represented by the dashed lines.

vFFR had a higher accuracy in the identification of patients with FFR values <0.90, AUC 0.98 (95% CI: 0.96-1.00) as compared to 3D-QCA AUC 0.62 (95% CI: 0.94-0.74), **Figure 4**.

A vFFR threshold of <0.90 was associated with a sensitivity and specificity of 80% and 97% respectively to identify FFR <0.90. The positive predictive value (PPV) and negative predictive value (NPV) were 94 % and 88% respectively.

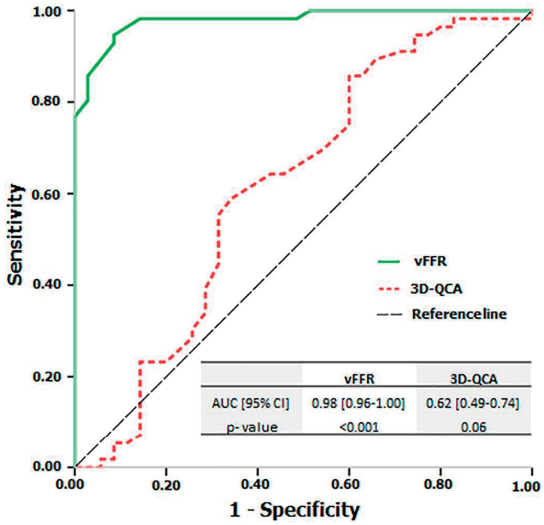



**Figure 4.** ROC Curves for vFFR and 3D-QCA. Comparison is made with an FFR at a cut point of 0.89. Abbreviations as in Table 1. 3D-QCA = Three dimensional quantitative coronary angiography; vFFR = Vessel Fractional Flow Reserve.

## DISCUSSION

The main findings of the FAST POST study can be summarized as follows: 1) vFFR allows to identify post PCI FFR <0.90 with a high **diagnostic** accuracy 2) vFFR, showed good correlation and agreement with post PCI FFR as measured using a dedicated microcatheter and 3) post PCI vFFR computation has a low inter-observer variability.

Pre-PCI FFR has become an important tool in detecting hemodynamically significant lesions in patients with stable and unstable coronary artery disease and FFR-guided PCI proved to significantly improve PCI outcomes as compared to angiography guided PCI alone. (4,5,15-17)

There has been increasing interest in the assessment of post PCI FFR since several studies demonstrated an increased risk of MACE in patient with low pressure wire- based post-PCI FFR. In contrast to the generally accepted pre PCI FFR cut off of 0.80, there is at present no generally accepted number related to post PCI assessment. Previous studies however demonstrated that the optimal threshold to predict clinical outcome appeared to be around 0.90. (18-26) The clinical relevance of the latter was recently strengthened by the results of the FFR-SEARCH registry, the largest microcatheter-based post PCI FFR study thus far, demonstrating that up to 56% of the patients had at least one lesion with a post PCI FFR ≤0.90 despite adequate angiographic results. (27) Almost 11% of the patients had at least one lesion with a post PCI FFR ≤0.80, a number that confirmed previous studies showing post PCI FFR rates ≤0.80 in 6 to 9.5% of the cases but was

significantly higher as compared to findings from the DK-CRUSH VII study (4%). (18) 22 (28) Two more recent studies conversely showed post PCI FFR rates ≤0.80 in even 18.5% and 36.5% of the cases respectively. (29,30) Differences in these rates have been explained by differences in baseline characteristics and linked to more complex lesion phenotypes like bifurcations, extensive calcification and diffuse disease, CTO, LAD lesions or in-stent restenosis (low post PCI FFR) and prior MI, presence of diabetes or presentation with ACS (higher post PCI FFR) . Finally, clear differences might arise from the position of the pressure sensor distal to the stented segment. In the present study post PCI FFR was measured 2cm distal from the most distal stent edge whereas in the studies of Uretsky et al and Lee et al, the pressure wire was advanced to the distal artery with the pressure transducer at a site with a diameter large enough to accept a currently available stent (≥2 mm).

A dedicated IVUS substudy of FFR-SEARCH demonstrated that residual proximal or distal lesions, or stent related problems including underexpansion, malapposition and edge dissections or hematomas were present in 84% of the patients with a post PCI FFR ≤0.85, despite adequate angiographic results. (31)

Nevertheless, despite strong recommendations and increasing evidence on the cost-effectiveness of FFR in case of pre-treatment lesion assessment, FFR is still underused in clinical practice.(32,33) This reality has been linked to reimbursement issues, the need for hyperemic agents like adenosine and possible concomitant adverse events like dyspnea, chest pain, rhythm disturbances and hypotension.(34,35) Although, the use of post PCI iFR has emerged as a non-hyperemic faster and easier method to evaluate post stenting physiological results, the need for a pressure wire remains a fact. (36) Moreover, in a number of cases, pressure wires that are used pre procedurally might get damaged and are often replaced during the course of the PCI which mitigates their user-friendliness in a post PCI setting. While the use of FFR microcatheters might solve part of this issue, the search towards less invasive methods to assess coronary physiology continues and several studies assessed the potential value of FFR derived from three-dimensional quantitative coronary angiography (3D-QCA) and computational flow modeling.(37,38)

In the FAST I study we recently demonstrated a good correlation between vFFR using CAAS 8.0 and pre PCI FFR measured using a conventional pressure wire along with a low inter-observer variability. (10) Similar results were found in the FAVOR studies using computational approaches to derive FFR from diagnostic coronary angiography (QFR) based on frame counting and contrast flow models as well as $FFR_{angio,}$ (CathWorks) which allows functional angiographic mapping of the entire coronary tree. (39-41) The PIONEER QFR substudy assessed the difference of QFR immediately post stenting and at nine months follow up between two different drug eluting stents and reported that the QFR did not differ between the groups. (42) The HAWKEYE study investigated the prognostic value of post PCI QFR and reported that lower values of post stenting QFR predict

clinical outcome.(43) However, in none of both studies pressure wire or microcatheter based FFR data were available as a reference. The present study is the first to validate vFFR against microcatheter based FFR in a post PCI setting. In the present study we were able to show an excellent correlation between vFFR and invasively measured FFR using a dedicated microcatheter and a high diagnostic accuracy to detect post PCI FFR <0.90. Interestingly, given the fact that the present population solely consisted of patients with optimal angiographic results, vFFR proved to be <0.90 in 41% of the cases. The present findings are at clear odds with recently reported data by Pizzato et al. who reported a weak correlation between vFFR and pressure wire based FFR. (44) However, several methodological and anatomic differences between both studies should be highlighted. At first, vFFR computation is based on aortic pressure. No mentioning about this step was made by Pizzato et al. It is unlikely the authors were able to retrospectively retrieve accurate real-time aortic pressures from >50 centers. If inadequate, a poorer correlation could be explained. Second, angiographic lesion severity was clearly different in both studies (53% vs. 37% in FAST I). The latter is however less likely to explain potential differences in accuracy.

Based on the results of the present study, the calculation of post stenting vFFR using the CAAS Workstation could be a useful tool to identify and potentially optimize the outcomes of patients at higher risk for future adverse cardiac events. Previous studies have shown that post stenting FFR reclassified 20% of angiographically satisfactory lesions, which required further intervention thereby providing an opportunity for complete functional optimization at the time of the index procedure. (45) Larger clinical outcome studies are warranted to assess the practicalities and value of angiography based post PCI FFR and its potential to optimize long-term outcomes.

## LIMITATIONS

Our study reflects a single-center experience with a relatively small patient sample size. The vFFR was compared to FFR using the Acist Navvus microcatheter. Microcatheter based FFR correlated well with conventional pressure-wire wire based FFR. The latter findings should be interpreted in the light of a known overestimation of microcatheter based FFR as compared to routine pressure wire based FFR recordings of approximately 0.03 reported in previous studies that was mainly linked to larger differences in smaller caliber vessels. (46,47) Furthermore, vFFR calculation was performed off-line by two independent observers, there was no independent core-lab involved. Both online and independent corelab adjudication of vFFR will be performed in the ongoing international multicenter FAST II study (ClinicalTrials.gov ID: NCT03791320). Furthermore, the accuracy of the technique is strongly dependent on the quality of the angiographic cine-images. Image acquisition should meet the criteria of non-overlapping images with at least 30 degrees differences in angulation. Although these are pre-requisites that theoretically should be fulfilled in all pre procedural angiographies, previous studies showed that up to 65% of routine angio-

grams are of insufficient quality to be used in angiography-based FFR software due to insufficient luminal contrast opacification, overlap or lack of adequate orthogonal views. Also costs of angio based FFR are currently a topic of debate between software vendors, hospitals and health care reimbursement plans. No definitive universal pricing models have been made for the different software packages available. Finally, the average FFR in the present cohort was relatively high, directly related to the post PCI nature of the patient cohort. Yet, still 41% had a post PCI vFFR of <0.90.

## CONCLUSION

The 3D-QCA derived vFFR post PCI correlates well with invasively measured microcatheter based FFR and has a high diagnostic accuracy to detect FFR <0.90 with low inter-observer variability.

## REFERENCES

1. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N and others. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367(11):991-1001.
2. Lindstaedt M, Spiecker M, Perings C, Lawo T, Yazar A, Holland-Letz T, Muegge A, Bojara W, Germing A. How good are experienced interventional cardiologists at predicting the functional significance of intermediate or equivocal left main coronary artery stenoses? Int J Cardiol 2007;120(2):254-61.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ and others. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2018.
4. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W and others. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol 2007;49(21):2105-11.
5. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG and others. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360(3):213-24.
6. Tu S, Echavarria-Pinto M, von Birgelen C, Holm NR, Pyxaras SA, Kumsars I, Lam MK, Valkenburg I, Toth GG, Li Y and others. Fractional flow reserve and coronary bifurcation anatomy: a novel quantitative model to assess and report the stenosis severity of bifurcation lesions. JACC Cardiovasc Interv 2015;8(4):564-74.
7. Wolfrum M, Fahrni G, de Maria GL, Knapp G, Curzen N, Kharbanda RK, Fröhlich GM, Banning AP. Impact of impaired fractional flow reserve after coronary interventions on outcomes: a systematic review and meta-analysis. BMC Cardiovascular Disorders 2016;16(1):177.
8. Rimac G, Fearon WF, De Bruyne B, Ikeno F, Matsuo H, Piroth Z, Costerousse O, Bertrand OF. Clinical value of post-percutaneous coronary intervention fractional flow reserve value: A systematic review and meta-analysis. Am Heart J 2017;183:1-9.
9. Kasula S, Agarwal SK, Hacioglu Y, Pothineni NK, Bhatti S, Ahmed Z, Uretsky B, Hakeem A. Clinical and prognostic value of poststenting fractional flow reserve in acute coronary syndromes. Heart 2016;102(24):1988-1994.
10. Masdjedi K, van Zandvoort LJC, Balbi MM, Gijsen FJH, Ligthart JMR, Rutten MCM, Lemmert ME, Wilschut J, Diletti R, De Jaegere P and others. Validation of 3-Dimensional Quantitative Coronary Angiography based software to calculate Fractional Flow Reserve: Fast Assessment of STenosis severity (FAST)-study. EuroIntervention 2019.
11. Gould KL, Kelley KO, Bolson EL. Experimental validation of quantitative coronary arteriography for determining pressure-flow characteristics of coronary stenosis. Circulation 1982;66(5):930-7.
12. Kirkeeide R. Coronary obstructions, morphology and physiologic significance. 1991:229–44.
13. Girasis C, Schuurbiers JC, Muramatsu T, Aben JP, Onuma Y, Soekhradj S, Morel MA, van Geuns RJ, Wentzel JJ, Serruys PW. Advanced three-dimensional quantitative coronary angiographic assessment of bifurcation lesions: methodology and phantom validation. EuroIntervention 2013;8(12):1451-60.
14. Schuurbiers JC, Lopez NG, Ligthart J, Gijsen FJ, Dijkstra J, Serruys PW, Van der Steen AF, Wentzel JJ. In vivo validation of CAAS QCA-3D coronary reconstruction using fusion of angiography and intravascular ultrasound (ANGUS). Catheter Cardiovasc Interv 2009;73(5):620-6.
15. Berger A, Botman KJ, MacCarthy PA, Wijns W, Bartunek J, Heyndrickx GR, Pijls NH, De Bruyne B. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. J Am Coll Cardiol 2005;46(3):438-42.

16. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, van't Veer M, Klauss V, Manoharan G, Engstrom T and others. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 2010;56(3):177-84.
17. Sels JW, Tonino PA, Siebert U, Fearon WF, Van't Veer M, De Bruyne B, Pijls NH. Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. JACC Cardiovasc Interv 2011;4(11):1183-9.
18. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, Escaned J, Tsurumi Y, Akasaka T, Samady H and others. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation 2002;105(25):2950-4.
19. Johnson NP, Toth GG, Lai D, Zhu H, Acar G, Agostoni P, Appelman Y, Arslan F, Barbato E, Chen SL and others. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. J Am Coll Cardiol 2014;64(16):1641-54.
20. Ishii H, Kataoka T, Kobayashi Y, Tsumori T, Takeshita H, Matsumoto R, Shirai N, Nishioka H, Hasegawa T, Nakata S and others. Utility of myocardial fractional flow reserve for prediction of restenosis following sirolimus-eluting stent implantation. Heart Vessels 2011;26(6):572-81.
21. Nam CW, Hur SH, Cho YK, Park HS, Yoon HJ, Kim H, Chung IS, Kim YN, Kim KB, Doh JH and others. Relation of fractional flow reserve after drug-eluting stent implantation to one-year outcomes. Am J Cardiol 2011;107(12):1763-7.
22. Agarwal SK, Kasula S, Almomani A, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Clinical and angiographic predictors of persistently ischemic fractional flow reserve after percutaneous revascularization. Am Heart J 2017;184:10-16.
23. Doh JH, Nam CW, Koo BK, Lee SY, Choi H, Namgung J, Kwon SU, Kwak JJ, Kim HY, Choi WH and others. Clinical Relevance of Poststent Fractional Flow Reserve After Drug-Eluting Stent Implantation. J Invasive Cardiol 2015;27(8):346-51.
24. Kimura Y, Tanaka N, Okura H, Yoshida K, Akabane M, Takayama T, Hirayama A, Tada T, Kimura T, Takano H and others. Characterization of real-world patients with low fractional flow reserve immediately after drug-eluting stents implantation. Cardiovasc Interv Ther 2016;31(1):29-37.
25. Leesar MA, Satran A, Yalamanchili V, Helmy T, Abdul-Waheed M, Wongpraparut N. The impact of fractional flow reserve measurement on clinical outcomes after transradial coronary stenting. EuroIntervention 2011;7(8):917-23.
26. Wolfrum M, Fahrni G, de Maria GL, Knapp G, Curzen N, Kharbanda RK, Frohlich GM, Banning AP. Impact of impaired fractional flow reserve after coronary interventions on outcomes: a systematic review and meta-analysis. BMC Cardiovasc Disord 2016;16(1):177.
27. van Bommel RJ, Masdjedi K, Diletti R, Lemmert ME, van Zandvoort L, Wilschut J, Zijlstra F, de Jaegere P, Daemen J, van Mieghem NM. Routine Fractional Flow Reserve Measurement After Percutaneous Coronary Intervention. Circ Cardiovasc Interv 2019;12(5):e007428.
28. Li SJ, Ge Z, Kan J, Zhang JJ, Ye F, Kwan TW, Santoso T, Yang S, Sheiban I, Qian XS and others. Cutoff Value and Long-Term Prediction of Clinical Events by FFR Measured Immediately After Implantation of a Drug-Eluting Stent in Patients With Coronary Artery Disease: 1- to 3-Year Results From the DKCRUSH VII Registry Study. JACC Cardiovasc Interv 2017;10(10):986-995.
29. Uretsky BF, Agarwal SK, Vallurupalli S, Al-Hawwas M, Hasan R, Miller K, Hakeem A. Prospective Evaluation of the Strategy of Functionally Optimized Coronary Intervention. J Am Heart Assoc 2020;9(3):e015073.

30. Lee JM, Hwang D, Choi KH, Rhee TM, Park J, Kim HY, Jung HW, Hwang JW, Lee HJ, Jang HJ and others. Prognostic Implications of Relative Increase and Final Fractional Flow Reserve in Patients With Stent Implantation. JACC Cardiovasc Interv 2018;11(20):2099-2109.
31. van Zandvoort LJC, Masdjedi K, Witberg K, Ligthart J, Tovar Forero MN, Diletti R, Lemmert ME, Wilschut J, de Jaegere PPT, Boersma E and others. Explanation of Postprocedural Fractional Flow Reserve Below 0.85. Circ Cardiovasc Interv 2019;12(2):e007030.
32. Siebert U, Arvandi M, Gothe RM, Bornschein B, Eccleston D, Walters DL, Rankin J, De Bruyne B, Fearon WF, Pijls NH and others. Improving the quality of percutaneous revascularisation in patients with multivessel disease in Australia: cost-effectiveness, public health implications, and budget impact of FFR-guided PCI. Heart Lung Circ 2014;23(6):527-33.
33. van Nunen LX, Zimmermann FM, Tonino PA, Barbato E, Baumbach A, Engstrom T, Klauss V, MacCarthy PA, Manoharan G, Oldroyd KG and others. Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial. Lancet 2015;386(10006):1853-60.
34. Gotberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson SE, Ohagen P, Olsson H, Omerovic E and others. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N Engl J Med 2017;376(19):1813-1823.
35. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, Bhindi R, Lehman SJ, Walters D, Sapontis J and others. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med 2017;376(19):1824-1834.
36. Jeremias A, Davies JE, Maehara A, Matsumura M, Schneider J, Tang K, Talwar S, Marques K, Shammas NW, Gruberg L and others. Blinded Physiological Assessment of Residual Ischemia After Successful Angiographic Percutaneous Coronary Intervention: The DEFINE PCI Study. JACC Cardiovasc Interv 2019;12(20):1991-2001.
37. Tu S, Barbato E, Koszegi Z, Yang J, Sun Z, Holm NR, Tar B, Li Y, Rusinaru D, Wijns W and others. Fractional flow reserve calculation from 3-dimensional quantitative coronary angiography and TIMI frame count: a fast computer model to quantify the functional significance of moderately obstructed coronary arteries. JACC Cardiovasc Interv 2014;7(7):768-77.
38. Papafaklis MI, Muramatsu T, Ishibashi Y, Lakkas LS, Nakatani S, Bourantas CV, Ligthart J, Onuma Y, Echavarria-Pinto M, Tsirka G and others. Fast virtual functional assessment of intermediate coronary lesions using routine angiographic data and blood flow simulation in humans: comparison with pressure wire - fractional flow reserve. EuroIntervention 2014;10(5):574-83.
39. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, Nef H, Tebaldi M, Murasato Y, Lansky A and others. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. JACC Cardiovasc Interv 2016;9(19):2024-2035.
40. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, Guo L, Sun Z, Li Z, Tian F and others. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. J Am Coll Cardiol 2017;70(25):3077-3087.
41. Fearon WF, Achenbach S, Assali TEA, Jeremias RSA, Fournier S, Kirtane AJ, Kornowski R, Greenberg G, Jubeh R, Kolansky DM and others. Accuracy of Fractional Flow Reserve Derived From Coronary Angiography. Ciculation 2018.
42. Asano T, Katagiri Y, Collet C, Tenekecioglu E, Miyazaki Y, Sotomi Y, Amoroso G, Aminian A, Brugaletta S, Vrolix M and others. Functional comparison between the BuMA Supreme biodegradable polymer sirolimus-eluting stent and a durable polymer zotarolimus-eluting coronary stent using quantitative flow ratio: PIONEER QFR substudy. EuroIntervention 2018;14(5):e570-e579.

43. Biscaglia S, Tebaldi M, Brugaletta S, Cerrato E, Erriquez A, Passarini G, Ielasi A, Spitaleri G, Di Girolamo D, Mezzapelle G and others. Prognostic Value of QFR Measured Immediately After Successful Stent Implantation: The International Multicenter Prospective HAWKEYE Study. JACC Cardiovasc Interv 2019;12(20):2079-2088.
44. Ely Pizzato P, Samdani AJ, Vergara-Martel A, Palma Dallan LA, Tensol Rodrigues Pereira G, Zago E, Zimin V, Grando Bezerra H. Feasibility of coronary angiogram-derived vessel fractional flow reserve in the setting of standard of care percutaneous coronary intervention and its correlation with invasive FFR. Int J Cardiol 2020;301:45-49.
45. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv 2016;9(10):1022-31.
46. Beygui F, Lemaitre A, Bignon M, Wain-Hobson J, Briet C, Ardouin P, Sabatier R, Parienti JJ, Blanchart K, Roule V. A head-to-head comparison of three coronary fractional flow reserve measurement technologies: The fractional flow reserve-device study. Catheter Cardiovasc Interv 2019.
47. Menon M, Jaffe W, Watson T, Webster M. Assessment of coronary fractional flow reserve using a monorail pressure catheter: the first-in-human ACCESS-NZ trial. EuroIntervention 2015;11(3):257-63.

# Chapter 16

# Coronary angiography-based vessel Fractional Flow Reserve for Fast Physiologic Assessment of Stenosis severity: the FAST II study

**Kaneshka Masdjedi, MD[1];** Nobuhiro Tanaka, MD, PhD[2] ; Eric Van Belle, MD, PhD[3] ; Sina Porouchani, MD[3]; Axel Linke, MD, PhD[4 5]; Felix J Woitek, MD, PhD[4]; Antonio L Bartorelli, MD, PhD[6] ; Ziad A. Ali, MD, DPhil[7 8] ; Wijnand K den Dekker, MD, PhD[1] ; Jeroen Wilschut, MD[1] ; Roberto Diletti, MD, PhD[1]; Felix Zijlstra, MD, PhD[1] ; Eric Boersma, MD, PhD[1] ; Nicolas M Van Mieghem, MD, PhD[1]; Ernest Spitzer, MD, PhD[1 9]; Joost Daemen, MD, PhD[1]**. And the FAST II Study Investigators.**

[1] Department of Cardiology, Erasmus Medical Center, The Netherlands

[2] Department of Cardiology, Tokyo Medical University, Hachioji Medical Center, Japan

[3] CHU Lille, Institut Cœur Poumon, Cardiology, Department of Interventional Cardiology for Coronary, Valves and Structural Heart Diseases, Inserm, U1011, Institut Pasteur de Lille, EGID, Université de Lille, Lille, France

[4] Technische Universität Dresden, University Clinic, Department of Internal Medicine/ Cardiology

[5] Dresden Cardiovascular Research Institute and Core Laboratories, Dresden, Germany

[6] Department of Cardiology, Centro Cardiologico Monzino, Italy

[7] Department of Cardiology, Columbia University, USA

[8] DeMatteis Cardiovascular Institute, St Francis Hospital & Heart Center, USA

[9] Cardialysis BV, Rotterdam, The Netherlands

**Journal: Submitted**

## ABSTRACT

**Background:** Fractional flow reserve (FFR)- guided percutaneous coronary intervention (PCI) is superior to angiography-guided PCI. However, the clinical uptake of FFR has been limited by the need to instrument the coronary artery, additional procedural costs and time and the need for hyperemic agents which can cause patient discomfort. FFR derived from routine coronary angiography eliminates these issues.

**Aim:** To assess the diagnostic performance and accuracy of three-dimensional quantitative coronary angiography (3D-QCA) based vessel FFR (vFFR) compared to pressure wire-based FFR (≤0.80).

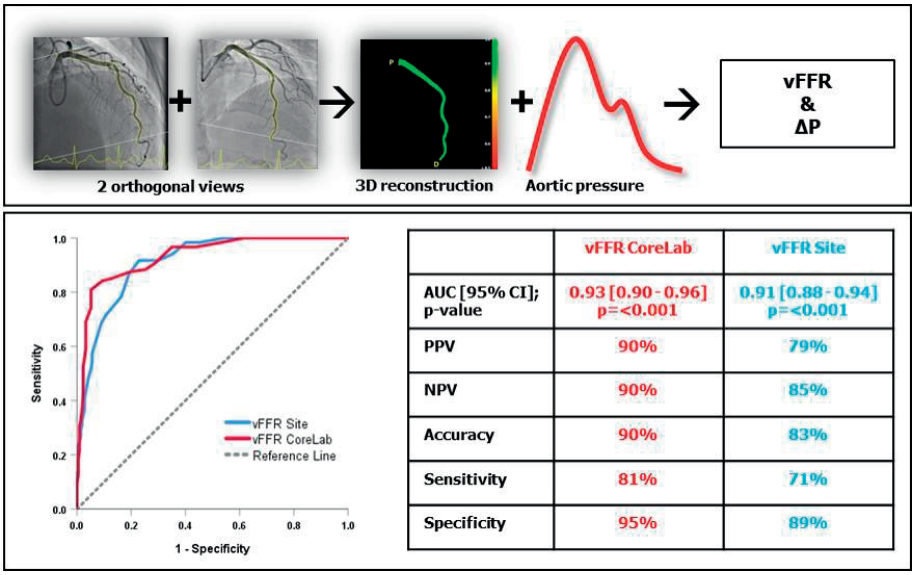
**Methods:** The FAST II (Fast Assessment of STenosis severity) study was a prospective observational multicenter study designed to evaluate the diagnostic accuracy of vFFR compared to the reference standard (pressure wire-based FFR ≤0.80). A total of 334 patients from 6 centers were enrolled. Both site-determined and blinded independent CoreLab vFFR measurements were compared to FFR .

