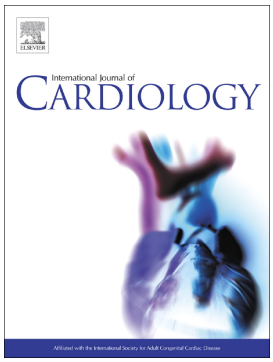

Vessel fractional flow reserve-based non-culprit lesion reclassification in patients with ST-segment elevation myocardial infarction: Impact on treatment strategy and clinical outcome (FAST STEMI I study)

Frederik T.W. Groenland, Jager Huang, Alessandra Scoccia, Tara Neleman, Annemieke C. Ziedses Des Plantes, Rutger-Jan Nuis, Wijnand K. den Dekker, Jeroen M. Wilschut, Roberto Diletti, Isabella Kardys, Nicolas M. Van Mieghem, Joost Daemen

PII: S0167-5273(22)01730-2

DOI: https://doi.org/10.1016/j.ijcard.2022.11.043

Reference: IJCA 30732

To appear in: *International Journal of Cardiology*

Received date: 23 September 2022

Revised date: 16 November 2022

Accepted date: 22 November 2022

Please cite this article as: F.T.W. Groenland, J. Huang, A. Scoccia, et al., Vessel fractional flow reserve-based non-culprit lesion reclassification in patients with ST-segment elevation myocardial infarction: Impact on treatment strategy and clinical outcome (FAST STEMI I study), *International Journal of Cardiology* (2022), https://doi.org/10.1016/j.ijcard.2022.11.043

Vessel fractional flow reserve-based non-culprit lesion reclassification in patients with ST-segment elevation myocardial infarction: Impact on treatment strategy and clinical outcome (FAST STEMI I study)

Frederik T.W. Groenland[1]*, MD, Jager Huang[1]*, BSc, Alessandra Scoccia[1], MD, Tara Neleman[1], BSc, Annemieke C. Ziedses des Plantes[1], BSc, Rutger-Jan Nuis[1], MD, PhD, Wijnand K. den Dekker[1], MD, PhD, Jeroen M. Wilschut[1], MD, Roberto Diletti[1], MD, PhD, Isabella Kardys[1], MD, PhD, Nicolas M. Van Mieghem[1], MD, PhD, Joost Daemen[1], MD, PhD

*Shared first authorship, both authors contributed equally

[1] Department of (Interventional) Cardiology, Thoraxcenter, Erasmus University Medical Center, Rotterdam, the Netherlands. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Corresponding Author:

Joost Daemen, MD, PhD, FESC

Department of Cardiology, Thoraxcenter, Erasmus University Medical Center

Dr. Molewaterplein 40, Room Rg-628, 3015 GD, Rotterdam, the Netherlands

Post office box: Room Rg-628, 3000 CA, Rotterdam, the Netherlands

Email: j.daemen@erasmusmc.nl, Tel: +31 10 7035260, Fax: +31 10 7035254

Acknowledgements of grant support / funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement:

Nicolas Van Mieghem received institutional research grant support from Abbott Vascular, Abiomed, Boston Scientific, Daiichi-Sankyo, Edwards Lifesciences, Medtronic, and PulseCath. Joost Daemen received institutional grant/research support from Astra Zeneca, Abbott Vascular, Boston Scientific, ACIST Medical, Medtronic, Pie Medical, and ReCor Medical. The remaining authors report no relationships that could be construed as a conflict of interest.

Keywords:

Coronary angiography-based physiology, multivessel disease, percutaneous coronary intervention, ST-segment elevation myocardial infarction, vessel fractional flow reserve.

Structured abstract

Background

Complete revascularization in patients with ST-segment elevation myocardial (STEMI) improves clinical outcome. Vessel fractional flow reserve (vFFR) has been validated as a non-invasive physiological technology to evaluate hemodynamic lesion significance without need for a dedicated pressure wire or hyperemic agent. This study aimed to assess discordance between vFFR reclassification and treatment strategy in intermediate non-culprit lesions of STEMI patients and to assess the clinical impact of this discordance.

Methods

This was a single-center, retrospective cohort study. From January 2018 to December 2019, consecutive eligible STEMI patients were screened based on the presence of a non-culprit vessel with an intermediate lesion (30-80% angiographic stenosis) feasible for offline vFFR analysis. The primary outcome was the percentage of non-culprit vessels with discordance between vFFR and actual treatment strategy. The secondary outcome was two-year vessel-oriented composite endpoint (VOCE), a composite of vessel-related cardiovascular death, vessel-related myocardial infarction, and target vessel revascularization.