**Results:** The CoreLab vFFR was 0.83±0.09 and pressure wire-based FFR 0.83±0.08. A good correlation was found between CoreLab vFFR and pressure wire-based FFR (R=0.74; p<0.001; mean bias 0.0029±0.0642). vFFR had an excellent diagnostic accuracy in identifying lesions with an invasive wire-based FFR≤0.80 (AUC 0.93; 95% CI [0.90-0.96]; p<0.001). Positive predictive value, negative predictive value, diagnostic accuracy, sensitivity and specificity of vFFR were 90%, 90%, 90%, 81% and 95% respectively.

**Conclusion:** 3D-QCA-based vFFR has excellent diagnostic performance to detect FFR ≤0.80.

The study was registered on clinicaltrials.gov under identifier NCT03791320.

**Keywords:** Coronary physiology, Fractional Flow Reserve, 3D-QCA




| | vFFR CoreLab | vFFR Site |
|---|---|---|
| AUC [95% CI]; p-value | 0.93 [0.90 - 0.96] p=<0.001 | 0.91 [0.88 - 0.94] p=<0.001 |
| PPV | 90% | 79% |
| NPV | 90% | 85% |
| Accuracy | 90% | 83% |
| Sensitivity | 81% | 71% |
| Specificity | 95% | 89% |

**CENTRAL ILLUSTRATION**

## INTRODUCTION

Contemporary guidelines have adopted the importance of physiological assessment of intermediate coronary artery lesions. [1] Numerous randomized controlled trials support the superiority of a FFR- versus angiography-guided approach to percutaneous coronary intervention (PCI). An FFR guided approach has been shown to reduce the number of stents, repeat revascularization, myocardial infarction and cost [2-5]. Despite a growing body of evidence, the use of FFR in clinical practice remains limited. Instrumentation of the coronary artery, consumable costs and patient discomfort related to hyperemia are some of the presumed hurdles to greater adoption.[6] Moreover, multi-vessel FFR is performed very infrequently, even in the presence of multiple intermediate lesions, due to the added time, risk and equipment changes required. We recently demonstrated in two retrospective single center studies (FAST I (Fast Assessment of STenosis severity) and FAST Extend) the feasibility and diagnostic accuracy of a novel 3-dimensional Quantitative Coronary Angiography (3D-QCA) based software tool to calculate vessel FFR (vFFR) as a more patient patient-friendly alternative to invasive physiology.[7, 8] The aim of the present multicenter, observational FAST II study was to prospectively assess the performance and accuracy of vFFR for the prediction of invasive pressure wire-based FFR, assessed in a blinded core laboratory.

## METHODS

### Study design and study population

The FAST II (Fast Assessment of STenosis severity) study was a prospective, international multicenter study designed to evaluate the diagnostic accuracy of offline vFFR in identifying physiologically-significant coronary artery disease (CAD) by using invasive pressure wire-based FFR (≤0.80) as the reference standard. The study protocol was approved by the local ethics committee of all participating sites and was conducted in accordance with Good Clinical Practices and in accordance with the Declaration of Helsinki (64$^{th}$ WMA General Assembly, Fortaleza, Brazil, October 2013). All patients provided written informed consent. The study was registered on clinicaltrials.gov under identifier NCT03791320.

Patients presenting with chronic coronary syndromes, unstable angina or non-ST elevation acute coronary syndrome (NSTEMI) undergoing diagnostic coronary angiography and/or PCI with an indication to perform invasive pre-PCI FFR assessment of coronary artery lesions were included. One vessel per patient was included in the study. Clinical exclusion criteria included ST-elevation myocardial infarction (STEMI) at presentation, previous coronary artery bypass graft (CABG), cardiogenic shock or severe hemodynamic instability and adenosine intolerance. Angiographic exclusion criteria included ostial left main (LM) or ostial right coronary artery (RCA) lesions, thrombus containing lesions and excessive overlap or tortuosity precluding vFFR computation.

## Study procedures

All procedures were performed according to standard clinical practice. Aortic root pressure measured at the catheter tip was recorded at the start of the FFR procedure in all cases. Pressure wire based FFR (Aeris™ Abbott) was performed in intermediate coronary lesions (defined as diameter stenosis of 30-70% by visual assessment). Angiographic lesion severity was assessed by two angiographic projections (at least 30 degrees apart, preferably orthogonal) after a bolus of 200mcg intracoronary nitroglycine. FFR measurements were performed under maximum hyperemia achieved by either intra coronary bolus of adenosine (200µg in the LCA and 100µg in the RCA) or continuous intravenous infusion of adenosine at a rate of 140 µg/kg/min through an antecubital vein for at least 2 minutes. FFR was defined as mean distal coronary artery pressure divided by mean aortic pressure during maximal hyperemia. One additional projection was recorded to capture the position of the pressure wire. Angiograms and pressure waveforms were stored as DICOM images format for offline analyses.

## 3D coronary reconstruction and computation of vFFR

All angiographic images, hemodynamic data including invasively measured aortic pressure and pressure waveform tracings were anonymized and sent to an independent-blinded core laboratory (Cardialysis B.V., Rotterdam, The Netherlands) for offline analysis. In addition, computation of vFFR was performed offline and assessed blinded by trained observers in the participating sites. A total of 3, two-dimensional images were exported to the CAAS workstation 8.2 (Pie Medical Imaging, Maastricht, the Netherlands): two orthogonal views to create a 3D reconstruction of the coronary arteries and one view to ascertain the position of the FFR pressure wire. Table movement during cine-angio acquisition was not allowed. Temporal alignment of the two orthogonal view phases in the cardiac cycle were performed automatically by ECG triggering. End diastolic frames were identified automatically. Contour detecting was performed automatically, delineating the vessel contour from the ostium to the position at which the pressure wire sensor was positioned (3 cm from the tip). Manual correction was allowed in case of suboptimal automatic contour detection following a standard operating procedure. Percent diameter stenosis, minimal lumen diameter, reference lumen diameter, minimal lumen area and lesion length were derived from the same 3D-QCA model from which the vFFR was derived. vFFR was calculated automatically using the invasively measured aortic root pressure as an input boundary condition, **Figure 1**.

Within CAAS Workstation vFFR the pressure drop is calculated instantaneously by applying physical laws including viscous resistance and separation loss effects present in coronary flow behavior, as described by Gould and Kirkeeide. [9, 10]. Vessel geometry was derived from well-validated 3D reconstructions [11, 12] reducing the effects of foreshortening, out of plane magnification and non-symmetric coronary lesions.

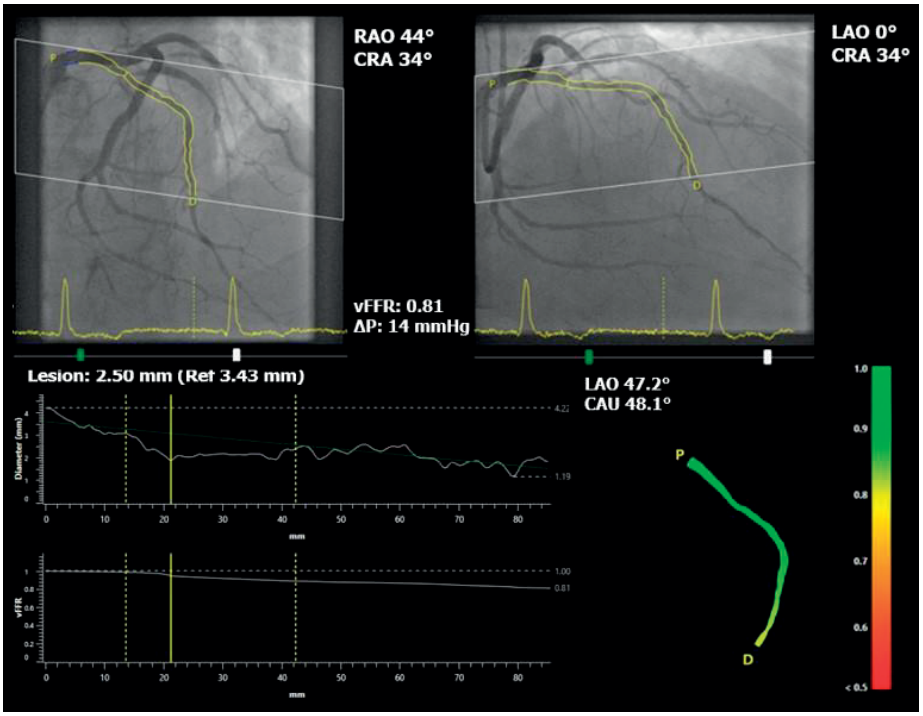



**Figure 1.** Three-dimensional reconstruction of coronary artery and computation of vessel-FFR, using 2 angiographic projections with at least 30 degrees apart and invasively measured aortic root pressure.

## Study endpoints

vFFR recordings were assessed offline by a blinded core laboratory. FFR was site reported and quality of wave-forms were centrally reviewed by the steering committee. While evaluating FFR, personnel was blinded for vFFR measurements and vice versa, as well as for any other patient-related data. The primary endpoint was the diagnostic accuracy of CoreLab defined offline vFFR to identify a physiologically significant coronary stenosis, defined as a lesion with invasive FFR ≤0.80. Key secondary endpoint was the diagnostic accuracy of site-determined vFFR to identify invasive FFR ≤0.80.

## Sample size

Sample size calculations were performed based on the results of the FAST I study in which 42% of the patients had a positive FFR defined as invasive FFR ≤0.80.[7] A vFFR threshold of 0.83 was associated with a sensitivity of 90% to identify FFR≤0.80 and a specificity of 77%. We aimed to confirm these findings and describe the sensitivity and specificity of vFFR to identify FFR≤0.80 in the target population with a 95% confidence interval (CI) of ±5%. Based on these data, we aimed to enroll a total of 330 patients (±140 with FFR ≤0.80).

### Statistical analysis

Normality of continuous variables is evaluated by visual inspection of histograms, and by Shapiro-Wilk tests. Variables with normal distribution are then presented as mean ± standard deviation (SD), while variables with non-normal distributions are reported as median (25th-75th percentile). Categorical variables are expressed as counts and percentages. The relation between vFFR and FFR was visualized in a scatter plot, and quantified as Pearson's correlation coefficient (r). The agreement between both indices, as well as the agreement between on-site (investigator) and offline (CoreLab) vFFR, was assessed by Bland-Altman plots with corresponding 95% limits of agreement. Receiver-operating characteristic (ROC) curves were plotted to visualize the diagnostic performance of vFFR for FFR≤80, whereas the area under the curve (AUC) was calculated. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were then determined for vFFR≤0.80 to predict FFR≤0.80. We present these metrics with corresponding 95% CI. Statistical analyses were performed using the SPSS statistical package version 24 (IBM, Armonk, North Castle, New York, USA). P-values are two-sided (unless specified otherwise), whereas a P-values <0.05 was considered statistically significant.

## RESULTS

### Enrolment

Participating sites were located in Europe, the United States and Japan and enrolled a total of 391 patients between October 2018 and September 2020. A total of 54 patients were excluded due to angiographic exclusion criteria including overlap (n=18), poor angiography quality (n=13), table movement during cine-angio acquisition (n=9), foreshortening (n=7), ostial lesions (n=5) and unknown position of the pressure wire (n=2). Three additional patients were excluded due

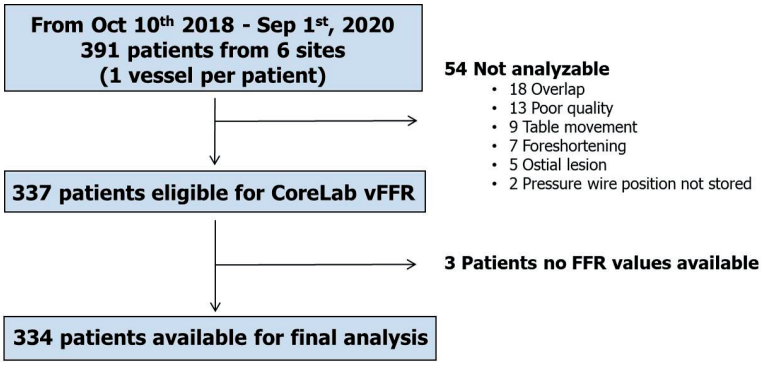



**Figure 2.** Flowchart of all included and excluded patients.

to absence of the FFR value, leaving a total of 334 patients (1 vessel per patient) for the final analysis. **Figure 2**.

## Patients and procedural data

Patient and procedural characteristics are reported in **Table 1**. Mean age was 66± 12 years and 73% of patients were male. The majority of patients had hypertension (72%), 27% were diabetic and 88% presented with stable- or unstable angina. Target vessels were left anterior descending arteries in 66%, left circumflex arteries in 9% and right coronary arteries in 25%. Mean % diameter stenosis was 42±11%, lesion length 20±13mm and minimal lumen diameter 1.69±0.40mm. The majority of the vessels had focal lesion (72%) and bifurcation lesions were present in 13% of the cases. Manual correction was applied to 9.3±9.2% of the automatically defined vessels contours. Mean invasive FFR was 0.83±0.08, CoreLab vFFR 0.83±0.09 and site-determined vFFR 0.82±0.10. Pressure wire-based FFR was ≤0.80 in 36%, CoreLab vFFR 34% and on-site vFFR 32%.

**Table 1.** Baseline characteristics.

| | **Total N = 334** |
|---|---|
| Age, y, mean±SD | 66 ± 12 |
| Male gender, n (%) | 244 (73) |
| BMI, mean±SD | 27 ± 4 |
| **Cardiovascular risk factors, n (%)** | |
| Hypertension | 240 (72) |
| Hyperlipidemia | 220 (66) |
| Diabetes Mellitus | 90 (27) |
| Current smoker | 56 (17) |
| Family with CAD | 120 (36) |
| Peripheral artery disease | 39 (12) |
| **Medical history and co-morbidity, mean±SD** | |
| eGFR, ml/min | 98±84 |
| Hemoglobine, (mmol/L) | 8.5±1.1 |
| Previous PCI | 135 (40) |
| **Lesions location and characteristics, n (%)** | |
| Left anterior descending artery (LAD) | 219 (66) |
| Left circumflex artery (LCX) | 31 (9) |
| Right coronary artery (RCA) | 84 (25) |
| Focal lesions | 239 (72) |
| Diffuse disease | 127 (38) |
| Bifurcation lesions | 42 (13) |
| Turtuositas | 27 (8) |
| Moderate or severe calcification | 48 (14) |

**Table 1.** Baseline characteristics. (continued)

| | Total N = 334 |
|---|---|
| **Coronary angiography indication, n (%)** | |
| Stable Angina | 278 (83) |
| Unstable Angina | 17 (5) |
| NSTEMI | 39 (12) |
| **3D- Quantitative Coronary Angiography, mean±SD** | |
| Lesion length, mm | 20±13 |
| Minimal lumen diameter, mm | 1.69±0.40 |
| Minimal lumen area, $mm^2$ | 2.37±1.12 |
| Diameter stenosis, % | 42±11 |
| Reference vessel diameter, mm | 2.92±0.54 |
| Contour correction, % mean±SD | 9.3 ± 9.2 |
| **Indices** | |
| FFR, mean±SD; median (IQR) | 0.83±0.08; 0.84 (0.78-0.89) |
| vFFR CoreLab, mean±SD; median (IQR) | 0.83±0.09; 0.85 (0.78-0.89) |
| vFFR Site, mean±SD; median (IQR) | 0.82±0.10; 0.84 (0.79-0.89) |
| FFR ≤ 0.80; n (%) | 120 (36) |
| vFFR Corelab ≤ 0.80; n (%) | 113 (34) |
| vFFR Site ≤ 0.80; n (%) | 108 (32) |
| Pd/Pa, mean±SD; median (IQR) | 0.93 ± 0.06; 0.93 (0.90-0.97) |

Values are n, mean±SD of n (%); BMI= Body Mass Index; eGFR= estimated glomerular filtration rate; FFR= Fractional Flow Reserve; NSTEMI= Non-ST-segment elevation myocardial infarction; vFFR= vessel Fractional Flow Reserve.

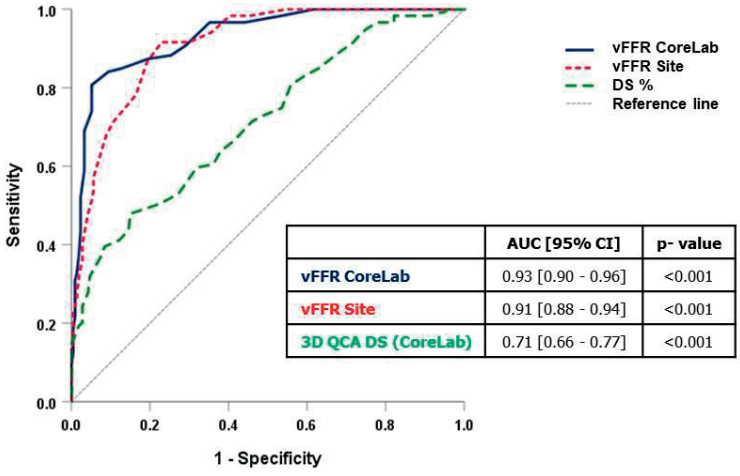



**Figure 3.** ROC for CoreLab vFFR, Site vFFR and 3D-QCA. Comparison is made with a pressure wire-based FFR at a cut point of 0.80.

## Correlation and diagnostic performance

Receiver operating characteristics (ROC) curve analysis revealed excellent accuracy of CoreLab vFFR in predicting FFR ≤0.80 (AUC 0.93; 95% CI [0.90 - 0.96]). Using a cutoff value of ≤0.80 for vFFR, sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 81%, 95%, 90%, 90%, and 90%, respectively. (**Figures 3)** A good correlation was found between CoreLab vFFR and pressure wire-based FFR (R=0.74; p<0.001) with a mean bias of 0.0029±0.0642. (**Figures 4**)

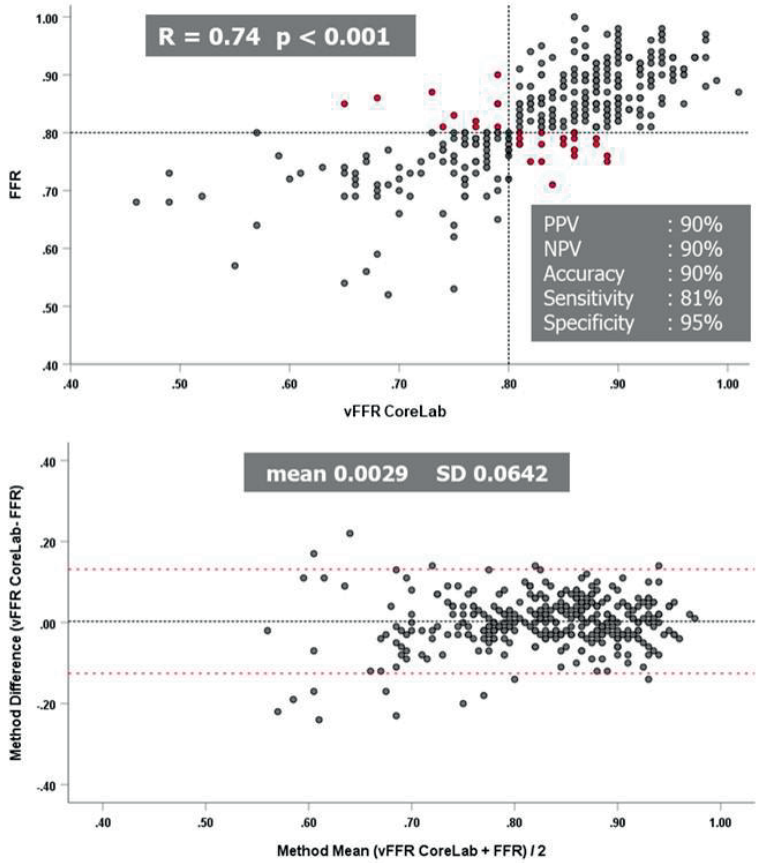



**Figure 4.** Scatter Plots showing the relationship between CoreLab vFFR vs. pressure wire-based FFR and Bland-Altman plots of differences against the means. The mean bias is represented by the solid grey line and the 95% confidence interval is represented by the dashed red lines. Grey dots represent true positive and true negative vFFR while red dots represent false positive and false negative vFFR.

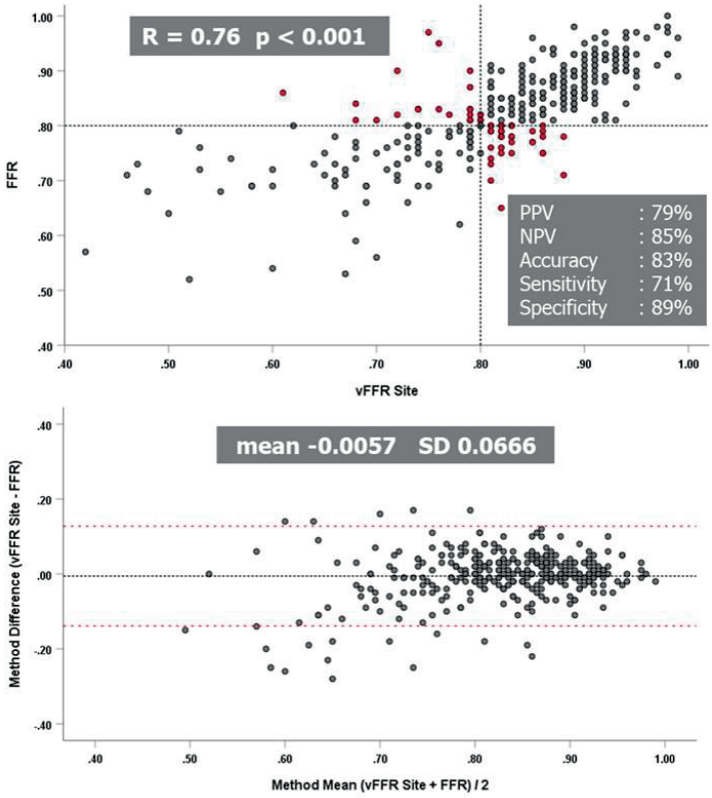



**Figure 5.** Scatter Plots showing the relationship between Site vFFR vs. pressure wire-based FFR and Bland- Altman plots of differences against the means. The mean bias is represented by the solid grey line and the 95% confidence interval is represented by the dashed red lines. Grey dots represent true positive and true negative vFFR while red dots represent false positive and false negative vFFR.

Similar findings were observed comparing on-site vFFR to invasive FFR ≤0.80 (AUC: 0.91; 95% CI [0.88 - 0.94]). Using a cutoff value of ≤0.80 for vFFR, sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 71%, 89%, 79%, 85%, and 83%, respectively. **(Figure 3)** A good correlation was found between site-reported vFFR and pressure wire-based FFR (R=0.76; p<0.001) with a mean bias of 0.0057±0.0666. (**Figures 5**)

A strong correlation was observed between CoreLab vFFR and on-site vFFR (R=0.87; p<0.001). Additional subanalyses in specific lesion and patient subsets showed consistent correlation figures: LAD (R=0.74), diabetic patients (R=0.78), focal lesions (R=0.74), diffuse disease (R=0.75), bifurcation (R=0.71) and calcified lesions (R=0.78) for CoreLab vFFR versus invasive FFR. (**Table 2**)

**Table 2.** Subanalysis

| | Pearsons R | AUC [95% CI]; p-value |
|---|---|---|
| Left anterior descending artery (LAD) | 0.74 | 0.91 [0.87 – 0.95]; <0.001 |
| Left circumflex artery (LCX) | 0.67 | 0.94 [0.85 – 1.00]; <0.001 |
| Right coronary artery (RCA) | 0.72 | 0.98 [0.93 – 1.00]; <0.001 |
| Diabetes Mellitus (N=90) | 0.78 | 0.95 [0.91 – 1.00]; <0.001 |
| Focal lesion (N=239) | 0.74 | 0.93 [0.90 – 0.97]; <0.001 |
| Diffuse disease (N=38) | 0.75 | 0.92 [0.87 – 0.97]; <0.001 |
| Bifurcation (N=13) | 0.71 | 0.91 [0.80 – 1.00]; <0.001 |
| Turtuositas (n=27) | 0.76 | 0.96 [0.90 – 1.00]; <0.001 |
| Calcification (n=48) | 0.78 | 0.94 [0.85 – 1.00]; <0.001 |

## DISCUSSION

The FAST II (Fast Assessment of STenosis severity) study was a prospective observational international multicenter study demonstrating an excellent diagnostic performance of 3D-QCA based vessel FFR (vFFR) in identifying a positive pressure wire-based FFR with high sensitivity, specificity, NPV and PPV. Additionally, vFFR correlated well to pressure wire based FFR.

The present study thereby confirms and strengthens the findings of the retrospective single center FAST I and FAST Extend studies in a prospective multicenter fashion with the use of a blinded CoreLab. [7, 8] With consistent correlation and diagnostic accuracy figures among all 3 studies, vFFR proves to be a powerful diagnostic alternative to invasive pressure wire based physiological lesion assessment and supports the upcoming of 3D-angiography based FFR in general.

In recent years, a number of 3D-angiography based FFR indices have been validated and showed consistent and comparable correlation and diagnostic accuracy figures with pressure wire based FFR as a reference. Having the use of simplified computation fluid dynamics as the common denominator in their functionality, significant differences should be noted in the workflow of each of the indices and software packages. As such, QFR (QAngio XA 3D prototype, Medis Medical Imaging System, Leiden, the Netherlands), with the largest body of evidence to date, is based on frame counting and contrast flow modeling on a per vessel basis.[13-17] $FFR_{angio}$ (CathWorks, Kfar-Saba, Israel) conversely is based on rapid flow analysis for the functional angiographic mapping of the entire coronary tree, a workflow that is more time-consuming as compared to indices with a per vessel approach. [18] The issue of speed of use was recently addressed in the recently published FLASH-FFR study which demonstrated the diagnostic performance of caFFR, a more recent computational pressure-fluid dynamics derived FFR (Rainmed Ltd, Suzhou, China).[19] The authors reported a total operation time of less than 5 minutes with less than one minute computation time. No mention was made about the operational time in the $FFR_{angio}$ study by Fearon et al. [18]

while Westra et al reported a median time to calculate QFR of 5 minutes which was shorter than the time to complete pressure wire based FFR (7 minutes). [14] All in all the value of computation time for a measurement that was not used for clinical decision making in single arm observations remains questionable.

As compared to other available angiography-based FFR technologies, vFFR as calculated using CAAS Workstation may offer advantages. At first, and in contrast to $FFR_{angio}$, vFFR allows physiological lesion assessment of a specific target segment or vessel of interest, precluding the need to perform an assessment of the full cardiac tree. The latter reduces the total number of dedicated and suitable angiographic images needed to adequately construct the 3D vessel geometry thereby saving time, contrast and radiation. Second, the vFFR algorithm applies automated and harmonized optimal end-diastolic frame selection in the two orthogonal projections by ECG triggering. This automated process saves time in finding and harmonized optimal frames. Third, vFFR uses the readily available aortic root pressure as boundary inlet condition without the need for contrast flow modeling using manual frame counting (QFR). Fourth, vFFR allows highly accurate contour detection as demonstrated by the low percentage (9.3%) of contouring that needs to be manually corrected due to for instance vessel overlap or suboptimal contrast opacification. The present study is thereby the first to report these figures as no data is available on the time and amount of necessary manual contour corrections by any of the alternative angiography-based FFR technologies.

With respect to interobserver variability, we demonstrated in the FAST I study a very low interobserver variability ($r=0.95$; $p>0.001$). [7] In the present study, we were able to confirm a low variability in the vFFR assessment as performed by a blinded CoreLab or by independent local personnel in the 6 individual participating centers ($r=0.87$; $p<0.001$). These promising results indicate the reliability of physiological lesion assessment using vFFR by trained local site personnel in the absence of a well-trained CoreLab.

Previous studies on alternative angiography based FFR technologies included only a limited amount of bifurcations, calcifications, tandem lesions, tortuosity and in some cases even excluded vessels with diffuse disease. [18] In the present study, the correlation between vFFR with pressure wire based FFR as a reference proved to be consistent among a broad range of specific patient and lesion subsets providing evidence for the applicability of the technologies in a broad range of patients and lesions.

Finally, sample size calculations for the present study were based on a rate of 42% positive FFR values in the FAST I study whereas in the present, only 36% of FFR values was positive. In the present study, the sensitivity, specificity and diagnostic accuracy of vFFR with a threshold of 0.83 were 88%; 80% and 83% respectively to detect a FFR≤0.80. In the meantime, FAST Extend

identified vFFR ≤0.80 as the most optimal binary cut-off. [8] Also in the present study, taking a vFFR threshold of ≤0.80, the diagnostic accuracy increased from 83% (with a threshold 0.83) to 90% with sensitivity and specificity figures of 81% and 95% respectively. Of note, only 1/334 case with a FFR<0.75 had a CoreLab defined vFFR>0.80 further strengthening the sensitivity figures in the present study.

Addressing the need for larger clinical outcome trials, the coronary angiography-based vessel Fractional Flow Reserve for Fast Physiologic Assessment of Stenosis severity: FAST III trial will randomize 2228 patients to vFFR vs invasive FFR with a 1 year patient oriented clinical endpoint.

### Limitations

Some study limitations have to be mentioned. First, the vFFR calculation was done offline, which means that its feasibility during the procedure remains unclear. Furthermore, the accuracy of the technique is strongly dependent on the quality of the angiographic cine-images and image acquisition should meet the criteria of non-overlapping images with at least 30 degrees differences in angulation. Although these are pre-requisites that theoretically should be fulfilled in all pre procedural angiographies, previous studies showed that up to 65% of routine angiograms are of insufficient quality to be used in angiography-based FFR software due to insufficient luminal contrast opacification, overlap or lack of adequate orthogonal views. The present study however demonstrated that with adequate site training the percentage of analyzable angiograms as identified by a dedicated CoreLab could go up to 88%. Finally, adequate and objective registration of the time needed to perform offline vFFR computation in the present study was not considered feasible and as such, we refrained from reporting vFFR computation times. Comparative procedure time associated with FFR vs. vFFR will be reported in the upcoming randomized FAST III trail.

## CONCLUSION:

3D-QCA-based vessel FFR as calculated by either a blinded CoreLab or site-personnel correlates well with pressure wire based FFR and has an excellent diagnostic performance to detect FFR ≤0.80.

## IMPACT ON DAILY PRACTICE

FFR guided decision making is still underused in real world practice. Using vFFR offers a less costly and less invasive alternative to the hemodynamic assessment of lesion severity. By discarding hyperemic agents and perhaps event invasive devices in general the arguments for not using physiological assessment become scarcer every day.

## REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO and Group ESCSD. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2018.
2. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Mobius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engstrom T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Juni P, Fearon WF and Investigators FT. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991-1001.
3. Fearon WF, Nishi T, De Bruyne B, Boothroyd DB, Barbato E, Tonino P, Juni P, Pijls NHJ, Hlatky MA and Investigators FT. Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease: Three-Year Follow-Up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). *Circulation*. 2018;137:480-487.
4. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W and de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol*. 2007;49:2105-11.
5. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF and Investigators FS. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213-24.
6. Toth GG, Toth B, Johnson NP, De Vroey F, Di Serafino L, Pyxaras S, Rusinaru D, Di Gioia G, Pellicano M, Barbato E, Van Mieghem C, Heyndrickx GR, De Bruyne B and Wijns W. Revascularization decisions in patients with stable angina and intermediate lesions: results of the international survey on interventional strategy. *Circ Cardiovasc Interv*. 2014;7:751-9.
7. Masdjedi K, van Zandvoort LJC, Balbi MM, Gijsen FJH, Ligthart JMR, Rutten MCM, Lemmert ME, Wilschut JM, Diletti R, de Jaegere P, Zijlstra F, Van Mieghem NM and Daemen J. Validation of a three-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: the FAST study. *EuroIntervention*. 2020;16:591-599.
8. Neleman T, Masdjedi K, Van Zandvoort LJC, Tomaniak M, Ligthart JMR, Witberg KT, Vermaire AA, Boersma E, Van Mieghem NM and Daemen J. Extended Validation of Novel 3D Quantitative Coronary Angiography-Based Software to Calculate vFFR: The FAST EXTEND Study. *JACC Cardiovasc Imaging*. 2021;14:504-506.
9. Gould KL, Kelley KO and Bolson EL. Experimental validation of quantitative coronary arteriography for determining pressure-flow characteristics of coronary stenosis. *Circulation*. 1982;66:930-7.
10. Kirkeeide R. Coronary obstructions, morphology and physiologic significance. 1991:229–44.
11. Girasis C, Schuurbiers JC, Muramatsu T, Aben JP, Onuma Y, Soekhradj S, Morel MA, van Geuns RJ, Wentzel JJ and Serruys PW. Advanced three-dimensional quantitative coronary angiographic assessment of bifurcation lesions: methodology and phantom validation. *EuroIntervention*. 2013;8:1451-60.
12. Schuurbiers JC, Lopez NG, Ligthart J, Gijsen FJ, Dijkstra J, Serruys PW, Van der Steen AF and Wentzel JJ. In vivo validation of CAAS QCA-3D coronary reconstruction using fusion of angiography and intravascular ultrasound (ANGUS). *Catheter Cardiovasc Interv*. 2009;73:620-6.
13. Tu S, Westra J, Yang J, von Birgelen C, Ferrara A, Pellicano M, Nef H, Tebaldi M, Murasato Y, Lansky A, Barbato E, van der Heijden LC, Reiber JH, Holm NR, Wijns W and Group FPTS. Diagnostic Accuracy of Fast Computational Approaches to Derive Fractional Flow Reserve From Diagnostic Coronary Angiography: The International Multicenter FAVOR Pilot Study. *JACC Cardiovasc Interv*. 2016;9:2024-2035.

14. Westra J, Andersen BK, Campo G, Matsuo H, Koltowski L, Eftekhari A, Liu T, Di Serafino L, Di Girolamo D, Escaned J, Nef H, Naber C, Barbierato M, Tu S, Neghabat O, Madsen M, Tebaldi M, Tanigaki T, Kochman J, Somi S, Esposito G, Mercone G, Mejia-Renteria H, Ronco F, Botker HE, Wijns W, Christiansen EH and Holm NR. Diagnostic Performance of In-Procedure Angiography-Derived Quantitative Flow Reserve Compared to Pressure-Derived Fractional Flow Reserve: The FAVOR II Europe-Japan Study. *J Am Heart Assoc*. 2018;7.
15. Westra J, Tu S, Campo G, Qiao S, Matsuo H, Qu X, Koltowski L, Chang Y, Liu T, Yang J, Andersen BK, Eftekhari A, Christiansen EH, Escaned J, Wijns W, Xu B and Holm NR. Diagnostic performance of quantitative flow ratio in prospectively enrolled patients: An individual patient-data meta-analysis. *Catheter Cardiovasc Interv*. 2019;94:693-701.
16. Westra J, Tu S, Winther S, Nissen L, Vestergaard MB, Andersen BK, Holck EN, Fox Maule C, Johansen JK, Andreasen LN, Simonsen JK, Zhang Y, Kristensen SD, Maeng M, Kaltoft A, Terkelsen CJ, Krusell LR, Jakobsen L, Reiber JHC, Lassen JF, Bottcher M, Botker HE, Christiansen EH and Holm NR. Evaluation of Coronary Artery Stenosis by Quantitative Flow Ratio During Invasive Coronary Angiography: The WIFI II Study (Wire-Free Functional Imaging II). *Circ Cardiovasc Imaging*. 2018;11:e007107.
17. Xu B, Tu S, Qiao S, Qu X, Chen Y, Yang J, Guo L, Sun Z, Li Z, Tian F, Fang W, Chen J, Li W, Guan C, Holm NR, Wijns W and Hu S. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. *J Am Coll Cardiol*. 2017;70:3077-3087.
18. Fearon WF, Achenbach S, Assali TEA, Jeremias RSA, Fournier S, Kirtane AJ, Kornowski R, Greenberg G, Jubeh R, Kolansky DM, McAndrew T, Dressler O, Maehara A, Matsumura M, Leon MB and Bruyne BD. Accuracy of Fractional Flow Reserve Derived From Coronary Angiography. *Ciculation*. 2018.
19. Li J, Gong Y, Wang W, Yang Q, Liu B, Lu Y, Xu Y, Huo Y, Yi T, Liu J, Li Y, Xu S, Zhao L, Ali ZA and Huo Y. Accuracy of computational pressure-fluid dynamics applied to coronary angiography to derive fractional flow reserve: FLASH FFR. *Cardiovasc Res*. 2020;116:1349-1356.

# Chapter 17

# Correlation between 3D-QCA based FFR and quantitative lumen assessment by IVUS for left main coronary artery stenoses

Mariusz Tomaniak, MD[1,2]; **Kaneshka Masdjedi, MD[1];** Laurens J van Zandvoort, BSc[1]; Tara Neleman, BSc[1]; Maria N Tovar, MD[1]; Alise Vermaire, RT[1]; Janusz Kochman, MD[2], PhD; Isabella Kardys, MD, PhD[1]; Wijnand den Dekker, MD, PhD[1]; Jeroen Wilschut, MD[1]; Roberto Diletti, MD, PhD[1]; Peter de Jaegere, MD, PhD[1]; Nicolas M Van Mieghem, MD, PhD[1]; Felix Zijlstra, MD, PhD[1]; Joost Daemen, MD, PhD[1].

**[1] Department of Cardiology, Erasmus Medical Center, University Medical Center Rotterdam, Thorax Centre, Rotterdam, The Netherlands**
**[2] First Department of Cardiology, Medical University of Warsaw, Poland**

**Journal:** Catheterization and Cardiovascular Interventions; 2020;1–7.

## ABSTRACT

**Objectives:** We aimed to evaluate the feasibility of using three dimensional-quantitative coronary angiography (3D-QCA) based fractional flow reserve (FFR) (vessel fractional flow reserve [vFFR], CAAS8.1, Pie Medical Imaging) and to correlate vFFR values with intravascular ultrasound (IVUS) for the evaluation of intermediate left main coronary artery (LMCA) stenosis.

**Background:** 3D-QCA derived FFR indices have been recently developed for less invasive functional lesion assessment. However, LMCA lesions were vastly underrepresented in first validation studies.

**Methods:** This observational single-center cohort study enrolled consecutive patients with stable angina, unstable angina, or non-ST-segment elevation myocardial infarction and nonostial, intermediate grade LMCA stenoses who underwent IVUS evaluation. vFFR was computed based on two angiograms with optimal LMCA stenosis projection and correlated with IVUS-derived minimal lumen area (MLA).

**Results:** A total of 256 patients with intermediate grade LMCA stenosis evaluated with IVUS were screened for eligibility; 147 patients met the clinical inclusion criteria and had a complete IVUS LMCA footage available, of them, 63 patients (63 lesions) underwent 3D-QCA and vFFR analyses. The main reason for screening failure was insufficient quality of the angiogram (51 patients,60.7%). Mean age was 65 ± 11 years, 75% were male. Overall, mean MLA within LMCA was 8.77 ± 3.17 mm2, while mean vFFR was 0.87 ± 0.09. A correlation was observed between vFFR and LMCA MLA (r=.792, p = .001). The diagnostic accuracy of vFFR ≤0.8 in identifying lesions with MLA < 6.0 mm2 (sensitivity 98%, specificity 71.4%, area under the curve (AUC) 0.95, 95% confidence interval (CI) 0.89–1.00, p = .001) was good.

**Conclusions:** In patients with good quality angiographic visualization of LMCA and available complete LMCA IVUS footage, 3D-QCA based vFFR assessment of LMCA disease correlates well to LMCA MLA as assessed by IVUS.

**Keywords:** 3D-QCA-based FFR, angiography-based FFR, intravascular ultrasound, left main disease, multimodality diagnostics, vessel fractional flow reserve.

## 1. INTRODUCTION

Evaluation of left main coronary artery (LMCA) lesion remains challenging and often warrants a multimodality approach, including intravascular imaging and functional assessment.[1-3] Concomitantly, reliable invasive fractional flow reserve (FFR) assessment of LMCA also carries some risks and limitations and is still underused in clinical practice despite strong recommendations in current revascularization guidelines.[1,4,5] Recently, three dimensional three dimensional-quantitative coronary angiography (3D-QCA) derived FFR indices have been developed for less invasive functional lesion assessment, demonstrating a high linear correlation with invasively measured FFR and a high accuracy to detect the lesions with FFR ≤0.8.[6-11] However, patients with LMCA lesions were vastly under-represented in first validation studies.[7-12] While pressure wire based FFR measurement demonstrated lowto-moderate correlation with intravascular ultrasound (IVUS) measurements in nonleft main coronary stenosis (also dependent on the vessel size),[13] a good correlation between IVUS LMCA quantitative lumen measurements and FFR values have been reported.14-17 Given this background, we aimed to evaluate the feasibility of using 3D-QCA based FFR for left main disease and to correlate vFFR values (CAAS 8.1 Workstation, Pie Medical Imaging)[7] with IVUS measurements for evaluation of intermediate to severe LMCA stenosis.

## 2. MATERIALS AND METHODS

### 2.1 Study population

This observational, retrospective, single-center study included consecutive patients presenting with stable angina, unstable angina, and non-ST-segment elevation myocardial infarction (NSTEMI) with nonostial LMCA stenoses who underwent IVUS evaluation between September 2008 and December 2016. Exclusion criteria involved: severe valvular heart disease, left ventricle ejection fraction <30%, previous coronary artery bypass grafting (CABG), insufficient quality of angiogram precluding vFFR computation (i.e., absence of a minimum of two angiographic projections with views of at least 30 apart, substantial foreshortening or overlap of the vessel, ostial LMCA stenosis, inadequate contrast flush), insufficient quality of IVUS pullback precluding quantitative luminal assessment, deep catheter intubation into LMCA precluding complete stenosis visualization, unavailability of baseline aortic root blood pressure required for vFFR computation, and significant downstream disease in both daughter arteries (>50% stenosis by visual estimation).[18,19]

### 2.2 vFFR analyses

Computation of vFFR was performed offline by trained analysts blinded to the IVUS measurements using a validated software CAAS workstation 8.1 (Pie Medical Imaging, Maastricht, the Netherlands). Within CAAS Workstation vFFR the pressure drop is calculated instantaneously by

applying physical laws including viscous resistance and separation loss effects present in coronary flow behavior, as previously described.[7]

A total of two 2-D angiograms with optimal visualization of LMCA stenosis were loaded into the software. Optimal visualization of LMCA stenosis was defined as angiograms visualizing the LMCA stenosis without overlap or significant foreshortening including the projection with the highest angiographic percentage diameter stenosis (%DS).

Although temporal alignment of the cardiac cycle between the two angiograms was performed automatically by electrocardiography triggering, manual frame selection was allowed. Contour detecting was performed semiautomatically, delineating the vessel contour from the ostium up to 3 cm distal to the LMCA lesion in either the left anterior descending (LAD) or left circumflex artery (LCX), depending on which was least diseased distally. This approach followed the methodology of invasive FFR for LMCA disease described in prior studies. [14,15] In case of distal LMCA stenoses and true bifurcation lesions, vFFR was analyzed up to 3 cm distal to the LMCA lesion in both LAD and LCX artery; the lower vFFR value and the corresponding IVUS measurements from the pullback acquired in the same daughter artery were included in the correlation analysis 14,15.

vFFR was calculated automatically incorporating the invasively measured aortic root pressure and automatically generated 3D-QCA values. The %DS was determined from the generated 3D models.

### 2.3 IVUS analyses

The LMCA segments were examined with an IVUS system with automatic pullback at 0.5 mm/s (OptiCross, Boston Scientific, Natick, MA; Eagle Eye, Volcano Corp, Rancho Cordova, CA; TVC Insight, InfraReDx, Burlington, MA) or 2.5 mm/sec (Kodama, Acist Medical, Eden Prairie, MN). IVUS imaging assessment was performed off-line in fixed 0.5 mm intervals between the LMCA ostium and its distal bifurcation using dedicated software (QCU-CMS, Leiden University Medical Center, LKEB, Division of Image Processing, version 4.69) by two dedicated academic intravascular imaging specialists, blinded to the vFFR results.

The proximal border of the LMCA, the ostium, was defined as the first frame, that contained a 360$^{o}$ luminal border of the LMCA.

The minimum lumen area (MLA) and external elastic membrane area were measured at the site within the LMCA coronary segment above the carina at which the lumen was smallest. The plaque burden at the MLA site was calculated as (external elastic membrane area– lumen area)/external elastic membrane area × 100 (%). Percent of area stenosis was also calculated as (reference lumen area − MLA)/ reference lumen area×100 (%).

## 2.4 Statistical analyses

The data distribution was assessed by Kolmogorov – Smirnov analysis. Normally distributed continuous variables are presented as the mean ± SD, and were compared using the Student t test. Non-normally distributed continuous variables are presented as median (25th–75th percentile), and were compared using the Mann–Whitney test. Categorical variables are displayed as counts and percentages, and were compared using chi-square or Fisher exact tests as appropriate. The correlation between vFFR and MLA and remaining IVUS-derived parameters was assessed calculating the Pearson R or Spearman's rank correlation coefficients, for variables with normal and non-normal distribution, respectively. Receiver-operating curve analyses were performed to assess the discriminative power of the vFFR and 3D-QCA based %DS to detect an IVUS derived MLA <6.0 mm2.1,14,17 Finally, exploratory analysis of the optimal cutoff values of vFFR for IVUS derived MLA <6.0 mm2 was conducted; the cut-off was identified as the values for which the sum of the sensitivity and specificity was greatest. All statistical analyses were performed using SPSS (version 25.0, SPSS, Inc., Chicago, Illinois). A p value of < .05 was considered as statistically significant.

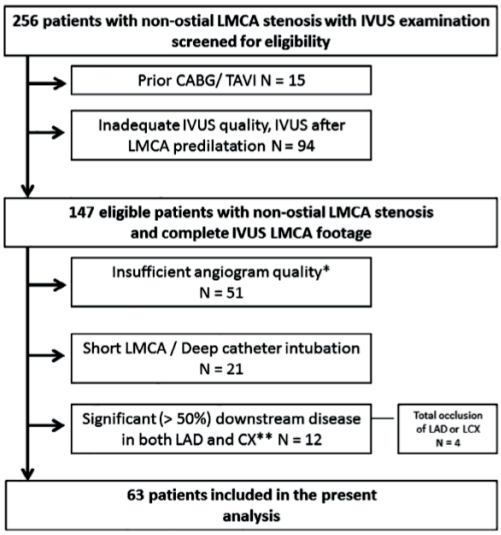



**Figure 1.** Study flow chart

* Including substantial foreshortening of the IVUS-corresponding vessel in at least one out of the two required optimal "most significant" stenosis views

** Or the presence of significant downstream stenosis (>90% diameter stenosis of FFR <0.45 in one daughter vessel (Fearon et al. JACC Cardiovasc Int 2015; Kim et al. JACC Cardiovasc Int. 2012; Yamamoto et al. 2016)

## 3 RESULTS

A total of 256 patients with intermediate grade LMCA stenosis evaluated with IVUS were screened for eligibility; 147 patients met the clinical inclusion criteria and had a complete IVUS LMCA footage available, of them, 63 patients (63 lesions) underwent 3D-QCA and vFFR analyses (Figure 1). The main reason for screening failure was insufficient quality of the angiogram (51 patients, 60.7%). Mean age was 65 ± 11 years, 75% were male. Thirty-three patients presented with stable angina, 10 patients with unstable angina, and 20 patients with NSTEMI. Overall, mean MLA within LMCA was 8.77 ± 3.17 mm2, while mean vFFR was 0.87 ± 0.09. Baseline clinical, IVUS and angiographic characteristics are presented in Table 1.