Results

A total of 441 patients (598 non-culprit vessels) met the inclusion criteria. Median vFFR was 0.85 (0.73-0.91). Revascularization was performed in 34.4% of vessels. Discordance between vFFR and actual treatment strategy occurred in 126 (21.1%)

vessels. Freedom from VOCE was higher for concordant vessels (97.5%) as compared to discordant vessels (90.6%)(p=0.003), particularly due to higher adverse event rates in discordant vessels with a vFFR ≤0.80 but deferred revascularization.

Conclusions

In STEMI patients with multivessel disease, discordance between vFFR reclassification and treatment strategy was observed in 21.1% of non-culprit vessels with an intermediate lesion and was associated with increased vessel-related adverse events.

1. Introduction

Approximately 50% of patients with ST-segment myocardial infarction (STEMI) have concomitant multivessel disease. (1) Previous studies demonstrated improved clinical outcome with complete revascularization. (2, 3)

Several trials challenged the additional value of fractional flow reserve (FFR) for intermediate non-culprit lesions. (4-6) Whereas no conclusive outcome data is available on the superiority of FFR- vs. angiography-guided complete revascularization in patients presenting with STEMI, the relevance of the topic is illustrated by the fact that FFR for intermediate non-culprit lesions with at least 50% angiographic diameter stenosis appeared negative in 30-50%, questioning the need for percutaneous coronary intervention (PCI). (4-6)

As FFR relies on the use of a dedicated pressure wire and hyperemic agent, simplified physiological tools could enhance the adoption of physiological lesion assessment in the acute setting. Vessel fractional flow reserve (vFFR), which is based on three-dimensional quantitative coronary angiography (3D-QCA), is a novel non-invasive physiological technology which showed a good diagnostic agreement with invasively measured FFR. (7, 8) Given its concept, the technology has the potential to better guide non-culprit lesion treatment, both in an acute or offline Heart Team setting, without the need for a dedicated pressure wire and hyperemic agent. (9)

The aim of this study was to assess discordance between vFFR reclassification and actual treatment strategy in intermediate non-culprit lesions of STEMI patients and to assess the clinical impact of this discordance.

2. Methods

2.1 Study design and patient population

This was a single-center, retrospective cohort study. Consecutive patients presenting with STEMI between January 1st, 2018, to December 31st, 2019, and admitted to the catheterization laboratory for primary PCI were screened for eligibility. Patients were eligible for enrollment if at least one intermediate lesion (30-80% angiographic diameter stenosis and a reference diameter ≥ 2.00 mm by visual estimation or offline 3D-QCA) was present in a non-culprit vessel. Patients with prior coronary bypass surgery, prior heart transplantation, or presentation with cardiac arrest or cardiogenic shock were excluded. Coronary angiograms were subsequently screened for criteria precluding the feasibility of vFFR computation (presence of aorta-ostial lesions, insufficient angiographic projections (two angiograms with a rotation/angulation of <30 degrees), severe overlap or foreshortening of the target lesion, and table movement during projection acquisition).

PCI was performed according to routine clinical practice and in correspondence with current guidelines, including the use of peri- and post-procedural antithrombotic therapy. (10) The use of FFR or non-hyperemic pressure ratios for the physiological assessment of non-culprit lesions in the acute setting was at the discretion of the operator.

The Ethical Committee of the Erasmus University Medical Center approved the study protocol and waived the need for informed consent, since the study was not subject to the Dutch Research on Humans Subject Act.

2.2 vFFR analysis

vFFR computations were performed offline by the Erasmus University Medical Center CoreLab. Two angiographic projections of the non-culprit vessel were exported to the CAAS workstation 8.5.1 (Pie Medical Imaging, Maastricht, the Netherlands). Temporal alignment of the two coronary angiograms was performed automatically by electrocardiogram triggering and optimal end diastolic frames were semi-automatically identified. Subsequently, semi-automatic contouring of the vessel was achieved for both angiographic projections, by selecting at least two points (at the ostium of the vessel and distal to the stenosis). Manual contour correction was allowed if deemed necessary. Results on interobserver variability of the methodology have been published previously. (7, 8, 11) The vessel contouring resulted in a 3D-QCA vessel model, providing the following parameters: lesion obstruction length (mm), lesion position (mm), minimal lumen diameter (mm), diameter stenosis (%) and reference diameter (mm). Based on this 3D-QCA model, the vFFR value was calculated automatically after entering the systolic and diastolic aortic root pressure.

2.3 Study outcomes

The primary and clinical secondary outcomes were assessed at vessel level.

The primary outcome was the percentage of vessels with discordance between offline vFFR and actual treatment strategy. Two treatment strategies were distinguished: 1) Subsequent revascularization, defined as revascularization at the time of primary PCI or in a staged setting (within 3 months); 2) Deferral from treatment. If treatment options were first discussed within a multidisciplinary Heart Team, the

recommended treatment strategy of the (ad-hoc) Heart Team was used for this study. Concordance was defined as a vFFR ≤0.80 with subsequent revascularization or a vFFR >0.80 with deferred revascularization. Discordance was defined as a vFFR ≤0.80 with deferred revascularization or a vFFR >0.80 with subsequent revascularization.

Secondary outcomes were 1) vessel-oriented composite endpoint (VOCE) at two years, including vessel-related cardiovascular death, vessel-related myocardial infarction and target vessel revascularization (TVR); 2) the diagnostic performance of offline vFFR with acute-setting FFR as the reference standard (cutoff value ≤0.80).

Events were designated as vessel related or non-vessel related. (12, 13) Cardiovascular death was defined as any death without a clear non-cardiovascular cause. If cardiovascular death was not clearly related to a specific coronary artery, vessel-related cardiovascular death was assumed. Likewise, vessel-related myocardial infarction was considered if no clear culprit vessel could be identified. Consequently, vessel-related cardiovascular death and myocardial infarction could be assigned to multiple non-culprit vessels per patient. (12, 13) TVR was defined as any revascularization of the non-culprit vessel.

2.4 Patient data and follow-up

Baseline and procedural data were extracted from the hospital's electronic medical record system and stored in a dedicated database. Follow-up data was collected by screening hospital's electronic medical records, telephone surveys and the use of a dedicated local online platform for automated collection of patient reported outcome measurements (CathSuite).

2.5 Statistical analysis

The Shapiro-Wilk test was used to evaluate whether continuous variables followed normal distribution. Normally distributed variables were presented as mean with standard deviation (SD), while non-normally distributed continuous variables were presented as median with 25^{th}-75^{th} percentiles. Categorical variables were reported as counts with percentages.

Continuous patient-level variables were compared using the independent-samples T test or Mann-Whitney U test, while categorical patient-level variables were compared using the Pearson's $\chi 2$ test or Fisher's exact test (as appropriate). Non-culprit lesion characteristics were compared using generalized linear mixed models to adjust for clustering of multiple non-culprit vessels per patient.

Cumulative freedom from event percentages were derived from the Kaplan-Meier function for discordant and concordant groups. Censoring was performed at the time of event, non-vessel-related cardiovascular death, last contact or after two years of follow-up. Univariate Cox regression models with robust standard errors to take into account clustering of multiple non-culprit vessels per patient were used to estimate hazard ratios (HRs) including 95% confidence intervals (CIs) for VOCE and its individual components. To test robustness of results, a sensitivity analysis including only a single non-culprit vessel per patient was performed. In patients with multiple vessels, the non-culprit vessel with the lowest vFFR value was used for this analysis. For this sensitivity analysis, Kaplan-Meier curves were compared with the log-rank test.

The correlation between offline vFFR and acute-setting FFR was displayed in a scatter plot and numerically expressed with the Pearson's correlation coefficient (r). The diagnostic performance of vFFR, including sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV) and negative predictive value (NPV), was determined for a cutoff value of ≤0.80 for both FFR and vFFR. Additionally, receiver operator characteristic (ROC) curve analysis was performed to evaluate the discriminative ability of vFFR. If a patient was included with multiple non-culprit vessels, only the vessel with the lowest FFR value was used for this subgroup analysis.

Statistical analysis was performed with SPSS version 28 and R (R Core Team 2021; version 4.1.0, packages: glmm, survival). A 2-sided $p<0.05$ was considered statistically significant.

3. Results

3.1 Study population

Of the 923 consecutive STEMI patients screened, 425 did not meet the clinical entry criteria due to cardiac arrest or cardiogenic shock at presentation (n=158), prior coronary artery bypass graft surgery (n=34), prior heart transplant (n=1), and absence of an intermediate lesion in a non-infarct-related artery (n=232) (supplemental figure A). Subsequently, 57 patients with aorta-ostial lesions (n=10) or insufficient angiographic projections precluding the feasibility of vFFR computation (n=47) were excluded. Finally, 441 patients (598 vessels) were included in the present study.