**Table 1.** Baseline clinical, intravascular ultrasound (IVUS) and angiographic characteristics.

| | N = 63 patients |
|---|---|
| **Clinical characteristics** | |
| Age, years (± SD) | 65±11 |
| Male, n (%) | 47 (74.6) |
| BMI, kg/m2 (± SD) | 26.3±4.7 |
| Diabetes mellitus, n (%) | 13 (20.6) |
| Hypercholesterolemia | 27 (42.8) |
| Hypertension | 36 (57.1) |
| Current smoking | 17 (27.0) |
| Family history of CVD | 20 (31.7) |
| **Quantitative IVUS parameters** | |
| Area stenosis at MLA, % (± SD) | 55.6±10.6 |
| MLA, mm2 (± SD) | 8.8±3.2 |
| Mean lumen area, mm2 (± SD) | 13.3±3.0 |
| MLD, mm (± SD) | 3.5±0.4 |
| Vessel area, mm2 (± SD) | 23.5±5.8 |
| Plaque burden area, mm2 (± SD) | 10.1±3.8 |
| Area stenosis at MLA, % (± SD) | 55.6±10.6 |
| **3D-QCA and vFFR** | |
| %DS (± SD) | 37.1±20.2 |
| vFFR (± SD) | 0.87±0.09 |

± SD – standard deviation, BMI – body mass index, CVD- cardiovascular disease, MLA – minimum lumen area; MLD – minimum lumen diameter; 3D-QCA – three-dimensional quantitative coronary angiography, %DS – percentage diameter stenosis, vFFR – vessel fractional flow reserve

A good correlation was observed between vFFR and LMCA MLA (r = .792, p = .001) (Figures 2 and 3a). The observed correlation remained significant regardless of clinical presentation (stable angina: r = .79, p = .001, acute coronary syndrome (unstable angina or NSTEMI): r = .80, p = .001). There was a moderate correlation between vFFR and mean lumen area (r = .622, p = .001) and

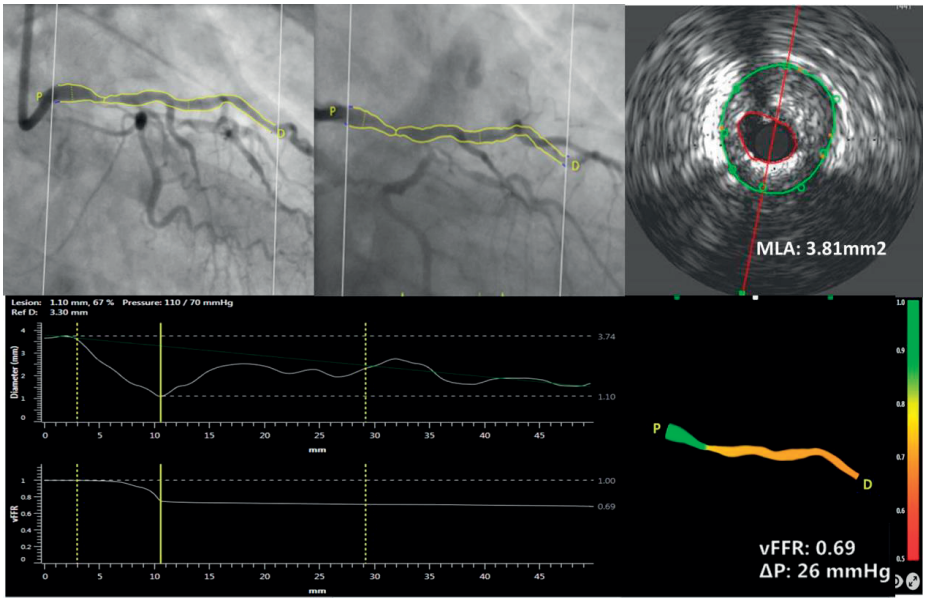



**Figure 2.** Case example of three-dimensional reconstruction of left main coronary artery (LMCA) and computation of vessel fractional flow reserve (vFFR), using two angiographic projections with at least 30 degrees apart and invasively measured aortic root blood pressure. Quantitative lumen assessment by intravascular ultrasound in LMCA.

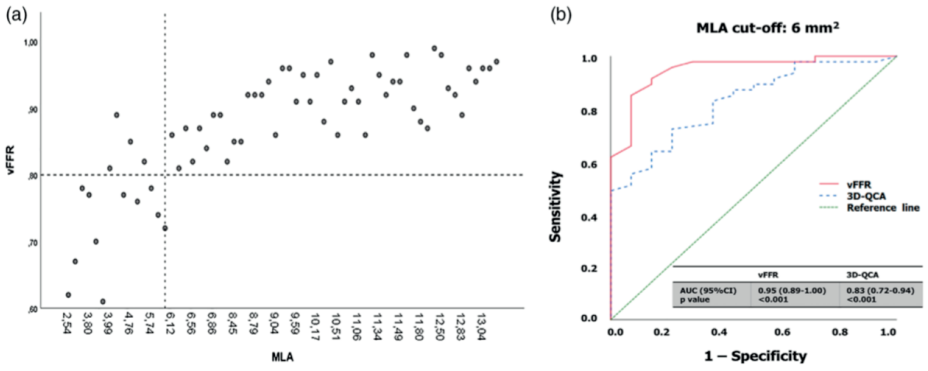



**Figure 3.** (a) Scatter plot illustrating corresponding 3D quantitative angiography based vessel fractional flow reserve (vFFR) and intravascular ultrasound (IVUS)-derived minimal lumen area (MLA) measurements in the left main coronary artery stenosis. (b) Receiver operating curve (ROC) for vFFR and 3D-QCA based percentage of diameter stenosis. Comparison is made with an IVUS-MLA below 6.0 mm2

average plaque burden area (r = .420, p = .003). The diagnostic accuracy of vFFR ≤0.8 in identifying lesions with MLA < 6.0 mm2 (sensitivity 98%, specificity 71.4%, area under the curve [AUC] 0.95, 95% confidence interval [CI] 0.89–1.00, p = .001) was good (Figure 3b). An inverse correlation was found between %DS by QCA and vFFR (r = −.485, p = .001). No significant correlation was observed between %DS by IVUS and vFFR (r = −.183, p = .212). Overall, revascularization was performed in 17 LMCA lesions: in 13 (93%) of 14 lesions with IVUS defined MLA < 6.0 m2 and in 4 (8%) out of 49 lesions with IVUS defined MLA ≥6.0 m2, corresponding to 10 (91%) of 11 lesions with vFFR ≤0.8, and 7 (14%) of 52 lesions with vFFR >0.8.

### 3.1 Exploratory analyses of optimal vFFR threshold compared with IVUS luminal assessment

Compared with the IVUS MLA threshold of 6.0 mm2 as a reference, a vFFR value of ≤0.83 had the highest sensitivity and specificity (91.8 and 85.7%, respectively).

## 4 DISCUSSION

The present study assessed for the first time a combined wire-free 3D-QCA based functional (vFFR) and IVUS evaluation of LMCA stenoses. In a selected patient population with sufficient angiogram quality, vFFR demonstrated a good linear correlation with IVUS-derived MLA and a good sensitivity to detect lesions with IVUS-confirmed significant disease. Our findings are of note, as LMCA lesions have been vastly under-represented or explicitly excluded in previous validation studies of 3D-QCA based FFR indices, including vFFR, quantitative flow ratio (qFR), or FFR angio.6-11,20 LMCA lesions have been also excluded in several trials using invasive FFR or iFR.[21-23]

We compared vFFR against IVUS as (a) it is a guideline-advocated (class II a, Level B) imaging modality for left main disease assessment,1 and (b) a good correlation between invasive FFR and IVUS has been demonstrated for LMCA stenoses. [14,15]

Notably, the strength of correlation between vFFR and IVUSderived MLA appeared similar to those previously reported in studies with invasive FFR and IVUS evaluation of LMCA. [14,15]

Given the limited number of concomitantly available data on appropriate invasive FFR, angiography, and IVUS evaluation, we could not compare vFFR directly against invasive FFR in this cohort. Nevertheless, in order to facilitate an indirect comparison between vFFR and FFR for LMCA assessment we used the same methodology as described preciously in invasive FFR studies, including the length of the 3D reconstruction within the LAD or Cx, at least 30 mm from the distal lesion border, resembling location of pressure wire sensor 14,15. Furthermore, we compared

vFFR sensitivity and specificity to identify IVUS-confirmed LMCA disease using MLA threshold of 6.0 mm2 that was indicative of significant LMCA stenosis by invasive FFR.[1,14,17]

Jasti et al. analyzed 55 patients with ambiguous LMCA stenoses with both IVUS and invasive FFR concluding that an MLA of 5.9 mm2 had the highest sensitivity and specificity (93 and 95%, respectively) for determining a functionally significant LMCA stenosis, defined as FFR < 0.75.[14] Park et al. showed that an IVUS-derived MLA of ≤4.5 $mm^2$ is a useful index of an invasive FFR of ≤0.80 (77% sensitivity, 82% specificity, AUC: 0.83, 95% CI: 0.76– 0.96; p < .001)[15]; these values, however, were obtained in an Asian population, and are not generally applicable to other populations.[1] A prospective study showed that a MLA ≥6 mm 2 is a safe threshold for deferring LMCA revascularization.[17] Using the latter MLA cut-off, we identified a vFFR cut-off value of ≤0.83 as having the highest diagnostic accuracy to reveal IVUS confirmed significant left main disease with the sensitivity and specificity (91.8 and 85.7%, respectively) similar to studies that identified this MLA cut-off using invasive FFR as a reference.[14,15]

The potentially higher threshold for vFFR for LMCA evaluation in this analysis needs to be interpreted cautiously and strictly as exploratory, considering that the challenges of angiographic visualization of severely stenotic LMCA[4,5], such as catheter wedging, intubation depth, risk of lesion dissection (in particular with repeated intubations) could impact the analyzability rates and the selection of patients in this retrospective analysis in favor of nonsignificant LMCA stenosis; as a consequence, it could also influence the identified highest diagnostic accuracy cut-off point to >0.80.

Nevertheless, the observed correlation between 3D-QCA based vFFR assessment of LMCA disease and LMCA MLA as assessed by IVUS in patients with good quality angiographic visualization of LMCA and available complete LMCA IVUS footage, warrants confirmation in larger dedicated clinical outcome trials.

Since we were forced to exclude a significant number of cases due to insufficient quality of the angiogram, this limitation could at least partially be addressed in a prospective study with protocolmandated angiogram acquisition respecting appropriate projections of >30$^o$ apart, along with a brisk contrast injection. Nevertheless, LMCA segments remain particularly challenging for optimal angiographic visualization, and if short, or in overlap with tortuous proximal segments of LAD and/or Cx precluding reliable contour tracing, might not be appropriate for vFFR, even in the setting of a dedicated, prospective study.

Cases included in our study involved LMCA disease of rather moderate severity. Nevertheless, MLA and %DS values were comparable to previous studies on the topic.[14,15] Future studies might provide more detailed data on the MLA – vFFR correlation in more severe LMCA lesions.

Considering the challenges in LMCA lesion evaluation and recognized limitations of IVUS and FFR/iFR in LMCA assessment, relevant is the search of novel strategies that could reinforce the currently available diagnostic options used in guideline-recommended multimodality approach to LMCA disease.[1,4,5] It is conceivable that less invasive and relatively straightforward nature of 3D-QCA derived FFR estimation could facilitate routine vFFR screening of all angiographically ambiguous LMCA lesions thereby aiding identification of patients requiring additional intravascular imaging or/and invasive pressure wire based physiological lesion assessment.

## 5 LIMITATIONS

The study has the following limitations: This was a single-centre, retrospective study. Although consecutive patients were screened for eligibility, selection bias cannot be excluded and presented correlations need to be confirmed in a larger, prospective study. Secondly, no invasive FFR measurements were available in majority of patients, precluding correlation of vFFR versus invasively measured FFR in LMCA. Finally, vFFR was assessed offline without independent core lab. The ongoing FAST II study will provide further insights on vFFR role and clinical utility in more complex lesions, including nonostial LMCA stenoses, with all vFFR being conducted by a dedicated core laboratory (NCT03791320).

## 6 CONCLUSIONS

In patients with good quality angiographic visualization of LMCA and available complete LMCA IVUS footage, 3D-QCA based vFFR assessment of LMCA disease correlates with LMCA MLA as assessed by IVUS.

## REFERENCES

1. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87-165.
2. Mintz GS, Lefevre T, Lassen JF, et al. Intravascular ultrasound in the evaluation and treatment of left main coronary artery disease: a consensus statement from the European bifurcation Club. EuroIntervention. 2018;14:e467-e474.
3. Cameron A, Kemp HG Jr, Fisher LD, et al. Left main coronary artery stenosis: angiographic determination. Circulation. 1983;68:484-489.
4. Ramadan R, Boden WE, Kinlay S. Management of left main coronary artery disease. J Am Heart Assoc. 2018;7(7):e008151. https;//doi. org/10.1161/JAHA.117.008151.
5. Hamilos M, Muller O, Cuisset T, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. Circulation. 2009;120:1505-1512.
6. Collet C, Onuma Y, Sonck J, et al. Diagnostic performance of angiography-derived fractional flow reserve: a systematic review and Bayesian meta-analysis. Eur Heart J. 2018;39:3314-3321.
7. Masdjedi K, van Zandvoort LJC, Balbi MM, et al. Validation of 3dimensional quantitative coronary angiography based software to calculate fractional flow reserve: fast assessment of stenosis severity (FAST)-study. EuroIntervention. 2019. May 14;EIJ-D-19-00466. doi: 10.4244/EIJ-D-19-00466. Online ahead of print.
8. Westra J, Tu S, Winther S, et al. Evaluation of coronary artery stenosis by quantitative flow ratio during invasive coronary angiography: the WIFI II study (wire-free functional imaging II). Circ Cardiovasc Imaging. 2018;11:e007107.
9. Westra J, Andersen BK, Campo G, et al. Diagnostic performance of in-procedure angiography-derived quantitative flow reserve compared to pressure-derived fractional flow reserve: the FAVOR II Europe-Japan study. J Am Heart Assoc. 2018;7(14):e009603. https:// doi.org/10.1161/JAHA.118.009603.
10. Xu B, Tu S, Qiao S, et al. Diagnostic accuracy of angiography-based quantitative flow ratio measurements for online assessment of coronary stenosis. J Am Coll Cardiol. 2017;70:3077-3087.
11. Pellicano M, Lavi I, De Bruyne B, et al. Validation study of imagebased fractional flow reserve during coronary angiography. Circ Cardiovasc Interv. 2017;10(9):e005259. https://doi.org/10.1161/ CIRCINTERVENTIONS.116.005259.
12. Fearon WF, Achenbach S, Engstrom T, et al. Accuracy of fractional flow reserve derived from coronary angiography. Circulation. 2019; 139:477-484.
13. Nascimento BR, de Sousa MR, Koo BK, et al. Diagnostic accuracy of intravascular ultrasound-derived minimal lumen area compared with fractional flow reserve–meta-analysis: pooled accuracy of IVUS luminal area versus FFR. Catheter Cardiovasc Interv. 2014;84:377-385.
14. Jasti V, Ivan E, Yalamanchili V, Wongpraparut N, Leesar MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. Circulation. 2004;110:2831-2836.
15. Park SJ, Ahn JM, Kang SJ, et al. Intravascular ultrasound-derived minimal lumen area criteria for functionally significant left main coronary artery stenosis. JACC Cardiovasc Interv. 2014;7:868-874.
16. Kang SJ, Lee JY, Ahn JM, et al. Intravascular ultrasound-derived predictors for fractional flow reserve in intermediate left main disease. JACC Cardiovasc Interv. 2011;4:1168-1174.
17. de la Torre Hernandez JM, Hernandez Hernandez F, Alfonso F, et al. Prospective application of predefined intravascular ultrasound criteria for assessment of intermediate left main coronary artery lesions results from the multicenter LITRO study. J Am Coll Cardiol. 2011;58:351-358.

18. Fearon WF, Yong AS, Lenders G, et al. The impact of downstream coronary stenosis on fractional flow reserve assessment of intermediate left main coronary artery disease: human validation. JACC Cardiovasc Interv. 2015;8:398-403.
19. Yamamoto E, Saito N, Matsuo H, et al. Prediction of the true fractional flow reserve of left main coronary artery stenosis with concomitant downstream stenoses: in vitro and in vivo experiments. EuroIntervention. 2016;11:e1249-e1256.
20. Asano T, Katagiri Y, Chang CC, et al. Angiography-derived fractional flow reserve in the SYNTAX II trial: feasibility, diagnostic performance of quantitative flow ratio, and clinical prognostic value of functional SYNTAX score derived from quantitative flow ratio in patients with 3-vessel disease. JACC Cardiovasc Interv. 2019;12:259-270.
21. Berry C, McClure JD, Oldroyd KG. Meta-analysis of death and myocardial infarction in the DEFINE-FLAIR and iFR-SWEDEHEART trials. Circulation. 2017;136:2389-2391.
22. Zimmermann FM, De Bruyne B, Pijls NHJ, et al. A protocol update of the fractional flow reserve versus angiography for multivessel evaluation (FAME) 3 trial: a comparison of fractional flow reserve-guided percutaneous coronary intervention and coronary artery bypass graft surgery in patients with multivessel coronary artery disease. Am Heart J. 2019;214:156-157.
23. Escaned J, Collet C, Ryan N, et al. Clinical outcomes of state-of-theart percutaneous coronary revascularization in patients with de novo three vessel disease: 1-year results of the SYNTAX II study. Eur Heart J. 2017;38:3124-3134.

# Chapter 18

# The Prognostic Value of Angiography-Based vessel-FFR after successful Percutaneous Coronary Intervention: The FAST Outcome study

**Kaneshka Masdjedi, MD;** Mariusz Tamoniak, MD, PhD; Jurgen M R Ligthart, RT; K. Witberg, RN; Alise Vermaire, RT; Isabella Kardys, MD, PhD; Tara Neleman, BSc; Jeroen Wilschut, MD; Roberto Diletti, MD, PhD; Wijnand K Den Dekker, MD, PhD; Peter de Jaegere, MD, PhD; Felix Zijlstra, MD, PhD; Nicolas M Van Mieghem, MD, PhD; Joost Daemen, MD, PhD.

**Department of cardiology, Thoraxcenter, Erasmus Medical Center**

**Journal:** Submitted

## ABSTRACT

**Background:** Vessel FFR (vFFR) as assessed by three-dimensional quantitative coronary angiography (3D-QCA) proved to have a high correlation with pressure wire based FFR in both a pre- and post PCI setting. The present study aims to assess the prognostic value of post PCI vFFR on the incidence of MACE, a composite endpoint of cardiac death, myocardial infarction and target vessel revascularization (TVR) at one year follow up.

**Methods:** Post PCI vFFR (CAAS 8.1, Pie Medical Imaging, Maastricht, the Netherlands) was calculated after angiographic successful PCI in a total of 810 patients with available orthogonal angiographic projections of the stented segment.

**Results:** Mean age was 64±12 years; 18% were diabetic; 51% had hypertension and 34% presented with an acute myocardial infarction (STEMI). Mean post PCI vFFR was 0.90±0.09. Despite angiographically good results, 37% of patients had a vFFR of ≤0.90 (n=298) and 12% had a post PCI vFFR ≤0.80. Comparing the one year clinical outcome of lower and upper tertiles of Post PCI vFFR no significant difference was found in terms of major adverse cardiac events (MACE; cardiac death, any myocardial infarction and target vessel revascularization) (8% vs. 5%, respectively; HR 1.62; 95% CI [0.82-3.20] p=0.168) or target vessel revascularization (TVR) (4% vs. 2%, respectively; HR 2.05; 95% CI [0.69-6.13] p=0.197). When adjusted to age, sex, hypertension, smoking, prior PCI, RCA, LAD and bifurcation, still no significant difference was found in MACE rate (HR 1.51, 95% CI [0.70-3.22], p=0.291) and TVR (HR 1.58, 95% CI [0.47-5.31] p=0.460). However, a trend was preserved in clinical outcome at one year, favoring the upper tertile.

**Conclusion:** Despite angiographically successful PCI results, a significant amount of the stented vessels end up with a post PCI vFFR ≤0.90. There was a strong trend towards higher rates future adverse events in the low post PCI vFFR cohort.

**Keywords:** Coronary Physiology, Fractional Flow Reserve, Quantitative Coronary Angiography, Percutaneous coronary intervention.

## INTRODUCTION

Both Fractional Flow Reserve(FFR) and the non-hyperemic pressure ratios (NHPR) are widely used to assess the hemodynamic importance of intermediate coronary artery lesions. (1-4) While the specific merits of each of these physiological indices have been mainly validated in a pre-percutaneous coronary intervention (PCI) setting, there is increasing interest in the use of either FFR or NHPR to assess the direct impact of stent placement on post-PCI physiology. The importance of the latter was demonstrated by several studies showing that despite optimal angiographic results, post PCI FFR was <0.90 in a considerable amount of patients resulting in a significantly increased risk for future major adverse cardiac events. (5-8)

At the same time several 3-Dimensional Quantitative Coronary Angiography (3D-QCA) based FFR methods proved to strongly correlate to invasive pressure wire based FFR technologies, both in a pre- and post PCI setting. (9) (10) The development of this new invasive technology might open up to field to a more liberal use of post PCI physiological assessment without the hassle to (re)use potentially damaged pre-PCI used pressure wires, need for hyperemic agents with potential side effects and associated time and costs.

As of today, no data are available on the prognostic value of post PCI vFFR on clinical outcome. Therefore, the present study aims to assess the prognostic value of post PCI vFFR on the incidence of MACE, a composite endpoint of cardiac death, myocardial infarction and target vessel revascularization (TVR) at 12 months follow up.

## METHODS

### Study design and population

The FAST Outcome study is a post-hoc analysis of the P-SEARCH study which was a single-center, prospective all-comer cohort study comparing 1-year clinical outcome data of patients treated with either durable polymer paclitaxel- or everolimus-eluting stents between 2012 and 2014 (N=2000). (11) The present study aimed to assess the prognostic value of post PCI vFFR, calculated by CAAS Workstation 8.1? (Pie Medical Imaging, Maastricht, the Netherlands), on the incidence of MACE, a composite endpoint of cardiac death, myocardial infarction and target vessel revascularization (TVR) at 12 months follow up.

Patients ≥18 years of age, presenting with stable angina or acute coronary syndrome who underwent PCI in at least one native coronary artery were eligible for the present study. Exclusion criteria were: patients with prior coronary artery bypass grafting (CABG), cardiogenic shock or severe hemodynamic instability, history of cardiac allograft transplantation and congenital heart

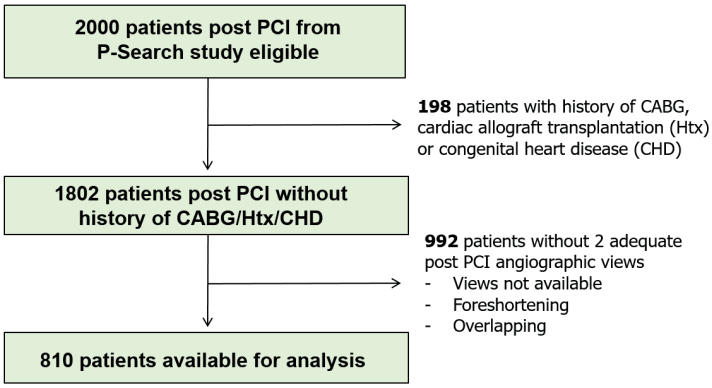



**Figure 1.** Flowchart showing all included and excluded patients.

disease (CHD). Post PCI vFFR was calculated in a total of 810 patients with angiographic successful PCI (TIMI grade 3 flow and final residual diameter stenosis <30%) as determined by two orthogonal angiographic projections of the stented segment, **Figure 1.**

## Computation of vFFR

Computation of vFFR was performed offline by trained analyst using a validated software CAAS workstation 8.1 (Pie Medical Imaging, Maastricht, the Netherlands). (9) Within CAAS Workstation vFFR the pressure drop is calculated instantaneously by applying physical laws including viscous resistance and separation loss effects present in coronary flow behavior, as described by Gould and Kirkeeide. (12, 13) The methods however are based on a single angiographic projection. Within CAAS vFFR, the geometry of the coronary artery is derived from well-validated 3D reconstructions (14, 15) which reduces the effects of foreshortening, out of plane magnification and non-symmetric coronary lesions.