3.2 Patient, procedural and culprit lesion characteristics

The baseline characteristics of the included patients are presented in table 1. Mean age was 65.8 (SD 11.6) years and 73.7% of patients were male. Diabetes was present in 15.2% of patients and 14.7% had undergone prior PCI.

Primary PCI of the culprit vessel was performed in 99.5% with final thrombolysis in myocardial infarction (TIMI) flow grade 3 in 93.7% (supplemental table A).

3.3 Non-culprit lesion characteristics

Non-culprit lesion characteristics are shown in table 2. The non-culprit vessel was the right coronary artery in 23.9%, the left main in 0.5%, the left anterior descending in 34.6% and the left circumflex in 41.0%. Median (25^{th}-75^{th} percentiles) 3D-QCA-based percentage diameter stenosis was 48.0 (39.0-58.0) and median vFFR was 0.85 (0.73-0.91). vFFR was ≤0.80 in 236 non-culprit vessels (39.5%). Invasive FFR measurement during primary PCI was performed in 45 vessels, with a mean FFR of 0.86 (SD 0.06).

PCI of the non-culprit vessel was performed in 32.4%, either ad-hoc (22.9%) or staged (9.5%). The median total stent length in the non-culprit vessels was 30.0 (18.0-41.5) mm and the median stent diameter was 3.0 (3.0-3.5) mm.

3.4 Discordance between vFFR and treatment strategy

Discordance between vFFR and actual treatment strategy occurred in 126 (21.1%) non-culprit vessels (table 3). More specifically, in vessels with a vFFR ≤0.80, treatment strategy was discordant in 78 (33.1%) vessels (deferred revascularization) and concordant in 158 (66.9%) vessels (direct PCI in 42.8%, staged PCI in 19.1%, and coronary artery bypass graft surgery (CABG) in 5.1%). In vessels with a vFFR >0.80, treatment strategy was discordant in 48 (13.3%) vessels (direct PCI in 9.9%, staged PCI in 3.3%, no CABG) and concordant in 314 (86.7%) vessels (deferred revascularization).

Baseline, culprit lesion and procedural characteristics did not differ significantly for patients with discordant and concordant non-culprit vessels, except for a higher rate of prior cerebrovascular accidents in discordant patients (10.7% vs. 5.3%, p=0.047) (supplemental table B and C). Comparing non-culprit lesion characteristics between discordant and concordant vessels revealed that the overall lesion severity as assessed by percentage diameter stenosis, minimal lumen diameter and (v)FFR was significantly worse in discordant vessels as compared to concordant vessels (supplemental table D). More specifically, revascularized vessels with a vFFR ≤0.80 (concordant) had a greater diameter stenosis (60.0% vs. 54.5%, p=0.002) and obstruction length (24.6 mm vs. 21.3 mm, p=0.0498), with a lower median vFFR (0.66 vs. 0.73, p=0.008), as compared

to vessels with a vFFR ≤0.80 that were not revascularized (discordant) (supplemental table E). The distribution of discordance and concordance within the different non-culprit vessels did not differ significantly (p=0.08, Fisher's exact test) (supplemental figure B).

3.5 Clinical outcome

Two-year follow-up was available in 88.1% (vessel based). Freedom from VOCE was significantly higher for concordant vessels (97.5%) as compared to discordant vessels (90.6%) (HR 3.8; 95% CI 1.6-9.0; p=0.003), particularly due to higher event rates in vessels with a vFFR ≤0.80 but deferred revascularization (figure 1 and supplemental figure C). More specifically, as compared to a event-free survival of 98.0% in concordant vessels with a vFFR >0.80 and deferred revascularization, event-free survival was 96.6% in concordant vessels with a vFFR ≤0.80 and subsequent revascularization (p=0.34), 97.9% in discordant vessels with a vFFR >0.80 and subsequent revascularization (p=0.96), and 85.8% in discordant vessels with a vFFR ≤0.80 but deferred revascularization (p<0.001) .

Freedom from vessel-related myocardial infarction and target vessel revascularization was significantly higher for concordant vessels as compared to discordant vessels (99.5% vs. 96.4%, p=0.029, and 99.1% vs. 96.3%, p=0.029, respectively), while vessel-related cardiovascular death did not differ significantly between both groups (98.4% vs. 96.6%, p=0.25) (supplemental table F).

In the sensitivity analysis, including one non-culprit vessel per patient, freedom from VOCE was higher for patients with a concordant vessel (97.4%) as compared to patients with a discordant vessel (89.9%) (p=0.002) (supplemental figure D).

3.6 Diagnostic performance of vFFR with acute-setting FFR as the reference standard

Acute-setting FFR measurement was performed in 42 patients. The correlation between offline vFFR and acute-setting FFR was moderate (r=0.61, p<0.001) (supplemental figure E). Diagnostic performance of offline vFFR with acute-setting FFR as the reference standard was characterized by a sensitivity of 70%, specificity of 87.5%, diagnostic accuracy of 83.3%, PPV of 63.3%, and NPV of 90.3%. The ROC curve analysis revealed a good discriminative ability of vFFR to predict FFR ≤0.80, with an area under the curve of 0.86 (p=0.001).

4. Discussion

The results of this study can be summarized as follows: 1) In STEMI patients with multivessel disease, discordance between physiological lesion classification based on vFFR and actual treatment strategy was present in 21.1% of non-culprit vessels; 2) Freedom from VOCE at two years was significantly higher for concordant non-culprit vessels as compared to discordant non-culprit vessels, particularly due to higher adverse event rates in vessels with a vFFR ≤0.80 but deferred revascularization; 3) offline vFFR showed good diagnostic performance with acute-setting FFR as the reference standard.

The present study demonstrates that vFFR has a potential role in guiding revascularization of intermediate non-culprit lesions in patients with STEMI. Discordance between offline vFFR and actual treatment strategy was observed in over one fifth of the non-culprit vessels. More specifically, 33.1% of vessels underwent no subsequent revascularization despite a vFFR of ≤0.80 whereas 13.3% of vessels with a vFFR >0.80 underwent subsequent PCI or CABG which likely could have been avoided. Event rates were significantly higher in the discordant group, particularly driven by events related to non-culprit lesions with a vFFR ≤0.80 but deferred revascularization. The latter follows the accepted concept of impaired clinical outcome related to incomplete revascularization and was also found in a small post-hoc analysis (n=110) of the EXAMINATION trial, demonstrating that deferring treatment of intermediate lesions in non-culprit vessels with a QFR<0.80 was associated with higher patient-oriented cardiac events at 5 year (HR 2.3; 95% CI 1.2-4.5; p=0.01). (2, 3, 14) Finally,

specifically addressing the potential role of vFFR in this subset of patients, also a small retrospective study (n=156) found a significant number of non-culprit lesions with a positive vFFR but deferred revascularization in STEMI patients. Likely due to a lack of power, this did not result in higher adverse event rates. (15)

Previous studies in patients presenting with STEMI demonstrated the limitations of visual lesion assessment to adequately interpret physiological lesion significance and reported negative FFR values for intermediate non-culprit lesions with at least 50% angiographic diameter stenosis in 30-50%. (4-6) With a more liberal definition in the present study (30-80% angiographic diameter stenosis), we found negative vFFR values in 60.5% of the cases. Whereas prospective randomized data on the superiority of physiology-guided non-culprit vessel PCI in patients presenting with STEMI is lacking, data derived from important registries showed low event rates in vessels with a negative FFR and no subsequent revascularization in patients presenting with stable or unstable angina, supporting a conservative approach. (16, 17) A meta-analysis of large national FFR registries extrapolated these findings to patients presenting with acute coronary syndrome (ACS) by demonstrating that FFR-based deferral to medical treatment was as safe as in patients with non-ACS (major cardiovascular event, 8.0% vs. 8.5%, p=0.83; revascularization, 3.8% vs. 5.9%, p=0.24; and freedom from angina, 93.6% vs. 90.2%, p=0.35). (18) Also in the present study, event rates related to lesions with a vFFR >0.80 were low irrespective of subsequent revascularization. The ongoing prospective FRAME-AMI trial (NCT02715518) will provide more evidence on the topic.

Thus far, the uptake of physiology in the primary PCI setting remains limited and is often restricted to staged settings. (19) The latter supports the development of faster and easier means of physiological lesion assessment. With a short analysis time (3.4 to 5.0 minutes on average), and no need for dedicated pressure wires, microcatheters and/or hyperemic agents, angiography-based FFR offers a unique opportunity for both acute-setting as well as offline physiological lesion assessment guiding complete revascularization or subsequent Heart Team discussion. (9, 20) Out of the 498 patients meeting clinical entry criteria in our study, vFFR computation appeared not feasible in only 57 patients (11.4%), illustrating that vFFR is a suitable technique for physiological lesion assessment in the majority of patients, even in a study population with no specific focus on proper image acquisition for the purpose of angiography-based FFR.