Although temporal alignment of the cardiac cycle between the two angiograms was performed automatically by ECG triggering, manual frame selection was allowed. Contour detecting was performed semi-automatically, delineating the vessel contour from the ostium to 20 mm distal from the distal stent edge. vFFR was calculated automatically integrating the invasively measured aortic root pressure and the automatically generated 3D QCA dimensions . vFFR was calculated instantaneously with a proprietary algorithm which incorporates the morphology of the 3D coronary reconstruction and routinely measured real-time aortic pressure.

## Endpoint definitions and clinical follow up

The primary endpoint consisted of major adverse cardiac events (MACE), defined as a composite of cardiac death, any myocardial infarction (MI) or TVR at 12 months. Secondary endpoints were all-cause mortality, target lesion revascularization (TLR), any revascularization and stent throm-

bosis. Clinical follow-up data were obtained from electronic medical records of the hospital and general practitioner. Survival data were obtained from the municipal civil registry. In addition, all living patients were contacted personally by specific queries on clinical outcome and/or telephone contact. Cardiac death was defined as any death due to a proximate cardiac cause, unwitnessed death or death of unknown cause. (16) Myocardial infarction at follow up was diagnosed by a rise in creatine kinase-MB farction (CK-MB) of 3 times the upper limit of normal, according to American Heart Association/ American College of Cardiology guidelines. (16) TVR was defined as a re-intervention driven by any lesion located in the same epicardial vessel. TLR was defined as a re-intervention of the treated segment within 5 mm proximal or distal to the stent. (16) ST was defined as angiographically defined thrombosis within the stent or 5 mm proximal or distal to the stent with presence of a flow limiting thrombus, accompanied by acute symptoms. Any revascularization was defined as PCI with stenting or coronary artery bypass graft (CABG) of any epicardial vessel. Event adjudication was performed by trained study personnel unaware of the final physiological assessment.

### Statistical analysis

Baseline, categorical variables are reported as either counts or percentages and compared using the Chi Squared test on patient level. Baseline, continuous variables are reported as mean ± standard deviation and are compared using the independent t-test on patient level. The association between vFFR and clinical endpoints was analyzed by Cox proportional hazard regression analysis. Univariate predictors of outcomes were identified using Cox proportional-hazards model. Predictors with a p-value < 0.1 were introduced in the multivariate Cox proportional-hazards model using the 'enter' method. Data are presented as Hazard-Ratio (HR) with a 95% confidence interval (CI 95%). All tests were two-tailed and a P value < 0.05 was considered statistically significant. The Kaplan-Meier method was applied to show the cumulative incidence of the primary and secondary endpoints, whereas log-rang tests were applied to evaluate differences between the groups. Patients that were lost to follow-up were censored at the date of the last contact. Statistical analyses were performed by using SPSS statistics for Windows, version 24.0 (SPSS, Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

## RESULTS

### Patients and vessels demographics

A total of 810 vessels from 810 patients were included. Patients and vessels baseline characteristics are depicted in **Table 1**. Mean age was 64±12 years and 71% were male. Diabetes was present in 18%, 51% hypertension and 41% dyslipidemia. Clinical presentation was stable angina in 28% of the cases, while 38% and 34% of the patients presented with unstable angina and STEMI

respectively. 10% of the stented lesions were bifurcation lesions, 8% were ostial and 22% of the stented lesions were calcified.

**Table 1.** Patient and vessel characteristics in the different tertiles according to post PCI vFFR; Lower (<0.90), middle (0.90-0.95) and upper (>0.94).

| | Total (n=810) | Lower (n=258) | Middle (n=265) | Upper (n=287) | p-value |
|---|---|---|---|---|---|
| Age (years) | 64±12 | 65±12 | 64±12 | 63±13 | |
| Male gender (n) | 572 (71) | 180 (70) | 196 (74) | 196 (68) | 0.322 |
| BMI, mean±SD | 27±4 | 27±5 | 27±4 | 28±4 | |
| Mean post PCI vFFR | 0.90±0.9 | 0.80±0.10 | 0.92±0.01 | 0.97±0.01 | |
| **Cardiovascular risk factors, n(%)** | | | | | |
| Hypertension | 414 (51) | 128 (50) | 125 (47) | 161 (56) | **0.094** |
| Hypercholesterolemia | 332 (41) | 109 (42) | 102 (39) | 121 (42) | 0.602 |
| Diabetes | 145 (18) | 51 (20 ) | 51 (19) | 43 (15) | 0.272 |
| Current smoker | 230 (28) | 67 (26) | 63 (24) | 100 (34) | **0.009** |
| Peripheral art. Disease | 57 (7) | 19 (4 ) | 14 (5) | 24 (8) | 0.357 |
| **Comorbidity, n(%)** | | | | | |
| Prior myocardial infarction | 166 (21) | 53 (21) | 52 (20) | 61 (21) | 0.903 |
| Prior PCI | 209 (26) | 80 (31) | 67 (25) | 62 (22) | **0.042** |
| **Indication for PCI, n(%)** | | | | | |
| Stable angina | 229 (28) | 72 (28) | 82 (31) | 75 (26) | 0.450 |
| Unstable angina / NSTEMI | 306 (38) | 98 (38) | 105 (40) | 103 (36) | 0.665 |
| STEMI | 275 (34) | 88 (34) | 78 (29) | 109 (38) | 0.106 |
| **Measured vessel, n (%)** | | | | | |
| Right coronary artery | 317 (39) | 60 (23) | 94 (36) | 163 (57) | **<0.001** |
| Left anterior descending artery | 358 (44) | 153 (59) | 122 (46) | 83 (29) | **<0.001** |
| Left circumflex artery | 134 (17) | 45 (17) | 49 (19) | 40 (14) | 0.318 |
| Bifurcation | 80 (10) | 34 (13) | 19 (7) | 27 (9) | **0.067** |
| Calcification | 180 (22) | 64 (25) | 62 (23) | 54 (19) | 0.210 |
| In-stent restenosis | 52 (6) | 16 (6) | 15 (6) | 21 (7) | 0.721 |
| Thrombus | 225 (28) | 72 (28) | 67 (25) | 86 (30) | 0.469 |
| Ostial | 63 (8) | 22 (9) | 21 (8) | 20 (7) | 0.783 |

BMI= Body Mass Index; PCI= percutaneous coronary intervention; (N)STEMI= (non) ST-elevation myocardial infarction

## Distribution of post PCI vFFR

Mean post PCI vFFR was 0.90±0.09. Post PCI vFFR was ≤0.80 in 12% of the vessels and ≤0.90 in 37% of the vessels. **Figure 2.**

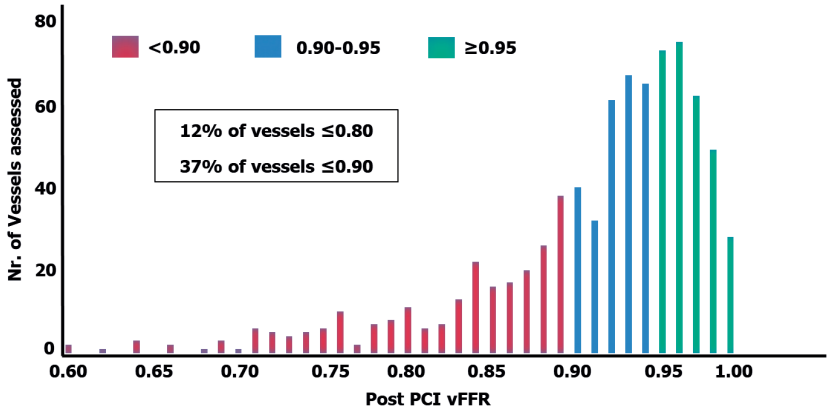



**Figure 2.** Distribution of post PCI vFFR

## Clinical outcome at 12 months follow up

Complete follow up was obtained in 97.2%of the patients. The cumulative incidence of MACE was 6.5% in the overall study population. No statistical difference were found in MACE rate between the lower and the upper tertiles (8% vs. 5%, respectively; HR 1.62; 95% CI [0.82-3.20] p=0.168) or target vessel revascularization (4% vs. 2%, respectively; HR 2.05; 95% CI [0.69-6.13] p=0.197). When adjusted to age, sex, hypertension, smoking, prior PCI, RCA, LAD and bifurcation, still no significant difference was found in MACE rate (HR 1.51, 95% CI [0.70-3.22], p=0.291) and TVR (HR 1.58, 95% CI [0.47-5.31] p=0.460). **Table 2 and Figure 3.**

**Table 2.** One year clinical outcome: comparison between lower (<0.90) vs. upper (>0.94) and middle (0.90-0.95) vs. upper tertitles according to post PCI vFFR.

| | Lower (n=258) | Middle (n=265) | Upper (n=287) | HR [95% CI] | p-value |
|---|---|---|---|---|---|
| **Unadjusted** | | | | | |
| MACE | 20 (8) | | 14 (5) | 1.62 [0.82-3.20] | 0.168 |
| Cardiac Death | 10 (4) | | 7 (2) | 1.60 [0.61-4.21] | 0.340 |
| Any MI | 4 (2) | | 5 (2) | 0.90 [0.24-3.34] | 0.873 |
| TVR | 9 (4) | | 5 (2) | 2.05 [0.69-6.13] | 0.197 |
| Any Revascularization | 51 (20) | | 46 (16) | 1.28 [0.86-1.90] | 0.228 |
| Stent thrombosis | 3 (1) | | 2 (0.2) | 1.70 [0.28-10.16] | 0.562 |
| **Adjusted for age, sex, hypertension, current smoker, prior PCI, RCA, LAD and Bifurcation** | | | | | |
| MACE | | | | 1.51 [0.70-3.22] | 0.291 |
| Cardiac Death | | | | 1.53 [0.52-4.48] | 0.441 |
| Any MI | | | | 1.25 [0.31-5.12] | 0.754 |
| TVR | | | | 1.58 [0.47-5.31] | 0.460 |
| Any Revascularization | | | | 1.27 [0.82-1.97] | 0.284 |

**Table 2.** One year clinical outcome: comparison between lower (<0.90) vs. upper (>0.94) and middle (0.90-0.95) vs. upper tertitles according to post PCI vFFR. (continued)

| | Lower (n=258) | Middle (n=265) | Upper (n=287) | HR [95% CI] | p-value |
|---|---|---|---|---|---|
| Stent thrombosis | | | | 2.16 [0.28-16.64] | 0.458 |
| **Unadjusted** | | | | | |
| MACE | | 19 (7) | 14 (5) | 1.49 [0.75-2.97] | 0.257 |
| Cardiac Death | | 9 (3) | 7 (2) | 1.40 [0.52-3.56] | 0.505 |
| Any MI | | 4 (2) | 5 (2) | 0.87 [0.23-3.25] | 0.838 |
| TVR | | 7 (3) | 5 (2) | 1.54 [0.49-4.85] | 0.461 |
| Any Revascularization | | 56 (21) | 46 (16) | 1.37 [0.93-2.02] | 0.117 |
| Stent thrombosis | | 1 (0.4) | 2 (0.2) | 0.55 [0.05-6.02] | 0.621 |
| **Adjusted for age, sex, hypertension, current smoker, prior PCI, RCA, LAD and Bifurcation** | | | | | |
| MACE | | | | 1.31 [0.64-2.71] | 0.460 |
| Cardiac Death | | | | 1.37 [0.49-3.83] | 0.553 |
| Any MI | | | | 0.77 [0.20-3.05] | 0.714 |
| TVR | | | | 1.23 [0.38-4.04] | 0.730 |
| Any Revascularization | | | | 1.33 [0.89-2.00] | 0.170 |
| Stent thrombosis | | | | 0.69 [0.05-10.02] | 0.787 |

## DISCUSSION

The main finding of the present FAST Outcome study are as follows: 1) despite angiographically successful PCI results, 37% of the stented vessels end with a post PCI vFFR ≤0.90. 2) There was a trend towards higher rates future adverse event rates in the lower Post PCI vFFR tertile as compared to the upper tertile.

To the best of our knowledge, the FAST Outcome study is the largest study on the distribution and prognostic value of post PCI angiography based FFR to date and the first to correlate post PCI vFFR to 12 months clinical outcome. We were able to demonstrate that despite optimal final angiographic results, assessed at the discretion of the operator, post PCI vFFR was ≤0.90 in 37% of the patients and even ≤0.80 in 12% of the patients. The latter implies that with a simple and fast non-invasive diagnostic tool we might be able to identify those patients at the highest risk for future adverse cardiac events and adds to previous literature on the post PCI physiological assessment using either pressure wire or microcatheter based FFR or NHPR. As such The FFR-SEARCH (Fractional Flow Reserve Stent Evaluation at Rotterdam Cardiology Hospital) registry which is the largest post PCI FFR study thus far, has shown that up to 56% of the patients had at least one lesion with a post PCI FFR ≤0.90 despite adequate angiographic results. (17) The clinical impact of low post PCI FFR was demonstrated by a series of studies demonstrating a strong correla-

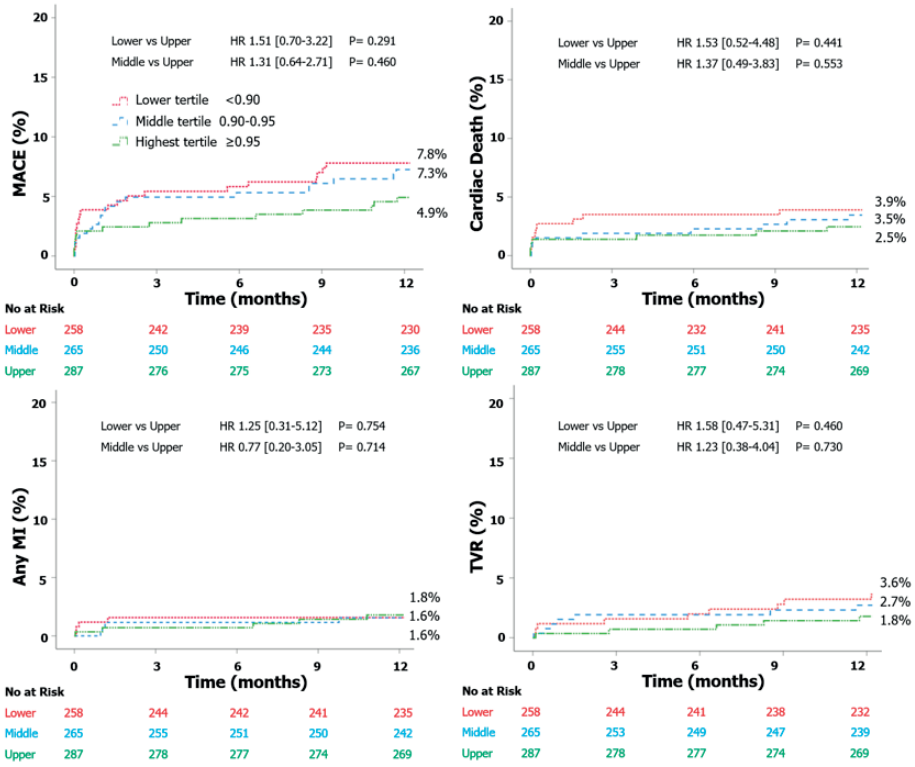



**Figure 3.** One year clinical outcome rates in lower, middle and upper post PCI vFFR tertiles. The hazard ratio's, 95% CI and p-values are all adjusted values.

tion between post PCI FFR and the risk for future adverse events. More specifically, event rates showed to linearly accrue when post PCI FFR values decreased. (18-21)

Despite the superiority of physiology as compared to angiography guided PCI, the uptake of the various physiological measurement tools and indices in real world practice, especially in a post PCI setting, is still limited. (18, 19, 21-23) The latter has been linked to the need for costly pressure wires or microcatheters, time, and hyperemic agents with known side effects. While the latter arguments proved to be invalid in dedicated studies, the introduction of vFFR might open up the door for a more liberal use of post PCI physiological assessment which might eventually lead to focused post PCI optimization with or without the use of intracoronary imaging. (24)

More insights into the explanation of low post PCI FFR have been provided by a dedicated IVUS substudy of FFR-SEARCH registry demonstrating that residual proximal or distal lesions, or stent related problems including underexpansion, malapposition and edge dissections or hematomas were present in 84% of the patients with a post PCI FFR ≤0.85. (25) Comparable findings were

observed when studying post PCI NHPR. The recently presented DEFINE PCI study showed that 24% of patients ended with post PCI iFR values of ≤0.89 which concluded that if all residual iFR detected focal lesions could be treated, the rate of significant ischemia could be theoretically reduced from 24% to 5%. (22)

The FAST Outcome study is a successor in a series of FAST studies which have shown a high correlation between conventional pressure wire or microcatheter based FFR and 3D-QCA based vFFR both in a pre- and post PCI setting. (9, 10) However, at present no data are available on the use of post PCI 3D QCA based physiological indices and their prognostic value.

In the present study, the mean post PCI vFFR was 0.90±0.09 which is in line with the mean post PCI pressure wire based FFR (0.90±0.07) of the FFR-SEARCH study. (17) Additionally, we were able to demonstrate that despite satisfactory angiographic results, 37%% of the patients had a post PCI vFFR ≤0.90. One year follow-up revealed numerically higher MACE rates in lower post PCI vFFR tertile. The latter is in line with the 2 year findings of the FFR SEARCH registry (13.7% vs. 11.8% in patients with FFR<0.90 and ≥0.90 respectively) in which the prognostic value of post PCI FFR as measured using a dedicated monorail microcatheter was assessed. (26) It should be acknowledged however that also the present study included all-comers including patients presenting with STEMI. When performing a sensitivity analyses on patients without STEMI, we found comparable results: MACE adjusted HR 1.2,1 95% CI [0.65-6.39] p=0.219 and for TVR adjusted HR 1.24 [0.31-4.94] p=0.764

### Limitations

Several limitations of the study need to be addressed. First, the FAST Outcome study results are based on a single-center experience in which the majority of the patients were excluded due to missing post PCI angiographic projection for vFFR calculation. Second, only 1-year follow-up was available precluding any statements on the long-term prognostic value of post PCI vFFR. Clinical large prospective outcome studies are eagerly awaited to assess the prognostic value of post PCI vFFR in routine clinical practice. Finally, in contrast to DEFINE PCI study which provided clear insights in the iFR gain in individual patients from pre- to post PCI (mean 0.24) and providing details on the exact position of the pressure drop within the treated vessel, in the present study no information is given on exact position of the pressure drop since no pullbacks were available.

## CONCLUSION

Despite angiographically successful PCI results, 37% of the stented vessels end up with a post PCI vFFR ≤0.90. There was a strong trend towards higher rates future adverse events in case post PCI vFFR was ≤0.90.

## REFERENCES

1. Davies JE, Sen S, Dehbi HM, Al-Lamee R, Petraco R, Nijjer SS, et al. Use of the Instantaneous Wave-free Ratio or Fractional Flow Reserve in PCI. N Engl J Med. 2017;376(19):1824-34.
2. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014;371(13):1208-17.
3. Gotberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, et al. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. N Engl J Med. 2017;376(19):1813-23.
4. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.
5. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv. 2016;9(10):1022-31.
6. Leesar MA, Satran A, Yalamanchili V, Helmy T, Abdul-Waheed M, Wongpraparut N. The impact of fractional flow reserve measurement on clinical outcomes after transradial coronary stenting. EuroIntervention. 2011;7(8):917-23.
7. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation. 2002;105(25):2950-4.
8. Kasula S, Agarwal SK, Hacioglu Y, Pothineni NK, Bhatti S, Ahmed Z, et al. Clinical and prognostic value of poststenting fractional flow reserve in acute coronary syndromes. Heart. 2016;102(24):1988-94.
9. Masdjedi K, van Zandvoort LJC, Balbi MM, Gijsen FJH, Ligthart JMR, Rutten MCM, et al. Validation of 3-Dimensional Quantitative Coronary Angiography based software to calculate Fractional Flow Reserve: Fast Assessment of STenosis severity (FAST)-study. EuroIntervention. 2019.
10. Masdjedi K M, Van Zandvoort LJC B, Balbi M M, Ligthart JMR R, Nuis RJ M, PhD, Vermaire A R, et al. Validation of novel 3-Dimensional Quantitative Coronary Angiography based software to calculate Fractional Flow Reserve post stenting. TCT 2018. 2018.
11. Lemmert ME, van Mieghem NM, van Geuns RJ, Diletti R, van Bommel RJ, van Domburg RT, et al. The Promus Premier everolimus-eluting platinum chromium stent with durable polymer evaluated in a real world all-comer population in Rotterdam cardiology hospital (the P-SEARCH registry). Int J Cardiol. 2017;240:103-7.
12. Gould KL, Kelley KO, Bolson EL. Experimental validation of quantitative coronary arteriography for determining pressure-flow characteristics of coronary stenosis. Circulation. 1982;66(5):930-7.
13. Kirkeeide R. Coronary obstructions, morphology and physiologic significance. 1991:229–44.
14. Girasis C, Schuurbiers JC, Muramatsu T, Aben JP, Onuma Y, Soekhradj S, et al. Advanced three-dimensional quantitative coronary angiographic assessment of bifurcation lesions: methodology and phantom validation. EuroIntervention. 2013;8(12):1451-60.
15. Schuurbiers JC, Lopez NG, Ligthart J, Gijsen FJ, Dijkstra J, Serruys PW, et al. In vivo validation of CAAS QCA-3D coronary reconstruction using fusion of angiography and intravascular ultrasound (ANGUS). Catheter Cardiovasc Interv. 2009;73(5):620-6.
16. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007;115(17):2344-51.
17. van Bommel RJ, Masdjedi K, Diletti R, Lemmert ME, van Zandvoort L, Wilschut J, et al. Routine Fractional Flow Reserve Measurement After Percutaneous Coronary Intervention. Circ Cardiovasc Interv. 2019;12(5):e007428.

18. Agarwal SK, Kasula S, Almomani A, Hacioglu Y, Ahmed Z, Uretsky BF, et al. Clinical and angiographic predictors of persistently ischemic fractional flow reserve after percutaneous revascularization. Am Heart J. 2017;184:10-6.
19. Ishii H, Kataoka T, Kobayashi Y, Tsumori T, Takeshita H, Matsumoto R, et al. Utility of myocardial fractional flow reserve for prediction of restenosis following sirolimus-eluting stent implantation. Heart Vessels. 2011;26(6):572-81.
20. Johnson NP, Toth GG, Lai D, Zhu H, Acar G, Agostoni P, et al. Prognostic value of fractional flow reserve: linking physiologic severity to clinical outcomes. J Am Coll Cardiol. 2014;64(16):1641-54.
21. Nam CW, Hur SH, Cho YK, Park HS, Yoon HJ, Kim H, et al. Relation of fractional flow reserve after drug-eluting stent implantation to one-year outcomes. Am J Cardiol. 2011;107(12):1763-7.
22. Allen Jeremias M, Msc, Justin Davis, manesh Patel, Gregg Stone, the DEFINE PCI Investigators. Blinded Physiological Assessment of Residual Ischemia after Successful Angiographic PCI. Oral presentation at ACC. 2019.
23. Doh JH, Nam CW, Koo BK, Lee SY, Choi H, Namgung J, et al. Clinical Relevance of Poststent Fractional Flow Reserve After Drug-Eluting Stent Implantation. J Invasive Cardiol. 2015;27(8):346-51.
24. van Zandvoort LJC, Masdjedi K, Tovar Forero MN, Lenzen MJ, Ligthart J, Diletti R, et al. 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. Am Heart J. 2019;213:66-72.
25. van Zandvoort LJC, Masdjedi K, Witberg K, Ligthart J, Tovar Forero MN, Diletti R, et al. Explanation of Postprocedural Fractional Flow Reserve Below 0.85. Circ Cardiovasc Interv. 2019;12(2):e007030.
26. Diletti RM, K; Van Zandvoort, L; Lemmert, M; Van Bommel, R; Den Dekker, WK; Wilschut, J; De Jaegere, P; Boersma, E; Zijlstra, F; Daemen, J; Van Mieghem, N. Routine fractional flow reserve measurement after PCI the FFR-search study 2-year follow-up. EuroPCR 2019. 2019.

# Chapter 19

# Coronary physiology assessment in a cardiac transplant patient

Laurens J.C. van Zandvoort, BSc; **Kaneshka Masdjedi, MD,** Maria N. Tovar Forero, MD, Olivier Manintveld MD, PhD, Joost Daemen, MD, PhD.

**Department of cardiology, Erasmus MC, Rotterdam, the Netherlands**

**Journal:** Netherlands Heart Journal; 2019 27:385–386

A 39-year-old male received a coronary angiography, 14 years after cardiac allograft transplantation, indicating a significant lesion in the left coronary artery (LAD). Coronary angiography revealed an intermediate lesion in the LAD, for which further physiological assessment was considered necessary. (figure 1). Subsequent pressure wire based $FFR_{pw}$ was 0.87, suggesting a non-significant lesion, however non-hyperemic 3D based quantitative coronary angiography based vessel fractional flow reserve (vFFR) was 0.74 (figure 1B). Given the discrepancies, optical coherence tomography was performed showing a fibrofatty plaque with a minimal lumen area (MLA) of 1.70$mm^2$. The LAD was subsequently treated with a 3.0x15mm stent. There has been ongoing debate on the validity of using FFR in denervated hearts due to high rates of microvascular dysfunction and an unreliable hyperemic response (1). Anatomical based assessment might be the preferable choice to assess the significance of intermediate coronary lesions in denervated hearts (2, 3).

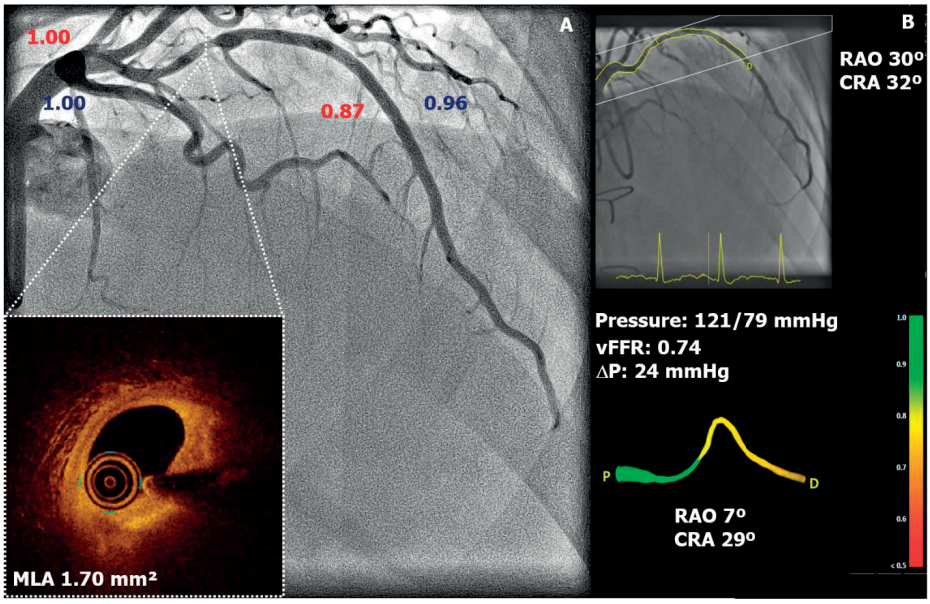



**Figure 1 A.** Coronary angiography of a patients, 14 years after allograft cardiac transplant. The LAD shows a angiograpic intermediate stenosis in the mid segment, Pd/Pa values in blue and FFR values in red. Optical coherence tomography of the LAD shows a 15 mm lesion with a minimal lumen area (MLA) of 1.70$mm^2$ and appropriate landing zones. B. Vessel fractional flow reserve (vFFR) of the LAD. The vFFR is 0.74, which indicates a significant lesion (threshold ≤0.80).

## REFERENCES

1. De Bruyne B, Fearon Wf, Pijls NHJ, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014;1533-4406.
2. Douglas PS, Pontone G, Hlatky MA, Patel MR, et al. Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of FFR(CT): outcome and resource impacts study. European Heart Journal. 2015;36(47):3359-67.
3. Masdjedi K. Validation of novel three-dimensional quantitative coronary angiography based software to calculate vessel FFR: the FAST study. Novel approaches to coronary physiology. Oral presentation. EuroPCR, Paris: 2018.

# PART V
## EPILOGUE

"In this earth. In this soil. In this pure field let's not plant any seed other than seeds of compassion and love"
—Mavlana J. Balkhi Rumi

# Chapter

# 20

# SUMMARY AND CONCLUSIONS

Fractional Flow Reserve (FFR) guided percutaneous coronary intervention (PCI) has been shown to improve both patient outcome and cost-effectiveness as compared to angiography guided PCI. (1-4) In the past years, FFR has become the gold standard for hemodynamic assessment of intermediate coronary artery lesions resulting in a class IA recommendation in current revascularization guidelines. (5, 6) At the same time, the use of post PCI physiological assessment is gaining attention. A strong and linear association has been demonstrated between post PCI FFR and the risk for both future repeat revascularization as well as hard clinical endpoints as death and myocardial infarction. (7-9) However, despite unequivocal evidence supporting the use of FFR to guide clinical decision-making, adoption into routine practice has been limited and in particular FFR assessment after stenting is rarely performed. The latter illustrates the need for tools that allow simple and fast post PCI physiological assessment without the need for a pressure wire and hyperemic agent. The aim of the present thesis was: 1) to evaluate the distribution of post-PCI FFR and to investigate its clinical impact on long terms clinical outcomes. 2) to validate a novel non-hyperemic diastolic pressure ratio and to evaluate its post PCI value in terms of clinical outcome and 3) to develop and to validate a 3D angiography based index allowing fast and easy physiological lesion assessment without the need for an invasive pressure wire in order to further lower the threshold for performing coronary physiology in routine practice.

## PART II – FFR AFTER ANGIOGRAPHICALLY SUCCESSFUL PCI

At present, several pressure wire systems are available and approved for FFR-measurements. The RXi Navvus system (ACIST Medical Systems, Eden Prairie, MN) is a novel monorail microcatheter with a lesion entry profile of 0.022” and an optical pressure sensor located close to the distal tip for FFR measurement. **Chapter 3** aimed to assess whether the theoretical advantages of the Navvus technology would result in overall reductions in contrast volume, radiation and costs in comparison with conventional wire based FFR. The CONTRACT study demonstrated that the use of the Navvus microcatheter to perform FFR in an everyday PCI proved to be similar to conventional, wire based FFR systems with respect to cost and the use of contrast and radiation. Previous studies have shown that the Navvus FFR microcatheter has several distinct features as compared to the conventional pressure wire systems. (8) First, the system allows the operator to use a first choice guidewire to deal with all kinds of lesions, including vessels with excessive tortuosity, acute angulation and calcification, without the need to rely on the sometimes suboptimal characteristics of conventional non-hydrophilic pressure wires. In theory, the latter might safe time, radiation and contrast and avoid the need to replace the FFR wire or use a more supportive guidewire in case needed. Second, the system allows multiple pullbacks while maintaining wire access. **Chapter 4** and **Chapter 5** represent the results of the FFR SEARCH study which was the largest prospective study investigating the prognostic value and determinants of post PCI FFR. A total of 1000 patients were included in this single centre registry in Rotterdam in whom the FFR

was measured after a successful PCI in 959 patients. While the primary endpoint consisted of clinical outcomes after two years (**Chapter 5**) , the initial study report in **chapter 4** focusses on the details of which physiological results can be expected after routine post PCI FFR assessment in a real world patient population linking those findings to 30 day outcome figures. The study demonstrated that: 1) Routine measurement of post-PCI FFR is safe and feasible. 2) Approximately one third of patients end up with a post-PCI FFR <0.90. 3) Suboptimal Post-PCI FFR has only a moderate impact on MACE but coronary arteries with a post-PCI FFR<0.90 have a higher rate of TVR. **Chapter 6,** which was a IVUS sub-study of the FFR SEARCH registry, demonstrated for the first time that clear signs of residual luminal narrowing, including focal lesions, underexpansion and malapposition, were present in a significant number of vessels with an impaired post PCI FFR. Findings that were not readily apparent on routine angiography. Several recent studies demonstrated the value of low post PCI FFR in predicting late adverse cardiac events. Unfortunately, details on the actual rationale for these low post PCI FFR values often remained elusive since no data on residual angiographically apparent disease were reported, nor were details presented on intravascular imaging findings. In our study detailed intravascular ultrasound analysis revealed specific morphologic explanations for suboptimal post PCI FFR. In the FFR SEARCH IVUS study we found a high proportion of residual focal lesions, stent underexpansion and malapposition in vessels with a post PCI FFR ≤0.85; findings that were not readily apparent on coronary angiography (10). The predefined long-term follow-up analysis demonstrated a clear trend towards higher rates of TVF at two years when IVUS derived residual lesions were found, **Chapter 7**. In order to provide a decisive answer as to what are the predictors of post procedural fractional flow reserve values, the study in **Chapter 8** was designed. We identified several independent patient and vessel related variables which predicted post PCI FFR. In a LME-model, adjusting for independent predictors of post PCI FFR, females had a significantly higher mean post PCI FFR as compared to men (adjusted ß=0.013, CI [0.005 to 0.02], p=0.001, R2 for the complete model=0.54). The vessel in which the physiological measurements were taken was the strongest predictor, resulting in an average of 0.06 lower post PCI FFR value in LAD vessels. Additionally, type A lesions, in-stent restenosis, CTO's, post PCI MLD and pre – and post dilatation were significant predictors for post PCI FFR.

Using intravascular ultrasound (IVUS) we are able to detect potential causes of low FFR post stenting. However, being continuously criticized for not providing clear recommendations on how to react to low post PCI FFR, we designed a prospective randomized trial to answer this question. In **Chapter 9** we describe the rationale and design of the FFR REACT trial, which 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 (defined as those with a post-PCI FFR < 0.90) will decrease the risk of target vessel failure at 1 year. Inclusion has been completed and the 1 year follow up data are expected in Q3 2021. 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.

## PART III – NOVEL NON-HYPEREMIC DIASTOLIC INDEX

In recent years, non-hyperemic pressure ratios (NHPR), such as the instantaneous wave-free ratio (iFR) and resting distal coronary artery pressure/aortic pressure (Pd/Pa), were introduced as alternative invasive indices to assess the severity of coronary artery stenosis. While Pd/Pa can be calculated from any type of pressure wire or microcatheter, the algorithm of iFR belongs to the iFR core laboratory (Imperial College, London, United Kingdom) and its use is restricted to the proprietary software of a single vendor (Philips Volcano). In **Chapter 10** we validated a generic diastolic pressure ratio (dPR), calculated using in-house developed novel software applicable to any type of pressure wire or microcatheter, to assess the correlation of dPR with iFR and to assess the diagnostic accuracy of dPR as compared to FFR and resting Pd/Pa. dPR proved to have an excellent linear correlation with iFR and a strong diagnostic accuracy in identifying lesions with an FFR ≤0.80. In **Chapter 11** we evaluated the distribution of dPR after angiographically successful PCI in an all-comer population and we studied its association with 2-year clinical outcome. Despite optimal angiographic PCI results, 15.2% of the patients ended up with a post PCI dPR of ≤0.89 which was associated with a significantly higher cardiac mortality rate and numerically higher rates of TVF. Our work thereby complements the findings of the DEFINE PCI study in which 22.6% of the treated vessels ended up with a post PCI iFR ≤0.89. (11) Our work however differed from the DEFINE PCI population by enrolling a larger and more real-world patient population in which patients with prior CABG, CTO treatment, ST segment myocardial infarction (STEMI) and TIMI flow <3 were not excluded. Especially the inclusion of patients presenting with STEMI and the lower number of patients with diabetes (19% vs 34% respectively) might explain the numerically lower number of cases of a post PCI dPR≤0.89 as compared to the DEFINE PCI study. Despite the restoration of epicardial blood flow through PCI, patients with STEMI have abnormal myocardial perfusion at the end of the procedure. (12) This phenomenon is thought to be related to microvascular obstruction due to distal embolization, reperfusion injury and tissue inflammation due to myocyte necrosis. (13) In addition physiologic assessment in patients with diabetes mellitus underestimates disease severity because of diffuse coronary atherosclerosis, microvascular disease and a tendency for negative remodeling. (14) The latter resulted in the pre-defined subanalysis in patients presenting with stable- or unstable angina or NSTEMI in which a more pronounced effect of post PCI dPR≤0.89 was seen to predict 2 year TVF rates.

## PART IV – INTRODUCTION AND VALIDATION OF 3D-QCA BASED FFR

Despite the advent of several non-hyperemic pressure ratio's, there is a clear need to simplify the use of coronary physiology because FFR is still not being performed in the majority of cases. The latter has been hypothesized to be due to the need for (in some countries) expensive hyperemic agents with known adverse events as dyspnea and arrhythmias and or intolerance due to pulmonary disease and the use of a costly pressure wire. In **Chapter 12** we summarized the development of FFR over the past years, from pressure wire based FFR to CTFFR and angiography based FFR. The FAST study (**Chapter 13**) is the first validation study of vessel FFR which is an angiography based FFR. The study confirmed the feasibility of novel 3D-QCA based software to calculate FFR without the use of a pressure wire or microcatheter. In the pre-clinical technical validation model vFFR proved to have a strong correlation with CFD and measured flow parameters. We were able to conclude that vFFR had ahigh linear correlation with pressurewired-based FFR (r=0.89), a high diagnostic accuracy (AUC 0.93) to detect FFR ≤ 0.80, along with a low inter-observer variability (r=0.95). We were able to confirm these findings in the subsequent FAST Extend study (**Chapter 14**) as well as in a post PCI setting. The FAST POST study (**Chapter 15**) demonstrated good correlation and agreement with post PCI FFR as measured using a dedicated microcatheter and has a low inter-observer variability. The Fast II study (**Chapter 16**) was an observational, prospective, multicenter, international study which validated CAAS Workstation to calculate vessel-FFR. vFFR calculations were performed by an independent core laboratory (Cardialysis BV). A good correlation was found between FFR and vFFR. vFFR had an excellent diagnostic accuracy in identifying lesions with an FFR≤0.80. 3D-QCA-based vFFR correlates well with pressure wire based FFR and has an excellent diagnostic performance to detect FFR ≤0.80. Positive predictive value, negative predictive value, diagnostic accuracy, sensitivity and specificity of vFFR were 90%, 90%, 90%, 81% and 95% respectively. The FAST LM study aimed to evaluate the feasibility of using vFFR for left main disease and to correlate vFFR values with IVUS measurements for evaluation of intermediate to severe LMCA stenosis (**Chapter 17**). In a selected patient population with sufficient angiogram quality, vFFR demonstrated a good linear correlation with IVUS-derived MLA and a good sensitivity to detect lesions with IVUS-confirmed significant disease (r=.792, p=0.001; sensitivity 98%, specificity 71.4% and area under the curve (AUC) 0.95, 95% confidence interval (CI) 0.89–1.00, p = .001)

The FAST Outcome study (**Chapter 18**) aimed to assess the prognostic value of post PCI vFFR on the incidence of MACE, a composite endpoint of cardiac death, myocardial infarction and target vessel revascularization (TVR) at 12 months follow up. The study demonstrated that despite angiographically successful PCI results, 37% of the stented vessels end up with a post PCI vFFR ≤0.90. There was a strong trend towards higher rates of future adverse events in the low post PCI vFFR cohort ((8% vs. 5%, respectively; HR 1.62; 95% CI [0.82-3.20] p=0.168) or target vessel revascularization (4% vs. 2%, respectively; HR 2.05; 95% CI [0.69-6.13] p=0.197). In **Chapter 19**

we proposed another potential group of patients who might benefit from 3D-QCA based vFFR: patients with possible epicardial disease after a cardiac transplant. In the early years after cardiac transplantation, both negative remodeling of the epicardial arteries as well as a decrease in microvascular resistance (IMR) are common findings. **Chapter 19** is a case of a 39 year old male patient, 14 years after allograft cardiac transplantation with a suspected significant lesion. Invasive assessment using conventional intracoronary physiology assessment using FFR showed a significant discrepancy with findings on OCT and the vFFR. Illustrated by the present case, we believe that a strong argument can be made towards to use of these novel technologies that might potential be superior to conventional assessment in the routine follow-up of these high risk patients.

## FUTURE PERSPECTIVES

The body of evidence on the superiority of physiology as compared to angiography guided PCI in both stable and unstable patients is still increasing and leaves little room for interpretation as reflected by current guideline recommendations. Whereas similar data is available related to the use of intravascular imaging, outcomes of contemporary PCI leave room for improvement. Although the latter could theoretically be realized by a more liberal use of coronary imaging and physiology both technologies are still underused in real world practice. With the introduction of simplified ways of physiological assessment, by discarding hyperemic agents (dPR) and perhaps even invasive devices in general (vFFR) the arguments for not using physiological assessment become scarcer every day. The latter also opens the door towards a more focused use of intracoronary imaging in an approach to preselect those vessels which might benefit the most from pre procedural image guided assessment and treatment as well as post PCI optimization (FFR REACT).

In order to further drive the adoption of this novel approach there is a need for dedicated randomized outcome trials including the FFR REACT trial that assess whether post PCI optimization in case of suboptimal post PCI FFR values is safe and able to improve long-term patient outcome. Similar future studies are needed to settle the role of angiography based FFR in contemporary practice. As such, the successor in the pipeline of FAST studies (the international multicenter randomized FAST III trial, NCT04931771) is currently being initiated to demonstrate the non-inferiority of vFFR as compared to conventional pressure wire based FFR.

## CONCLUSIONS

NHPRs including dPR comprise valuable diagnostic alternatives to conventional hyperemic pressure wire based FFR. Along with device advancements like dedicated microcatheters allowing persistent guidewire access, these technology confer a first step in simplifying physiological lesion assessment that might help to increase the use of coronary physiology in both pre- and post PCI settings.

Building on this concept, 3D-QCA based FFR might comprise a generation breakthrough technology that could simplify physiological lesion assessment by incorporating an index (vFFR) with a high diagnostic accuracy as compared to conventional pressure wire based FFR and a low interobserver variability applicable to wide variety of patients.

Finally, we demonstrated in a series of studies the clinical relevance of extending physiological lesion assessment (using both conventional and novel indices) to a post PCI setting. Suboptimal post PCI physiology proved to correlate to future adverse cardiac events that could potentially in part be avoided by focused use of invasive coronary imaging and subsequent optimization maneuvers.

## REFERENCES:


1. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014;371(13):1208-17.
2. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol. 2010;56(3):177-84.
3. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007;49(21):2105-11.
4. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.
5. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124(23):e574-651.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2018.
7. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv. 2016;9(10):1022-31.
8. Leesar MA, Satran A, Yalamanchili V, Helmy T, Abdul-Waheed M, Wongpraparut N. The impact of fractional flow reserve measurement on clinical outcomes after transradial coronary stenting. EuroIntervention. 2011;7(8):917-23.
9. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation. 2002;105(25):2950-4.
10. van Zandvoort LJC, Masdjedi K, Witberg K, Ligthart J, Tovar Forero MN, Diletti R, et al. Explanation of Postprocedural Fractional Flow Reserve Below 0.85. Circ Cardiovasc Interv. 2019;12(2):e007030.
11. Jeremias A, Davies JE, Maehara A, Matsumura M, Schneider J, Tang K, et al. Blinded Physiological Assessment of Residual Ischemia After Successful Angiographic Percutaneous Coronary Intervention: The DEFINE PCI Study. JACC Cardiovasc Interv. 2019;12(20):1991-2001.
12. Stone GW, Webb J, Cox DA, Brodie BR, Qureshi M, Kalynych A, et al. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. JAMA. 2005;293(9):1063-72.
13. Shah NR, Al-Lamee R, Davies J. Fractional flow reserve in acute coronary syndromes: A review. Int J Cardiol Heart Vasc. 2014;5:20-5.
14. Bishop AH, Samady H. Fractional flow reserve: critical review of an important physiologic adjunct to angiography. Am Heart J. 2004;147(5):792-802.

# Chapter 21

# Nederlandse samenvatting

## SAMENVATTING EN CONCLUSIES

Percutane coronaire interventie (PCI) o.b.v. Fractional Flow Reserve (FFR) verbetert zowel de uitkomst voor de patiënt als de kosteneffectiviteit in vergelijking met PCI op basis van angiografie. (1-4) In de afgelopen jaren is FFR de gouden standaard geworden voor hemodynamische beoordeling van intermediaire vernauwingen van de kransslagader, wat heeft geresulteerd in een klasse IA-aanbeveling in de huidige richtlijnen voor revascularisatie. (5, 6) Tegelijkertijd krijgt het gebruik van post-PCI fysiologische beoordeling steeds meer aandacht. Er is een sterke en lineaire associatie aangetoond tussen post PCI FFR en het risico op zowel toekomstige herhaalde revascularisatie als harde klinische eindpunten zoals overlijden en myocardinfarct. (7-9) Ondanks het bewijs dat het gebruik van FFR als leidraad de klinische besluitvorming ondersteunt, is het gebruik in de dagelijkse praktijk echter beperkt en met name post PCI FFR wordt zelden uitgevoerd. Dit illustreert de behoefte aan hulpmiddelen die een eenvoudige en snelle fysiologische beoordeling na PCI mogelijk maken zonder de noodzaak van een drukdraad en hyperemisch middel. Het doel van dit proefschrift was: 1) om de verdeling van post-PCI FFR waarden te evalueren en om de klinische impact ervan op lange termijn uitkomsten te onderzoeken. 2) om een nieuwe niet-hyperemische diastolische index te valideren en de post PCI-waarde ervan te evalueren op lange termijn uitkomsten en 3) om een nieuwe, snelle en gebruiksvriendelijke op angiografie gebaseerde FFR-techniek te ontwikkelen en het te valideren om het gebruik van coronaire fysiologie in onze dagelijkse praktijk te bevorderen.

### DEEL II FFR NA ANGIOGRFISCH SUCCESVOLLE PCI

Momenteel zijn er verschillende drukdraadsystemen beschikbaar en goedgekeurd voor FFR-metingen. Het RXi Navvus-systeem (ACIST Medical Systems, Eden Prairie, MN) is een nieuwe monorail-microkatheter met een profiel van 0,022 inch en een optische druksensor die zich dicht bij de distale tip bevindt voor FFR-meting. **Hoofdstuk 3** was beoogd om te beoordelen of de theoretische voordelen van de Navvus-technologie zouden resulteren in een algehele vermindering van het contrastgebruik, de straling en de kosten in vergelijking met conventionele FFR gemeten met een drukdraad. De CONTRACT-studie toonde aan dat het gebruik van de Navvus-microkatheter om FFR uit te voeren in een alledaagse PCI vergelijkbaar bleek te zijn met conventionele FFR-systemen als het gaat om de kosten, straling en het gebruik van contrast. **Hoofdstuk 4** en **Hoofdstuk 5** hadden tot doel de FFR-waarden prospectief te evalueren na angiografisch succesvolle PCI in een groot cohort van opeenvolgende patiënten en om te kijken of er een verband bestaat tussen post-PCI FFR en klinische uitkomst na respectievelijk 30 dagen en 2 jaar. We ontdekten dat: 1) Routinematige metingen van post-PCI FFR veilig en haalbaar zijn. 2) Ongeveer een derde van de patiënten heeft een post-PCI FFR <0.90. 3) Suboptimale post-PCI FFR heeft slechts een matige/beperkte impact op MACE, maar vaten met een post-PCI FFR <0.90 hebben een hogere kans op TVR. **Hoofdstuk 6**, een IVUS-substudie van de FFR SEARCH studie, toonde voor de eerste keer aan dat duidelijke tekenen van residuele luminale vernauwing, inclusief focale laesies, onderex-

pansie en malappositie, aanwezig waren in een aanzienlijk aantal vaten met een verminderde post-PCI FFR. Dit waren bevindingen die niet direct duidelijk waren bij routinematige angiografie. Verschillende recente onderzoeken hebben de waarde aangetoond van een lage post-PCI FFR bij het voorspellen van late cardiovasculaire events. Helaas bleven details over de achterliggende gedachte/oorzaak voor deze lage post-PCI FFR-waarden vaak ongrijpbaar. Details over angiografisch danwel op intravasculaire imaging vastgelegde data omtrent restziektes residuele ziekte ontbraken. In onze studie demonstreerden wij gedetailleerde IVUS specifieke morfologische verklaringen voor de suboptimale post PCI FFR. (10). De vooraf gedefinieerde follow-up analyse op de lange termijn toonde een duidelijke trend naar hogere percentages TVF na twee jaar in het geval van residuele ziekte op IVUS, **Hoofdstuk 7**. In **Hoofdstuk 8** identificeerden we het geslacht, de LAD en de post PCI MLD als onafhankelijke voorspellers van post PCI FFR. Met behulp van IVUS zijn we in staat om mogelijke oorzaken van lage post PCI FFR op te sporen. Het is momenteel niet bekend of aanvullende interventies die bedoeld zijn om de FFR na de procedure te optimaliseren, de uitkomst voor de patiënt verbeteren. In **hoofdstuk 9** beschrijven we de rationale en het opzet van de FFR REACT-studie, een door de onderzoeker geïnitieerde prospectieve, gerandomiseerde gecontroleerde single-center studie, uitgevoerd in het Erasmus Medisch Centrum, ontworpen om te beoordelen of FFR-geleide PCI-optimalisatie geleid door IVUS bij patiënten met een verhoogd risico voor MACE (post-PCI FFR onder 0.90) zal het beoogde TVR na 1 jaar verminderen. De inclusie is voltooid en de eerste follow-up gegevens zullen naar verwachting in 2021 voltooid zijn. De mogelijke bevindingen en klinische implicaties van deze studie zouden het frequenter gebruik van post-PCI fysiologische beoordeling bevorderen met het doel om de incidentie van MACE te reduceren.