Finally, offline vFFR showed good diagnostic performance with acute-setting FFR as the reference standard. However, the use of angiography-based technologies in the acute setting needs further validation, especially since acute-setting FFR slightly underestimates the hemodynamic significance of non-culprit lesions due to microvascular vasoconstriction and a blunted hyperemic response. (21, 22) Conversely, angiography-based physiological tools that do not include TIMI frame counting in their computational model, such as vFFR, are likely not affected by changes in the microvasculature or an insufficient hyperemic response. Our subgroup analysis showed promising results with a diagnostic accuracy of 83.3%. Using competitive technologies, small studies demonstrated a good correlation between acute-setting QFR and acute-setting FFR, as well as between offline QFR and staged FFR. (14, 23) Nevertheless, a

dedicated prospective validation study is needed to further investigate the use of angiography-based technologies in patients with STEMI.

4.1 Limitations

This study has several limitations that should be acknowledged. First, this was a single-center, retrospective cohort study. All types of bias related to its single-center design and retrospective nature should thus be considered. In addition, multivariable Cox regression analysis to adjust for any potential confounding was not performed due to the low number of events. Second, angiography-based iFR technologies, including ischemic cutoff values, have largely been validated in patients with stable coronary artery disease and non-ST-segment elevation acute coronary syndrome. Despite promising results in patients with STEMI, a prospective validation study investigating the diagnostic performance of non-invasive physiological tools with acute-setting and/or staged FFR as the reference standard is needed. Third, two-year follow-up was available in 88.1% (vessel based), indicating that events could have been missed.

5. Conclusions

In STEMI patients with multivessel disease, discordance between vFFR reclassification and actual treatment strategy was observed in 21.1% of non-culprit vessels with an intermediate lesion and was associated with increased vessel-related adverse events, particularly driven by deferred revascularization in vessels with a vFFR ≤0.80. Offline vFFR showed good diagnostic performance with acute-setting FFR as the reference standard.

6. Acknowledgements

None.

7. References

1. Park DW, Clare RM, Schulte PJ, et al. Extent, location, and clinical significance of non-infarct-related coronary artery disease among patients with ST-elevation myocardial infarction. Jama. 2014;312(19):2019-27.

2. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med. 2013;369(12):1115-23.

3. Mehta SR, Wood DA, Storey RF, et al. Complete Revascularization with Multivessel PCI for Myocardial Infarction. N Engl J Med. 2019;381(15):1411-21.

4. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3--PRIMULTI): an open-label, randomised controlled trial. Lancet. 2015;386(9994):665-71.

5. Smits PC, Abdel-Wahab M, Neumann FJ, et al. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. N Engl J Med. 2017;376(13):1234-44.

6. Puymirat E, Cayla G, Simon T, et al. Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction. N Engl J Med. 2021;385(4):297-308.

7. Masdjedi K, van Zandvoort LJC, Balbi MM, et al. Validation of a three-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: the FAST study. EuroIntervention. 2020;16(7):591-9.

8. Masdjedi K, Tanaka N, Van Belle E, et al. Vessel fractional flow reserve (vFFR) for the assessment of stenosis severity: the FAST II study. EuroIntervention. 2021.

9. Tomaniak M, Masdjedi K, Neleman T, et al. Three-dimensional QCA-based vessel fractional flow reserve (vFFR) in Heart Team decision-making: a multicentre, retrospective, cohort study. BMJ Open. 2022;12(4):e054202.

10. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-77.

11. Scoccia A, Neleman T, Kardys I, et al. Reproducibility of 3D vessel Fractional Flow Reserve (vFFR): A core laboratory variability analysis of FAST II study. Cardiovasc Revasc Med. 2022.

12. Biscaglia S, Tebaldi M, Brugaletta S, et al. Prognostic Value of QFR Measured Immediately After Successful Stent Implantation: The International Multicenter Prospective HAWKEYE Study. JACC Cardiovasc Interv. 2019;12(20):2079-88.

13. Piroth Z, Toth GG, Tonino PAL, et al. Prognostic Value of Fractional Flow Reserve Measured Immediately After Drug-Eluting Stent Implantation. Circ Cardiovasc Interv. 2017;10(8).

14. Spitaleri G, Tebaldi M, Biscaglia S, et al. Quantitative Flow Ratio Identifies Nonculprit Coronary Lesions Requiring Revascularization in Patients With ST-Segment-Elevation Myocardial Infarction and Multivessel Disease. Circ Cardiovasc Interv. 2018;11(2):e006023.

15. Chang CC, Chuang MJ, Lee YH, et al. Vessel fractional flow reserve in assessment of non-culprit lesions in ST elevation myocardial infarction. Open Heart. 2021;8(2).