## DEEL III NIEUWE NIET-HYPEREMISCHE DIASTOLISCHE INDEX

In de afgelopen jaren zijn niet-hyperemische druk indices (NHPR), zoals de instantaneous wave-free ratio (iFR) en Pd/Pa, geïntroduceerd als alternatieve invasieve indices om de ernst van kraanslagader vernauwingen te onderzoeken. Hoewel Pd/Pa kan worden berekend op basis van elk type drukdraad of microkatheter, behoort het algoritme van iFR toe aan het iFR-laboratorium (Imperial College, Londen, Verenigd Koninkrijk) en is het gebruik ervan beperkt tot de eigen software van een enkele leverancier (Philips Volcano). In **Hoofdstuk 10** hebben we een generieke diastolische drukratio (dPR) gevalideerd, die is berekend met behulp van een zelf ontwikkelde nieuwe software die toepasbaar is op elk type drukdraad of microkatheter. Wij hebben gekeken naar de correlatie van dPR met iFR en onderzochten de diagnostische nauwkeurigheid van dPR in vergelijking met FFR en Pd/Pa. dPR bleek een uitstekende lineaire correlatie te hebben met iFR en een sterke diagnostische nauwkeurigheid bij het identificeren van laesies met een FFR ≤0.80. In **Hoofdstuk 11** hebben we de verdeling van dPR geëvalueerd na angiografisch succesvolle PCI in een all-comer populatie en hebben we de associatie met 2-jaars klinische resultaten onderzocht.

Ondanks optimale angiografische PCI-resultaten eindigde 15,2% van de patiënten met een post--PCI dPR ≤0.89, wat geassocieerd was met een significant hogere cardiale mortaliteit en een trend naar hogere percentages TVF.

## DEEL IV DE KOMST EN VALIDATIE VAN FFR OP BASIS VAN 3D-QCA

Ondanks de komst van verschillende niet-hyperemische druk indices, is er een duidelijke behoefte om het gebruik van coronaire fysiologie te vereenvoudigen zodat het vaker gebruikt zou worden in de dagelijkse klinische praktijk. In **Hoofdstuk 12** hebben we de ontwikkeling van FFR in de afgelopen jaren samengevat, van de drukdraad tot aan de CTFFR en FFR op basis van angiografie. **Hoofdstuk 13** is de eerste validatiestudie van vessel-FFR (vFFR), een op angiografie gebaseerde FFR. De FAST-studie bevestigde de haalbaarheid van de nieuwe, op 3D-QCA gebaseerde software om FFR te berekenen zonder het gebruik van een drukdraad of microkatheter. In het preklinische technische validatiemodel bleek vFFR een sterke correlatie te hebben met CFD en gemeten flowparameters. In onze klinische validatiestudie bevestigden we een goede overeenkomst en hoge diagnostische nauwkeurigheid van vFFR in vergelijking met invasief gemeten FFR. Ten slotte toonden we aan dat vFFR een lage intra-observer variabiliteit had. We waren in staat om deze bevindingen te bevestigen in de daaropvolgende FAST Extend-studie (**Hoofdstuk 14**) en in een post-PCI-setting. De FAST POST studie (**Hoofdstuk 15**) toonde een goede correlatie en overeenkomst aan met post PCI FFR zoals gemeten met een microkatheter en heeft een lage inter-observer variabiliteit. De FAST II-studie (**Hoofdstuk 16**) was een observationele, prospectieve, multicenter, internationale studie die CAAS Workstation valideerde om de FFR te berekenen. De vFFR-berekeningen zijn uitgevoerd door een onafhankelijk core-laboratorium (Cardialysis BV). Er werd een goede correlatie gevonden tussen FFR en vFFR. vFFR had een uitstekende diagnostische nauwkeurigheid bij het identificeren van laesies met een FFR≤0.80. 3D-QCA-gebaseerde vFFR correleert goed met op drukdraad gebaseerde FFR en heeft uitstekende diagnostische performance om FFR ≤0.80 te detecteren. De FAST LM-studie had als doel om de haalbaarheid van het gebruik van vFFR voor hoofdstam lesies te evalueren en om vFFR-waarden te correleren met IVUS-metingen voor evaluatie van intermediaire tot ernstige LMCA-vernauwing (**Hoofdstuk 17**). In een geselecteerde patiëntenpopulatie met voldoende kwaliteit van het angiogram vertoonde vFFR een goede lineaire correlatie met IVUS-afgeleide MLA en een goede gevoeligheid voor het detecteren van laesies met door IVUS bevestigde significante ziekte. De FAST Outcome-studie (**Hoofdstuk 18**) had als doel de prognostische waarde van post PCI vFFR te beoordelen op de incidentie van MACE, een samengesteld eindpunt van cardiale mortaliteit, myocardinfarct en target vessel revascularisatie (TVR) na 12 maanden follow-up. De studie toonde aan dat ondanks angiografisch succesvolle PCI-resultaten, een aanzienlijk aantal vaten eindigen met een post-PCI vFFR ≤0.90. Er was een sterke trend naar een hogere incidentie van MACE in het lage post-PCI vFFR-cohort.

## TOEKOMSTPERSPECTIEVEN

De hoeveelheid bewijslast omtrent de superioriteit van PCI op geleide van fysiologie in vergelijking met PCI op geleide van angiografie bij zowel stabiele als onstabiele patiënten neemt nog steeds toe en laat weinig ruimte over voor interpretatie, zoals weerspiegeld wordt door de huidige richtlijn-aanbevelingen. Terwijl vergelijkbare gegevens beschikbaar zijn met betrekking tot het gebruik van intravasculaire beeldvormingsresultaten van hedendaagse PCI, is er nog ruimte voor verbetering. Hoewel dit laatste theoretisch zou kunnen worden gerealiseerd door een meer liberaal gebruik van coronaire beeldvorming en fysiologie, worden beide technologieën nog steeds onderbenut in de praktijk. Met de introductie van vereenvoudigde manieren van fysiologische beoordeling (dPR en vFFR) worden de argumenten om geen fysiologische beoordeling te gebruiken elke dag zwakker. Dit opent ook de deur naar een meer gericht gebruik van intracoronaire beeldvorming in een benadering om die vaten te selecteren die het meest kunnen profiteren van pre-procedurele IVUS beoordeling en behandeling, evenals post-PCI-optimalisatie (FFR REACT). Om de acceptatie van deze nieuwe benadering verder te stimuleren, is er behoefte aan specifieke gerandomiseerde uitkomstonderzoeken, waaronder de FFR REACT-studie die beoordeelt of post-PCI-optimalisatie in het geval van suboptimale post-PCI FFR-waarden veilig is en in staat is om de uitkomst voor de patiënt op lange termijn te verbeteren. Vergelijkbare toekomstige studies zijn nodig om de rol van op angiografie gebaseerde FFR in de hedendaagse praktijk vast te stellen. Als zodanig wordt momenteel de opvolger in de pijplijn van FAST-onderzoeken (de internationale multicenter gerandomiseerde FAST III-studie) gestart om de non-inferioriteit van vFFR in vergelijking met conventionele op drukdraad gebaseerde FFR aan te tonen.

## CONCLUSIES

NHPR's waaronder dPR omvatten waardevolle diagnostische alternatieven voor conventionele hyperemische drukdraad-gebaseerde FFR. De technologie biedt een eerste stap in het vereenvoudigen van fysiologische laesiebeoordeling die zou kunnen helpen om het gebruik van coronaire fysiologie in zowel pre- als post-PCI-setting te vergroten. Voortbouwend op dit concept kan op 3D-QCA gebaseerde FFR een uitstekende en veelbelovende technologie zijn die de fysiologische laesiebeoordeling zou kunnen vereenvoudigen door een index (vFFR) op te nemen met een hoge diagnostische nauwkeurigheid in vergelijking met conventionele op drukdraad gebaseerde FFR. Daarnaast heeft het een lage interobserver variabiliteit die toepasbaar is op een breed scala van patiënten. Ten slotte hebben we in een reeks onderzoeken de klinische relevantie aangetoond van het uitbreiden van fysiologische laesiebeoordeling (met behulp van zowel conventionele als nieuwe indices) naar een post-PCI-setting. Suboptimale post-PCI-fysiologie bleek te correleren met cardiovasculaire uitkomsten die mogelijk gedeeltelijk zouden kunnen worden vermeden door gericht gebruik van invasieve coronaire beeldvorming en daaropvolgende handelingen ter optimalisatie.

## REFERENTIES

1. De Bruyne B, Fearon WF, Pijls NH, Barbato E, Tonino P, Piroth Z, et al. Fractional flow reserve-guided PCI for stable coronary artery disease. N Engl J Med. 2014;371(13):1208-17.
2. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol. 2010;56(3):177-84.
3. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007;49(21):2105-11.
4. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360(3):213-24.
5. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124(23):e574-651.
6. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2018.
7. Agarwal SK, Kasula S, Hacioglu Y, Ahmed Z, Uretsky BF, Hakeem A. Utilizing Post-Intervention Fractional Flow Reserve to Optimize Acute Results and the Relationship to Long-Term Outcomes. JACC Cardiovasc Interv. 2016;9(10):1022-31.
8. Leesar MA, Satran A, Yalamanchili V, Helmy T, Abdul-Waheed M, Wongpraparut N. The impact of fractional flow reserve measurement on clinical outcomes after transradial coronary stenting. EuroIntervention. 2011;7(8):917-23.
9. Pijls NH, Klauss V, Siebert U, Powers E, Takazawa K, Fearon WF, et al. Coronary pressure measurement after stenting predicts adverse events at follow-up: a multicenter registry. Circulation. 2002;105(25):2950-4.
10. van Zandvoort LJC, Masdjedi K, Witberg K, Ligthart J, Tovar Forero MN, Diletti R, et al. Explanation of Postprocedural Fractional Flow Reserve Below 0.85. Circ Cardiovasc Interv. 2019;12(2):e007030.

# Chapter 22

List of publications

1. **Masdjedi K**, Van Mieghem NM, Diletti R, van Geuns RJ, de Jaegere P, Regar E, Zijlstra F, van Domburg RT, Daemen J. *Navvus FFR to reduce CONTRAst, Cost and radiaTion (CONTRACT); insights from a single-centre clinical and economical evaluation with the RXi Rapid-Exchange FFR device.* ***Int J Cardiol.*** 2017 Apr 15.
2. **Masdjedi K**, Daemen J, Diletti R, Wilschut J, Utens E, de Jaegere PP, Lemmert ME, Kappetein AP, Zijlstra F, van Domburg R, Van Mieghem NM. *A case-vignette based assessment of patient's perspective on coronary revascularization strategies, the OPINION study.* **J Cardiol.** 2018 Aug
3. **Masdjedi K**, Ligthart J, Witberg K, Mastik F, van Zandvoort L, Lemmert ME, Wilschut J, Diletti R, de Jaegere P, Zijlstra F, Kardys I, Van Mieghem NM, Daemen J. *Validation of Resting Diastolic Pressure Ratio Calculated by a Novel Algorithm and Its Correlation With Distal Coronary Artery Pressure to Aortic Pressure, Instantaneous Wave-Free Ratio, and Fractional Flow Reserve.* **Circ Cardiovasc Interv.** 2018 Dec
4. **Masdjedi K**, Diletti R, Daemen J, van Zandvoort LJC, Neleman T, Wilschut J, Den Dekker WK, van Bommel RJ, Lemmert M, Kardys I, Cummins P, de Jaegere P, Zijlstra F, Van Mieghem NM. *Impact of Poststenting Fractional Flow Reserve on Long-Term Clinical Outcomes: The FFR-SEARCH Study.* **Circ Cardiovasc Interv.** 2021 Mar
5. **Masdjedi K**, van Zandvoort LJC, Balbi MM, Gijsen FJH, Ligthart JMR, Rutten MCM, Lemmert ME, Wilschut JM, Diletti R, de Jaegere P, Zijlstra F, Van Mieghem NM, Daemen J. *Validation of a three-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: the FAST study.* **EuroIntervention**, 2020;16:591-599.
6. **Masdjedi K**, van Zandvoort LJ, Balbi MM, Nuis RJ, Wilschut J, Diletti R, de Jaegere PPT, Zijlstra F, Van Mieghem NM, Daemen J. *Validation of novel 3-dimensional quantitative coronary angiography based software to calculate fractional flow reserve post stenting.* **Catheter Cardiovasc Interv.** 2020 Oct 6.
7. **K. Masdjedi, MD;** J. Daemen, MD, PhD**.** *Angiography-Based FFR: Reevaluating the Role of the Pressure Wire: Reviewing the nuances of coronary angiography–based FFR and results of initial validation studies* **Cardiac Interventions Today;** May/June 2019 Vol. 13, No.3
8. **Masdjedi K,** Tanaka K, Van Belle E, Porouchani S, Linke A, Woitek FJ, Bartorelli AL, Ali ZA, Den Dekker WK, Wilschut J, Diletti R, Zijlstra F, Boersma E, Van Mieghem NM, Spitzer E, Daemen J, *Coronary angiography-based vessel Fractional Flow Reserve for Fast Physiologic Assessment of Stenosis severity: the FAST II study,* ***Submitted.***
9. **Masdjedi K**, Van Zandvoort JC, Kardys I, Ligthart, Den Dekker WK, Diletti R, Zijlstra F, Van Mieghem NM, Daemen J. *Prognostic Value of Post PCI Diastolic Pressure Ratio in a real-world PCI registry* **Submitted.**
10. **Masdjedi K**, Tamoniak M, Ligthart JRM, Witberg K, Vermaire A, Kardys I, Neleman T, Wilschut J, Diletti R, Den Dekker WK, de Jaegere P, Zijlstra F, Van Mieghem NM, Daemen J. *The Prognostic Value of Angiography-Based vessel-FFR after successful Percutaneous Coronary Intervention: The FAST Outcome study.* **Submitted.**

11. Van Zandvoort LJC, **Masdjedi K**, Tovar Forero MN, Manintveld O, Daemen J. *Coronary physiology assessment in a cardiac transplant patient.* **Neth Heart J.** 2019 Jul
12. Van Zandvoort LJC, **Masdjedi K**, Witberg K, Ligthart J, Tovar Forero MN, Diletti R, Lemmert ME, Wilschut J, de Jaegere PPT, Boersma E, Zijlstra F, Van Mieghem NM, Daemen J. *Explanation of Postprocedural Fractional Flow Reserve Below 0.85.* **Circ Cardiovasc Interv.** 2019;12:e007030.
13. Van Bommel RJ, **Masdjedi K**, Diletti R, Lemmert ME, van Zandvoort L, Wilschut J, Zijlstra F, de Jaegere P, Daemen J, van Mieghem NM. *Routine Fractional Flow Reserve Measurement After Percutaneous Coronary Intervention.* **Circ Cardiovasc Interv.** 2019;12:e007428.
14. Neleman T, **Masdjedi K**, Van Zandvoort LJC, Tomaniak M, Ligthart JMR, Witberg KT, Vermaire AA, Boersma E, Van Mieghem NM, Daemen J. *Extended Validation of Novel 3D Quantitative Coronary Angiography-Based Software to Calculate vFFR: The FAST EXTEND Study.* **JACC Cardiovasc Imaging.** 2020 SSN 1936-878X.
15. Tomaniak M, **Masdjedi K**, van Zandvoort LJ, Neleman T, Tovar Forero MN, Vermaire A, Kochman J, Kardys I, den Dekker W, Wilschut J, Diletti R, de Jaegere P, Van Mieghem NM, Zijlstra F, Daemen J. Correlation between 3D-QCA based FFR and quantitative lumen assessment by IVUS for left main coronary artery stenoses. **Catheter Cardiovasc Interv.** 2021 Mar;97(4):E495-E501.
16. Van Zandvoort LJC, **Masdjedi K**, Neleman T, Tovar Forero MN, Wilschut J, den Dekker W, de Jaegere PPT, Diletti R, Zijlstra F, Van Mieghem NM, Daemen J. *Impact of intravascular ultrasound findings in patients with a post PCI fractional flow reserve ≤0.85 on 2 year clinical outcome.* **Int J Cardiol.** 2020 Oct
17. van Zandvoort LJC, **Masdjedi K**, Tovar Forero MN, Lenzen MJ, Ligthart J, Diletti R, Lemmert ME, Wilschut J, de Jaegere PPT, Zijlstra F, van Mieghem NM, Daemen J. *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.* **Am Heart J.** 2019 Jul.
18. Van Zandvoort LJC, **Masdjedi K**, Tovar Forero MN, Lenzen MJ, Ligthart J, Diletti R, Lemmert ME, Wilschut J, de Jaegere PPT, Zijlstra F, van Mieghem NM, Daemen J. *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.* **Am Heart J.** 2019 Jul.
19. Tovar Forero MN, Zanchin T, **Masdjedi K**, van Zandvoort LJC, Kardys I, Zijlstra F, Häner J, Windecker S, Van Mieghem NM, Räber L, Daemen J. *Incidence and predictors of outcomes after a first definite coronary stent thrombosis.* **EuroIntervention**. 2020 Jul 17.
20. van Zandvoort LJC, Tomaniak M, Tovar Forero MN, **Masdjedi K**, Visseren L, Witberg K, Ligthart J, Kardys I, Lemmert ME, Diletti R, Wilschut J, de Jaegere P, Zijlstra F, Van Mieghem NM, Daemen J. *Predictors for Clinical Outcome of Untreated Stent Edge Dissections as Detected by Optical Coherence Tomography.* **Circ Cardiovasc Interv.** 2020

21. Tovar Forero MN, Scarparo P, den Dekker W, Balbi M, **Masdjedi K**, van Zandvoort L, Kardys I, Ameloot K, Daemen J, Lemmert M, Wilschut J, de Jaegere P, Zijlstra F, Van Mieghem N, Diletti R. *Revascularization Strategies in Patients Presenting With ST-Elevation Myocardial Infarction and Multivessel Coronary Disease.* **Am J Cardiol.** 2020 May.
22. Tovar Forero MN, van Zandvoort L, **Masdjedi K**, Diletti R, Wilschut J, de Jaegere PP, Zijlstra F, Van Mieghem NM, Daemen J. *Serial invasive imaging follow-up of the first clinical experience with the Magmaris magnesium bioresorbable scaffold.* **Catheter Cardiovasc Interv.** 2020 Feb.
23. Van Zandvoort LJC, van Bommel RJ, **Masdjedi K**, Tovar Forero MN, Lemmert MM, Wilschut J, Diletti R, de Jaegere PPT, Zijlstra F, van Mieghem NM, Daemen J. *Long-term outcome in patients treated with first- versus second-generation drug-eluting stents for the treatment of unprotected left main coronary artery stenosis.* **Catheter Cardiovasc Interv.** 2020 May.
24. Van Zandvoort LJC, Tovar Forero MN, **Masdjedi K**, Lemmert ME, Diletti R, Wilschut J, de Jaegere P, Zijlstra F, Van Mieghem NM, Daemen J. *References for left main stem dimensions: A cross sectional intravascular ultrasound analysis.* **Catheter Cardiovasc Interv.** 2019 Feb
25. Balbi MM, Scarparo P, Tovar MN, **Masdjedi K**, Daemen J, Den Dekker W, Ligthart J, Witberg K, Cummins P, Wilschut J, Zijlstra F, Van Mieghem NM, Diletti R. *Culprit lesion detection in patients presenting with non-ST elevation acute coronary syndrome and multivessel disease.* **Cardiovasc Revasc Med**. 2021 Mar .

# Chapter 23

PHD- PORTFOLIO

Name PhD Candidate: Kaneshka Masdjedi (Ken)

Department: Cardiology

Research school: Cardiovascular Research School Erasmus MC (COEUR)

PhD Period: Nov 2017 – May 2021.

Title thesis: Coronary Physiology: Advancements in technology and post procedural use

Promotor: Prof. Dr. N.M. Van Mieghem

Co promotor: Dr. J. Daemen

Date defense: October 5th 2021

| | Year | Workload (ECTS) |
|---|---|---|
| **General skills & academic courses** | | |
| Basic introduction Course on SPSS | 2017 | 1.0 |
| Pathophysiology of Ischemic Heart Disease | 2018 | 0.5 |
| Research Integrity | 2018 | 1.0 |
| Imaging for Ischemic Heart and Brain Disease | 2018 | 0.5 |
| | | |
| **Courses** | | |
| Coronary Physiology in the CathLab (Nice, France) | 2017 | 2.0 |
| Advances in Coronary Physiology (London, UK) | 2017 | 1.2 |
| Open Clinica, (Rotterdam, NL) | 2018 | 0.3 |
| Interventional Cardiology Fellows Course at EuroPCR (Paris, France) | 2019 | 1.0 |
| Interventional Cardiology Fellow Course (CVOI) (Eindhoven & Utrecht, NL) | 2019 | 0.6 |
| IVUS Course/Training (Boston Scientific) | 2019 | 0.6 |
| | | |
| **Presentations** | | |
| OPINION study, EuroPCR (Paris, France) | 2017 | 0.6 |
| POPCORN study, ESC 2017 (Barcelona. Spain) | 2017 | 0.6 |
| The dPR study, CRT Meeting (Washington DC, USA) | 2018 | 0.6 |
| FAST I study, EuroPCR (Paris, France) | 2018 | 0.6 |
| FFR and Pd/Pa vs. dPR, EuroPCR (Paris, France) | 2018 | 0.6 |
| 1 year FU of dPR Search, ESC Congress (Munich, Germany) | 2018 | 0.6 |
| FAST POST study, TCT (San Diego, USA) | 2018 | 0.6 |
| Coronary Physiology in heart transplant, CRT Meeting (Washington DC, USA) | 2019 | 0.6 |
| 2 year FU of dPR Search, EuroPCR (Paris, France) | 2019 | 0.6 |

| | | |
|---|---|---|
| **National and International conferences** | | |
| EuroPCR (Paris, France) | 2017 | 1.5 |
| European Society of Cardiology Congress (Barcelona, Spain) | 2017 | 1.5 |
| Cardiovascular Research Technologies (CRT) Meeting, Washington DC, USA) | 2018 | 1.5 |
| EuroPCR (Paris, France) | 2018 | 1.5 |
| European Society of Cardiology Congress (Munich, Germany) | 2018 | 1.5 |
| TCT Congress (San Diego, USA) | 2018 | 1.5 |
| Cardiovascular Research Technologies (CRT) Meeting, Washington DC, USA) | 2019 | 1.5 |
| The Netherlands Society of Cardiology, NVVC (Voorjaarscongres) | 2019 | 0.9 |
| The Netherlands Society of Cardiology, NVVC (Najaarscongres) | 2019 | 0.9 |
| EuroPCR (Paris, France) | 2019 | 1.5 |
| TCT Congress (San Francisco, USA) | 2019 | 1.5 |
| Dutch Revascularization & Electrophysiology Summit Meeting (DRES), Nijkerk, NL) | 2019 | 0.9 |
| Tour d'Horizon (Papendal, NL) | 2020 | 0.9 |
| Joint Interventional Meeting (participation in live case included) | 2021 | 1.2 |
| | | |
| **Teaching activities/Supervising** | | |
| Cath Conference: Angiography Based FFR, Erasmus MC | 2018 | 0.9 |
| Coronary Physiology at CathLab, Erasmus MC (for technicians and nurses) | 2018 | 0.9 |
| TED Talk Course, Delft | 2019 | 0.6 |
| Supervising Master Thesis | 2019 | 1.2 |
| Myocardial Revascularization Guidelines, Erasmus MC (for technicians and nurses) | 2019 | 0.3 |
| Presentatie: "Vrouwen met hartklachten" | 2019 | 0.3 |
| Cath Conference: Pitfalls of Coronary Physiology, Erasmus MC | 2019 | 0.9 |
| Complete vs. Culprit Only Revascularization in ACS, Maasstad Hospital (Rotterdam, NL) | 2020 | 0.3 |
| Cath Conference: Challenging Cases, Erasmus MC | 2020 | 0.3 |
| | | |
| **Grant/Prize** | | |
| Best abstract presentation ESC Congress (Munich, Germany) | 2019 | |
| | | |
| **TOTAL** | | **38.60** |

# Chapter 24

# ABOUT THE AUTHOR

Kaneshka (Ken) Masdjedi was born in 1983 in the Parwan province, Afghanistan. Due to the political upheaval in the 1990's , together with his family, he immigrated to the Netherlands. Upon graduating from the 't Hooghe Landt College in Amersfoort (VWO), he commenced his medical study at the Erasmus University of Rotterdam in 2003. He graduated with his thesis entitled: "*Clinics, demography and the treatment of congestive heart failure patients treated by heart failure specialist vs. general cardiologist in a tertiary referral center*" (Supervisors Dr. A.H.M.M. Balk and Dr. K. Caliskan). In October 2009 he was awarded the degree of Medical Doctor. Subsequently, he started working as a resident (ANIOS) at the department of cardiology for two years at the Reinier de Graaf Gasthuis and the Erasmus Medical Center. In November 2011, he began his cardiology training at the Thoraxcenter, Erasmus Medical Center (Trainers Dr. F.J. ten Cate, Prof. Dr. F. Zijlstra). The first two years he followed the preparatory training in internal medicine in the Maasstad Hospital in Rotterdam (Supervisor Dr. M.A. van den Dorpel). Hereafter, he followed his training in the Amphia Hospital in Breda at the department of cardiology for one year ( Supervisor Dr. A.M.W. Alings). During three years of academic modules within the training at Erasmus MC, he participated in various research projects which has resulted in a PhD project in the field of coronary physiology and intracoronary imaging. In November 2017, he was awarded the degree of general cardiologist. From November 2017 until May 2019 he worked fulltime as a research fellow at the department of interventional cardiology on his PhD, titled: *"Coronary physiology: Advancements in technology and post procedural use"* (Promotor Prof. Dr. M. Van Mieghem and Co-promotor Dr. J. Daemen). From May 2019 until 2021 Kaneshka followed the program of clinical fellowship in interventional cardiology at Erasmus MC (Supervisor Prof. Dr. M. Van Mieghem). In the summer of 2021 Kaneshka was awarded with the degree of interventional cardiologist.