16. Zimmermann FM, Ferrara A, Johnson NP, et al. Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial. Eur Heart J. 2015;36(45):3182-8.

17. Kuramitsu S, Matsuo H, Shinozaki T, et al. Five-Year Outcomes After Fractional Flow Reserve-Based Deferral of Revascularization in Chronic Coronary Syndrome: Final Results From the J-CONFIRM Registry. Circ Cardiovasc Interv. 2022;15(2):e011387.

18. Van Belle E, Baptista SB, Raposo L, et al. Impact of Routine Fractional Flow Reserve on Management Decision and 1-Year Clinical Outcome of Patients With Acute Coronary Syndromes: PRIME-FFR (Insights From the POST-IT [Portuguese Study on the Evaluation of FFR-Guided Treatment of Coronary Disease] and R3F [French FFR Registry] Integrated Multicenter Registries - Implementation of FFR [Fractional Flow Reserve] in Routine Practice). Circ Cardiovasc Interv. 2017;10(6).

19. Elbaz-Greener G, Masih S, Fang J, Roifman I, Wijeysundera HC. Temporal Trends in Fractional Flow Reserve Use in Patients Undergoing Coronary Angiography: A Population-Based Study. CJC Open. 2019;1(1):10-8.

20. Scoccia A, Tomaniak M, Neleman T, Groenland FTW, Plantes A, Daemen J. Angiography-Based Fractional Flow Reserve: State of the Art. Curr Cardiol Rep. 2022.

21. Thim T, van der Hoeven NW, Musto C, et al. Evaluation and Management of Nonculprit Lesions in STEMI. JACC Cardiovasc Interv. 2020;13(10):1145-54.

22. van der Hoeven NW, Janssens GN, de Waard GA, et al. Temporal Changes in Coronary Hyperemic and Resting Hemodynamic Indices in Nonculprit Vessels of Patients With ST-Segment Elevation Myocardial Infarction. JAMA Cardiol. 2019;4(8):736-44.

23. Lauri FM, Macaya F, Mejía-Rentería H, et al. Angiography-derived functional assessment of non-culprit coronary stenoses in primary percutaneous coronary intervention. EuroIntervention. 2020;15(18):e1594-e601.

8. Tables

Table 1. Baseline characteristics

Variable	n=441
Mean age (years)	65.8 (11.6)
Male gender	325 (73.7)
Hypertension	207 (46.9)
Dyslipidemia	135 (30.6)
Diabetes	67 (15.2)
Family history	151 (34.2)
Current smoker	147 (33.3)
Prior PCI	65 (14.7)
Prior MI	59 (13.4)
Prior CVA/TIA	30 (6.8)
Prior renal failure	18 (4.1)

Values are mean (standard deviation) or n (%).

CVA = cerebrovascular accident, MI = myocardial infarction, PCI = percutaneous coronary intervention, TIA= transient ischemic attack.

Table 2. Non-culprit lesion characteristics

Variable	n=598
Non-culprit vessel	
RCA	143 (23.9)
LM	3 (0.5)
LAD	207 (34.6)
LCx	245 (41.0)
3D quantitative coronary angiography	
Median diameter stenosis (%)	48.0 (39.0-58.0)
Median reference diameter (mm)	2.9 (2.5-3.3)
Median obstruction length (mm)	20.4 (13.2-29.8)
Median position of lesion (mm)	34.7 (24.4-51.7)
Median minimal lumen diameter (mm)	1.5 (1.2-1.8)
Median vFFR	0.85 (0.73-0.91)
Mean vFFR	0.81 (0.14)
vFFR ≤0.80	236 (39.5)
FFR performed*	45 (7.5)
Mean FFR	0.86 (0.06)
Median FFR	0.86 (0.81-0.90)
FFR ≤0.80	10/45 (22.2)
PCI non-culprit lesion**	194 (32.4)
Stenting	189/194 (97.4)

DES use	189/189 (100.0)
Median total stent length (mm)	30.0 (18.0-41.5)
Median Max. stent diameter (mm)	3.0 (3.0-3.5)

Values are mean (standard deviation), median (25^{th}-75^{th} percentiles) or n (%).

*During primary PCI.

**During primary PCI or in staged setting.

DES = drug eluting stent, FFR = fractional flow reserve, LAD = left anterior descending, LCx = left circumflex, LM = left main, PCI = percutaneous coronary intervention, RCA = right coronary artery, vFFR = vessel fractional flow reserve.

Table 3. Discordance and concordance between vFFR classification of intermediate non-culprit lesions and treatment strategy

	vFFR ≤0.80 n=236	vFFR >0.80 n=362	Total n=598
Subsequent revascularization	158 (66.9)	48 (13.3)	206 (34.4)
Direct PCI	101 (42.8)	36 (9.9)	137 (22.9)
Staged PCI	45 (19.1)	12 (3.3)	57 (9.5)
CABG	12 (5.1)	0 (0.0)	12 (2.0)
Deferred revascularization	78 (33.1)	314 (86.7)	392 (65.6)
Discordant	78 (33.1)	48 (13.3)	126 (21.1)

Values are n (%).

CABG = coronary artery bypass graft surgery, PCI = percutaneous coronary intervention, vFFR = vessel fractional flow reserve.

9. Figure legends

Figure 1

Two-year vessel-oriented composite endpoint: Kaplan-Meier curves for discordant and concordant non-culprit vessels

Legend: CI = confidence interval, HR is hazard ratio, vFFR = vessel fractional flow reserve, VOCE = vessel-oriented composite endpoint.

(color online, black and white print)

Supplemental figure A

Title: Study flowchart

Legend: CABG = coronary artery bypass graft surgery, STEMI = ST-segment elevation myocardial infarction, vFFR = vessel fractional flow reserve.

(color online, print not applicable)

Supplemental figure B

Title: Distribution of discordance and concordance within the different non-culprit vessels

Legend: LAD = left anterior descending, LCx = left circumflex, LM = left main, RCA = right coronary artery.

(color online, print not applicable)

Supplemental figure C

Title: Two-year vessel-oriented composite endpoint: Kaplan-Meier curves for discordant and concordant non-culprit vessel subgroups

Legend: VOCE = vessel-oriented composite endpoint, vFFR = vessel fractional flow reserve.

(color online, print not applicable)

Supplemental figure D

Title: Sensitivity analysis for the vessel-oriented composite endpoint: Two-year Kaplan-Meier curves for discordant and concordant non-culprit vessels

Legend: Sensitivity analysis including only one non-culprit vessel per patient.

VOCE = vessel-oriented composite endpoint, vFFR = vessel fractional flow reserve.

(color online, print not applicable)

Supplemental figure E

Title: Diagnostic performance of offline vFFR with acute-setting FFR as the reference standard

Legend: The green dots indicate agreement between offline vFFR and acute-setting FFR, while the red dots indicate disagreement between offline vFFR and acute-setting FFR (based on the cutoff value of ≤0.80). The grey box below displays the diagnostic performance of vFFR with FFR as the reference standard.

NPV = negative predictive value, PPV = positive predictive value.

(color online, print not applicable)

Graphical abstract

Title: vFFR reclassification of non-culprit vessels with an intermediate lesion in patients presenting with STEMI: Impact on treatment strategy and clinical outcome

Legend: CI = confidence interval, HR = hazard ratio, STEMI = ST-segment elevation

myocardial infarction, vFFR = vessel fractional flow reserve, VOCE = vessel-oriented composite endpoint.

(color online, black and white print if applicable)

Author contribution statement

Frederik Groenland*: Conceptualization, Investigation, Methodology, Project administration, Software, Visualization, Writing – Original draft **Jager Huang*:** Conceptualization, Investigation, Methodology, Project administration, Software, Visualization, Writing – Original draft **Alessandra Scoccia:** Conceptualization, Methodology, Investigation, Software, Writing – Review & editing **Tara Neleman:** Methodology, Formal analysis, Software, Validation, Writing – Review & editing **Annemieke C. Ziedses des Plantes:** Methodology, Validation, Visualization, Writing – Review & editing **Rutger-Jan Nuis:** Conceptualization, Writing – Review & editing **Wijnand den Dekker:** Methodology, Writing – Review & editing **Jeroen Wilschut:** Methodology, Writing – Review & editing **Roberto Diletti:** Conceptualization, Writing – Review & editing **Isabella Kardys:** Conceptualization, Formal analysis, Methodology, Writing – Review & editing **Nicolas Van Mieghem:** Conceptualization, Methodology, Writing – Review & editing **Joost Daemen:** Conceptualization, Methodology, Software, Supervision, Writing – Review & editing.

*Shared first authorship, both authors contributed equally

Graphical Abstract

Highlights

- This study reclassified non-culprit lesions in STEMI patients using vFFR.
- Discordance between vFFR and treatment strategy was observed in 21.1%.
- Discordance was associated with increased vessel-related adverse events.
- Adverse event rates were highest for deferred lesions with a vFFR ≤0.80.
- vFFR has the potential to guide revascularization of non-culprit lesions.