Kaneshka married Nilam on March 25, 2016 and they have two daughters: Parisa Nettie Masdjedi (born July 20, 2018) and Donya Khorshid Masdjedi (born May 5, 2020) and in November 2021 they are expecting their third child.

# Chapter 25

# Acknowledgements / Dankwoord

Promoveren in het Erasmus MC is de kers op de taart van mijn tijd in het Erasmus MC, deze begon in 2003 als 1e jaars geneeskunde student op de polikliniek harttransplantatie bij dr. Balk. Mijn hart was gestolen en dat resulteerde van achtereenvolgens ANIOS-schap, opleiding cardiologie, klinische fellowship tot interventie cardioloog en dit proefschrift. Vandaag kijk ik terug op de afgelopen 18 jaren met de nadruk op de laatste 4.

Promoveren doe je niet alleen. Je hebt mensen om je heen nodig die je soms inspireren en mensen die je motiveren. Mensen die je praktisch maar ook mentaal steunen als het even niet meezit, mensen die dingen in je zien die jij zelf nooit hebt gezien. Maar ook je naaste omgeving die jou vaker moet missen maar je in de uren die je met ze doorbrengt je weer opladen om nog harder door te gaan met waar je gebleven was. Ik ben een gezegend mens dat ik al deze mensen om me heen heb en daarom ben ik iedereen enorm dankbaar voor de steun en het vertrouwen in me.

**Dr. Daemen**, beste Joost, ik heb je heel even als mede AIOS mee mogen maken niet wetende dat je jaren later mijn copromotor zou worden. Als er één iemand is zonder wie ik dit project nooit had kunnen realiseren dan ben jij het. In het vijfde cardiologie opleidingsjaar heb ik aangegeven geïnteresseerd te zijn in deelname aan onderzoeksprojecten. Jij enthousiasmeerde me enorm, het begon klein en van het een kwam het ander en ineens zat ik met jou, Nicolas en prof Zijlstra aan tafel om te praten over een PhD traject. Ik had geen enkele ervaring met onderzoek doen maar we hebben vaak samengezeten, meningen uitgewisseld en je hebt me stap voor stap laten zien hoe het moest. Je was altijd heel laagdrempelig bereikbaar voor mij en stond altijd open voor ideeën. Daar ben ik je enorm dankbaar voor. Niet alleen op onderzoeksgebied maar ook naast je aan tafel op cathlab hebben wij veel kunnen brainstormen over coronaire fysiologie. Ik bewonder je ook enorm als mens, hoe jij het gezinsleven, je sociale leven met vrienden zo goed kunt combineren met het klinisch werk en het begeleiden van veel promovendi met ieder een tigtal projecten. Dank voor alles Joost.

**Prof. Van Mieghem**, beste Nicolas, kerel. Ik weet niet waar ik moet beginnen. Ik ken je inmiddels meer dan 12 jaar en daar kan ik, zoals je weet, veel over vertellen. Ik heb ongelooflijk veel respect en bewondering voor jouw gedrevenheid, passie en liefde voor het vak. Je bent een voorbeeld van “sky is the limit” en streeft altijd naar perfectie. Ik heb van jou geleerd dat door gestructureerd, geroutineerd, georganiseerd en goed voorbereid aan een procedure te beginnen, je het beste uit jezelf en uit het team kunt halen en daarmee de beste zorg aan je patient levert. Dat zal ik ook altijd proberen na te streven. Ik dank je enorm voor je altijd snelle feedback op onze stukken. En de niet zakelijke kant van je, de goede vriendschap die door de jaren heen tussen ons ontstaan is, is wat mij betreft minstens zo van waarde. Naast een goede wetenschapper en gedreven leermeester ben je ook een vriend met een goed hart *“kan ik je vertellen”.* We hebben vele mooie herinneringen maar ik bespaar mezelf een *“djoef”.* Ik dank je voor alles en ik ben ontzettend blij met jou als promotor voor dit proefschrift.

Beste **Prof. Zijlstra,** ik heb u de afgelopen jaren niet alleen als hoofd van de afdeling cardiologie meegemaakt maar ook als leermeester op het cathlab. Ik heb bewondering voor uw brede kennis van het vak en sta iedere keer versteld van de rust die u uitstraalt. Ik dank u dan ook hartelijk voor de mogelijkheden die ik van u heb mogen krijgen.

**Prof. Boersma and dr. Kardys,** beste Eric en Isabella, jullie input en wetenschappelijke bijdrage is onmisbaar voor vele onderzoekers in het thoraxcentrum, zo ook voor mij. Ik dank jullie enorm voor alle "brainstormmomenten", jullie begeleiding en de kritische beoordeling van mijn stukken.

Ik wil graag ook alle leden van de kleine en de grote commissie bedanken voor hun expertise en hun deelname aan de commissie. In het bijzonder **dr. Balk** die mij als jonge student enthousiasmeerde voor het vak cardiologie. Vandaag ben ik vereerd en trots om u in de promotiecommissie te mogen hebben. Ook is het voor mij een eer om **prof. Pijls,** een belangrijke pioniers in de coronaire fysiologie (FFR) te bedanken. **Prof. Van Royen, beste Niels,** ik ben ontzettend blij en vereerd om u met zoveel ervaring en expertise op dit gebied in de commissie te mogen verwelkomen. **Prof. De Groot,** hartelijk dank voor uw bereidheid om deel te nemen in de kleine commissie. En **prof. Duncker,** na het in ontvangst nemen van mijn propedeuse en het doctoraal waarbij u destijds ook in de commissie heeft gezeten ben ik erg blij u ook tijdens mijn promotie in de commissie te hebben. Dank allen.

Mijn directe co-onderzoekers **(Rg6)**: zonder jullie had ik de afgelopen jaren iets minder leuk ervaren. Naast de *"noise cancelling ON"* momenten zal ik al onze culturele, politieke en maatschappelijke discussies niet vergeten en al helemaal niet jullie *"droge en bijzonder voorspelbare"* humor (dat vinden zij van mij). **Dr. Van Zandvoort,** beste Laurens, ondanks je jonge leeftijd, groeide jij uit tot een belangrijke onderzoeker binnen de groep coronaire fysiologie en intracoronaire imaging. Wij hebben vele wetenschappelijke en sociale events samen bijgewoond. Dank voor je voornamelijk statistische bijdrage in onze stukken. Naast een gedreven onderzoeker geloof ik er heilig in dat jij een goede klinische dokter gaat worden voor je patienten. Ook dank ik jouw opvolger **Tara** *(de nieuwe Laurens).* Bedankt Tara voor al je tijd en energie die jij gestoken hebt in mijn projecten naast alle drukte rondom FFR-REACT studie en je opleiding. Je bent op de goede weg en ik twijfel er geen moment aan dat jij de volgende zult zijn die bij Joost gaat promoveren. **Lida (Dr. Feyz)** *(ze is een Afghaanse vrouw en geen Oezbeekse),* jouw leven kent de afgelopen jaren meer dynamiek dan de *Python* in de Efteling, maar wat heb jij het allemaal goed kunnen managen. Dank voor de gezelligheid en je vriendschap. Ik kijk er naar uit om met jou als toekomstige collega cardioloog samen te werken. De T**AVI boys (Manta Maarten, Joris Express, Thijmen Unload en Sentinel Herbert)** en de jongens **Toine** en **Fredeqrique** die later bijkwamen: dank voor alle leuke momenten samen. En je weet het he, ik ben "uitgeJACCt" en ik heb alle vertrouwen dat jullie dat op korte termijn ook gaan doen. **Dr. Tovar,** dear Natalia, my fellow and physiology and imaging-mate, first of all, tell me: *"what is the status of the stentthromnosis paper? ☺"* It all

started with you, Laurens, me and the headphones. You came to Erasmus MC as a great clinical doctor from Columbia through Spain and you became here an expert in intracoronary imaging and you left us as a great interventional cardiologist. It was always a pleasure working with you. Thank you for everything you have done for me and above all, thank you for your friendship. I wish you all the best in Mallorca and as I promised you, I will definitely visit you soon.

Mijn klinische fellowship tot interventiecardioloog zit er ook op. Twee hele bijzondere jaren waar ik veel mensen dankbaar voor ben, in het bijzonder de interventiecardiologen in het Erasmus MC die mij het vak hebben geleerd. Beste **Jeroen Wilschut,** ik bewonder jouw skills al vanaf dag een. Dank voor je tips en tricks, met name de laatste maanden waarbij ik veel van jou en Roberto heb kunnen leren tijdens de CTO procedures. Pasticcione, **Roberto Diletti,** *the retrograde doctor "you look good my friend* ☺ " Thank you for everything. We spent a lot of time also outside the cathlab, working on FFR Search study resulting in a first co-authorship in *Circulation CVI.* Thank you for the collaboration and also for the fun we always had, I really appreciate it and wish you all the best. I will never pronounce the words *"fantastic"* and *"as expected"* without thinking of you ☺. **Wijnand Den Dekker,** Ik was een maand eerder klaar met de opleiding cardiologie en hoopte ooit jou te leren dotteren, maar het omgekeerde is een feit: jij begon als klinische fellow en ik ging het onderzoek in. En al snel bleek jij een handige interventiecardioloog te zijn geworden. Dank voor je vertrouwen tijdens de procedures. Ik was enorm blij met jou als "main-includer" van FAST II studie, dank daarvoor. Ook dank ik mijn fellowmaatje **Rutger Jan** voor de samenwerking en zijn, rooster-technisch gezien, creatieve oplossingen.

Naast de stafleden, wil ik ook het cathlab personeel bedanken voor hun bijdrage. Ik dank alle technici **(John, Eelco, Tom, Lianne, Marleen, Quintin** en in het bijzonder **Martin en Alice** voor jullie hulp rondom FAST Post en dPR studie), en verpleegkundigen **(Stefan, Luis, Sanna, Shurenska & Danielle)** en in het bijzonder de mensen waarmee ik als jonge dokter samengewerkt heb en door de jaren veel van geleerd heb **(Linda, Houda, Angelique, Martine, Marianne & Paggy).** Dank voor alle leerzame en met name leuke momenten. Ook voor de inclusie van patienten in onze studies. Jullie zijn een topteam en ik ben trots samen met jullie gewerkt te mogen hebben. Ook een bijzonder dank aan **Jurgen Ligthart** en **Karen Witberg,** het duo dat al jaren alles wat betreft fysiologie en imaging georganiseerd opslaat en analyseert. Ik dank jullie voor alle onderwijsmomenten en in het bijzonder onze samenwerking Jurgen met **Frits Mastik** rondom de validatiestudie van het dPR software. Ik hoop nog veel meer van je te kunnen leren in de toekomst. Ook bedank ik het interventieteam van het Maasstad ziekenhuis waar ik 6 maanden gewerkt heb en veel heb geleerd (met name **Dr. Smits, Anton, Ben, Henk en Jan10**). Dank voor de warme ontvangst en het afscheid.

Onderzoek doen zonder een dedicated trial bureau zou iets stressvoller en minder goed georganiseerd verlopen. Daarom bedank ik het trial bureau voor hun tijd en energie die ze gestoken

hebben in onze studies. **Arno** bedankt voor het bijhouden van de Open Clinica database. **Mattie Lenzen,** ik denk dat niemand in het thoraxcentrum onderzoek doet zonder jouw hulp. Bedankt voor jouw tijd en energie die je gestoken hebt in onze projecten. **Paul Cummins,** met jou was het naast hard werken ook altijd dolle pret. Ik waardeer de vele uren die wij samen doorgebracht hebben om de 2 jaars follow up van de FFR Search studie te voltooien. Als Liverpool fanaat is je motto altijd: *"You never walk alone"* en dat heb jij me ook goed bewezen waarvoor dank. Wie ook erg veel tijd en energie gestoken heeft in FFR Search studie is **Rutger van Bommel.** Bedankt Rutger voor alles.

Verder wil ik alle cardiologen uit het Erasmus MC bedanken en in het bijzonder mijn opleiders achtereenvolgens: **dr. ten Cate, prof. dr. Deckers, dr. Dubois en dr. Galema** die mij gedurende mijn opleiding hebben begeleid. Sommige collegae groeien uit tot goede vrienden waar je veel mee optrekt ook buiten de ziekehuismuren en die je een duwtje in de rug geven als het nodig is. Tot deze groep mensen behoren **Sakir Akin en Cihan Simsek** (*dank jullie kardash voor de vriendschap),* **Julio vd Swaluw** *(samen zijn wij de badboys op reis),* **Miguel Lemmert** *(jammer dat ik je net misgelopen ben als senior, maar een goede vriendschap is zeker ontstaan),* **Pieter Vriesendorp** *(Pietertje, thanx voor je vriendschap en hoop je snel weer te zien in het land),* **Admir Dedic** *(mijn fellowmaatje, voetbalmaatje maar bovenal een goede vriend. Weet nog steeds niet "zashto moja majka me rodila"),* **Sing Yap** *(eerst samen als assistenten, later jaren lang mijn supervisor en bovenal voor altijd een goede vriend)* en **Maarten van Leeuwen**. Beste Maarten, we hebben heel kort samengewerkt voordat je naar Amsterdam vertrok maar het contact daarna is alleen maar intensiever geworden. Je bent een geweldige all-round interventiecardioloog geworden en bovenal een goede vriend waar ik op kan rekenen als het nodig is. De uren-durende gesprekken die wij nog steeds voeren over van alles en nog wat zou ik nooit willen missen *(Mirjam: jullie zijn ook echt nooit uitgepraat* ☺). Dank voor je altijd vrolijke uitstraling en positieve energie die je overbrengt. Ik ben blij om jou tijdens mijn verdediging naast me te hebben als paranimf. Dank daarvoor Maarten.

Het zijn ongelooflijk bijzondere tijden geweest voor iedereen. De *"social distancing"* door Corona heeft ons met beide benen op de grond gezet en de waarde van familie en vrienden laten beproeven. Ik dank mijn collegamedici en goede vrienden **Faiz, Anwar, Nasir, Rammesh, Ashraf, Fahim, Farzin, Khoshal, Shafi, Zabi** en **Hamid**. De momenten die wij periodiek samen doorbrengen, ervaringen uitwisselen, muziek maken en lol hebben zijn goud waard voor me. We hebben allemaal dezelfde weg bewandeld en dat maakt onze vriendschap bijzonder. Zoals Mavlana Balkhi zegt: *"The one who has a good friend doesn't need any mirror".*

Een belangrijke periode in mijn leven zijn de eerste jaren in Nederland waar ik enorm veel steun heb gehad van mensen die ik eeuwig dankbaar zal blijven (**o.a. Paul, Efri, Peter, Monique en Frits**). Ik ben trots en blij om jullie in mijn vriendenkring te mogen hebben.

**Familie**: Jullie zijn mijn grootste rijkdom. Ik hou zielsveel van jullie. Dank voor jullie begrip dat ik soms (volgens jullie vaak) familiebijeenkomsten heb moeten missen wegens diensten en/of onderzoeksuren in mijn "vrije tijd". Maar jullie zijn de motor achter alles wat ik heb bereikt in het leven.

**Kaka Masoum,** je bent soms als een vriend, soms als een grote broer en soms zelfs als een vader. In de moeilijkste tijden van ons leven stond jij naast ons en je liet ons het lichtpunt in de tunnel zien. Dank daarvoor. We hebben vaak hevige discussies over van alles en nog wat en ik ben blij dat wij deze gesprekken kunnen voeren met elkaar. Ik dank je voor alles en weet dat ik er altijd voor je zal zijn.

Lieve zussen, Rammesh en ik zijn gezegend dat wij jullie als zussen hebben. **Shiwa**, jij bent de oudste van ons en dat is goed te zien aan je gedrag. Je klaagt nooit en je bent samen met **Sabour** er altijd voor ieder van ons. Jullie kids (Kambiz, Kawous en Zohaal) zijn groot geworden met eigen verantwoordelijkheden. **Kambiz**, ik ben trots op hoe jij in het leven staat met je prachtige vrouw **Charlotte** en onze "Kamboy" **Elias. Kawous,** jij bent de sfeermaker in de familie en durft risico's te nemen in het leven, daar kan ik alleen maar bewondering voor hebben. Ik wens je veel liefde en gezondheid samen met **Natasja. Zohaal,** zoveel schoonheid en liefde in een mens is oneerlijk. Jarenlang was jij de jongste in onze familie en inmiddels ben je een prachtige vrouw en bovenal onmisbaar in de familie. Dank dat jullie er altijd zijn voor ons, vooral voor onze prinsesjes.

**Aria**, ik ben trots op alles wat jij bereikt hebt in het leven. We schelen niet zoveel in leeftijd maar toch heb ik veel van je geleerd als kind al, hoe moedig je was en hoe je altijd voor je rechten opkwam. Iets wat nu terug te zien is in jouw prachtige dochter **Susan** die met de dag wijzer wordt. Ik weet dat je er altijd bent en zult zijn voor ons en dat je liefde voor ons onvoorwaardelijk is. Dank daarvoor en weet dat die gevoelens wederzijds zijn.

**Arian**, jij bent het kleine zusje van het gezin maar inmiddels ook al mama. Ik ben blij dat je na vele malen switchen van studie uiteindelijk geworden bent wat je gelukkig maakt. Samen met **Rich** en de kleine krullebol (**Davion**) wens ik jullie het allerbeste in jullie nieuw plekkie. Dank voor je liefde voor onze kinderen en alle oppasmomenten. Ik zal er ook altijd voor jullie zijn.

**Rammesh**, mijn kleine broertje, jij en ik zijn twee handen op een buik. Onze band is speciaal omdat we niet veel schelen in leeftijd en omdat we veel samen hebben doorlopen, van middelbare school tot jarenlang voetbal en uiteindelijk onze studie geneeskunde. Dat jij uiteindelijk neuroloog bent geworden is je eigen schuld (☺ Ik zou geen andere dokter aan mijn bed willen hebben). Ik ben oprecht trots op alles wat jij en je lieve vrouw Evelien hebben bereikt ondanks alle hobbels die jullie leven kent de afgelopen jaren. Jullie hebben vier prachtige kinderen (**Laila, Mashal, Roshan & Fereshta**) die met hun lach de wereld doen veranderen. Ik ben blij en dankbaar

dat ik hun "Kaka Ken" mag zijn. **Eef**, jij bent als schoonzus van de familie een *"shining star"* en we zullen je geen seconde willen missen. Dank voor je luisterend oor (uitstekende eigenschap voor een huisarts) als ik even met een "doktergenoot" wilde praten over werk. Jullie leven kent veel verdriet de afgelopen jaren rondom Mashalak en ik heb respect en bewondering voor de kracht en de positieve energie die jullie in elkaar naar boven halen en dat op de rest van de familie projecteren. Weet dat ik er altijd onvoorwaardelijk voor jullie zal zijn. We zullen het leven moeten omarmen, ook de verdrietige momenten. Dank voor wat jullie zijn voor Nilam, Parisa, Donya en voor mij.

Ik wil graag ook mijn schoonfamilie (**Mir, Farida, Nilab en Nawid**) hartelijk bedanken, voor de wekelijkse zorg en de liefde die jullie opbrengen voor onze dochters. **Niginajan**, jij bent het maatje van Pari, ze zou geen seconde haar *"Nijna"* willen missen. Dank daarvoor.

Lieve **Cees & Nettie**, mijn leven had er een stuk anders uitgezien zonder jullie. Nettie, jij bent al jaren het station waar ik beland als ik ergens mee zit. Dank voor de liefde en het luisterend oor als ik je nodig heb. Ik zal nooit onze uren durende telefoongesprekken vergeten: *"Ha kind, hoe is het met promoveren?"* Cees, dank voor het opofferen van je Ajax-hart door telkens langs de Kuip te moeten rijden om mij op te zoeken. Ooit zal ik je de binnenkant van het mooiste stadion van Nederland laten zien.

**Papa en Mama:** Ieder kind heeft een voorbeeldfiguur nodig om naar op te kijken. Aghajan, jij bent voor mij zolang ik me kan herinneren een voorbeeldfiguur op alle vlakken. Jij hebt me geleerd dat een mens nooit uitgeleerd is. Je niet blijven ontwikkelen is achteruitgang. Maar ook als mens hoop ik ooit in de buurt te kunnen komen van wat jij bent, als echtgenoot, als vriend, als opa en bovenal als vader. Wij zijn gezegend met jou als papa en hopen nog vele jaren van jou en mama te mogen genieten. Bibijan, jij bent de beste mama die ik me kan voorstellen. Zoveel liefde zie ik in jouw ogen en je lach. Met jou in mijn buurt voel ik me altijd weer dat kleine jochie. Samen met papa hebben jullie zoveel moeten achterlaten en moeten opofferen om ons in veiligheid te brengen. Ik ben er omdat jullie er zijn en daarom kus ik jullie handen paps en mams.

Last but not least, mijn 3 prinsesjes: **Nilam, Parisa & Donya**. Lieve **Nilam**, mijn wederhelft, cliché maar met jou aan mijn zijde voel ik me de gelukkigste man op aarde, zeker nu we 2 prinsesjes rijker zijn en ons derde kind op komst is. Jij bent de eerste die ik vroeg toen een promotieonderzoek ter sprake kwam, omdat ik wist dat jij het meeste van iedereen de gevolgen zou merken. Maar omdat jij wist dat het belangrijk voor mij was en ik het leuk vond, heb jij nog enthousiaster gereageerd dan ik zelf. Lieverd, dank voor je begrip en bovenal je liefde en het feit dat je er altijd bent. Jij bent een geweldige moeder voor onze dochters en het maakt me blij als ik zie hoe gelukkig en trots zij zijn met jou als mama. Mijn prinsesjes, zoals ik jullie altijd zal blijven nomen: **PariPadar** *(papa's elfje)* en **DonyaPadar** *(papa's wereld),* jullie zijn het mooiste wat mama en mij

overkomen is, zo klein, onschuldig en kwetsbaar. Vanaf het moment dat jullie er zijn heeft het woord “geluk” een andere betekenis voor ons en kunnen niet wachten tot jullie zusje er ook is. Dank voor jullie glimlach. Papa en mama zullen er eeuwig en onvoorwaardelijk voor jullie zijn. We houden zielsveel van jullie en zullen samen het leven vieren, elke dag weer…

**With my promotor Prof. Dr. N.M. Van Mieghem (L) and co-promotor Dr. J. Daemen (R)**