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Angiography-derived functional assessment of non-culprit coronary stenoses during primary percutaneous coronary intervention for ST-elevation myocardial infarction.

Brief title: QFR use in non-culprit coronary stenosis in the acute phase of STEMI

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Abstract

Aims

Functional assessment of non-culprit lesions (NCL) in patients presenting with ST-elevation myocardial infarction (STEMI) and multivessel disease constitutes an unmet need. This study aims to evaluate the diagnostic accuracy of Quantitative Flow Ratio (QFR) in functional assessment of NCL during acute phase of STEMI.

Methods and Results

Retrospective, observational, multicenter study including patients with STEMI and staged Fractional Flow Reserve (FFR) assessment of NCL. QFR in NCL was calculated from the coronary angiogram acquired during primary PCI in a blinded fashion with respect to FFR.

The diagnostic value of QFR in the STEMI population was compared with a propensity-score-matched population of stable angina patients. 82 patients (91 NCL) were included. Target lesions were of both angiographic and functional (mean FFR 0.82 ± 0.09) intermediate severity. Diagnostic performance of QFR was high (AUC 0.91 [95% CI, 0.85-0.97]) and similar to that observed in the matched control population (AUC 0.91 vs. 0.94, $p=0.5$). The diagnostic accuracy of QFR was very high (>95%) in those vessels (61.5%) with QFR values out of a ROC-defined “grey zone” (0.75-0.85). A hybrid FFR/QFR approach (FFR only when QFR in grey zone) would adequately classify 96.7% NCL, avoiding 58.5% of repeat diagnostic procedures.

Conclusions

QFR has a good diagnostic accuracy in assessing functional relevance of NCL during primary PCI, similar to the accuracy observed in stable patients.

Condensed abstract

This retrospective, observational, multicenter study aims to evaluate the diagnostic accuracy of QFR in functional assessment of non-culprit lesions (NCL) during acute phase of STEMI. 91 NCL (82 patients with STEMI and staged FFR) were included. QFR analysis was blinded to FFR. Diagnostic performance of QFR was high and similar to that observed in the matched control population (AUC 0.91 vs. 0.94, $p=0.5$). QFR had higher diagnostic accuracy (>95%) for QFR values out of a ROC-defined “grey zone” (0.75-0.85). A hybrid approach (FFR only when QFR in grey zone) would adequately classify 96.7% NCL.

Abbreviation list

- AUC: area under the curve
- CAD: coronary artery disease
- DS: diameter stenosis
- IQR: interquartile range
- FFR: fractional flow reserve
- MVD: multivessel disease
- NCL: non-culprit lesions
- NPV: negative predictive value
- PCI: percutaneous coronary intervention
- PPV: positive predictive value
- 3D-QCA: 3-dimension quantitative coronary angiography
- QFR: quantitative flow ratio
- ROC: receiving operator characteristic
- SD: standard deviation
- STEMI: ST-elevation myocardial infarction
- TIMI: Thrombolysis In Myocardial Infarction

INTRODUCTION

Around 40-50% of patients presenting with acute ST-elevation myocardial infarction (STEMI) present with significant multivessel coronary artery disease (MVD) (1). Recently, two large trials (2,3) have shown a clinical benefit of a complete fractional flow reserve (FFR)-guided revascularization of non-culprit lesions (NCL), compared with a strategy of revascularization restricted to the infarct-related artery. However, even when considering NCL interrogation at a staged procedure in the subacute STEMI phase, repeated invasive procedures and the associated risks, cost of pressure wires, hyperemic agents, inadequate financial reimbursement and time constraints within the catheterization laboratory are potential obstacles.

All the above justifies need to obtain functional information on NCL during primary PCI, without additional intracoronary instrumentation, in a standardized, reproducible method. Functional coronary imaging indices based on computational fluid dynamics (CFD) are potential candidates for this role. These indices have the potential to non-invasively discriminate functionally significant lesions while avoiding intracoronary instrumentation and administration of adenosine, thus not interfering with the workflow of primary PCI in STEMI. One of these novel indices is the quantitative flow ratio (QFR), an adenosine-free angiography-based method that allows fast online computation of FFR (4). Evidence of good agreement between QFR and FFR is becoming increasingly available for patients with stable coronary artery disease (CAD) (4-10); however, data regarding its potential role in functional assessment of NCL in patients with STEMI remains limited (11,15).

The present study aims to investigate the reliability of QFR for assessing NCL at the time of STEMI presentation and primary PCI, comparing it against FFR measured in a staged procedure as the reference standard.

METHODS

Study design

This was a retrospective, observational, multi-center, international study. Patients were enrolled at three tertiary centers from three different countries: Hospital Clínico Universitario San Carlos, (Madrid, Spain), King's College Hospital (London, United Kingdom) and Toda Chuo General Hospital (Toda, Japan). QFR in NCL was performed at a blinded core laboratory using the coronary angiogram during primary PCI, and its diagnostic performance was compared with that of a matched control group of stable angina patients, using FFR as the reference standard (**Figure 1**).

Study population

Patients ≥ 18 years of age with confirmed STEMI receiving primary PCI within a maximum of 12 hours after symptoms onset were assessed for eligibility. All NCL in non-infarct-related vessels (≥ 2.0 mm) that were subsequently assessed with FFR in a second procedure were included in the analysis.

The exclusion criteria were left main (LM) and ostial right coronary artery (RCA) target lesions, previous by-pass grafting involving a non-infarcted territory and absence of coronary angiography calibration metadata. Moreover, bifurcation lesions were excluded because of specific limitations of the present QFR application. Patients fulfilling inclusion criteria were finally excluded in case of inadequate image quality of the angiography, vessel overlapping or tortuosity.

Data Collection

Patient baseline demographics, clinical and procedural characteristics were collected and inputted into a dedicated electronic database by the co-investigators of the participating

centers. Coronary angiograms obtained at the time of primary angioplasty were sent to the core laboratory at Hospital Clinico Universitario San Carlos, where they were anonymized for QFR analysis and those performing analysis were blinded to FFR values and final management.

Fractional Flow Reserve

As per study criteria, FFR-guided revascularization of NCL was performed in a staged procedure after primary PCI, either during initial hospitalization or at scheduled follow-up. FFR was measured according to a state-of-the-art practice in all the 3 participating centers, using intravenous adenosine as the standard. FFR was defined as the lower ratio between the mean distal coronary pressure and the mean aortic pressure during steady-state maximum hyperemia and was considered potentially flow limiting if ≤ 0.80 .

Quantitative Flow Ratio

QFR is an angiography-based method of calculating FFR using anatomical and functional principles. Therefore, its values are equivalent to FFR scale of grading severity (i.e., from 0 to 1, with a cutoff point of ≤ 0.80 (12). QFR is calculated by applying CFD to 3-dimensional quantitative coronary angiography (3D-QCA) derived from 2 angiographic projections. Additionally, QFR incorporates a flow-dependent individualized adjustment based on Thrombolysis In Myocardial Infarction (TIMI) frame count (9). In this study, 3D-QCA and QFR were obtained using the QAngio-XA 3D software (Medis, Leiden, The Netherlands). Briefly, QFR analysis was performed as follows: two angiographic projections separated at least 25 degrees were selected from coronary angiography performed at the time of primary PCI to obtain a 3D reconstruction of each target coronary artery (≤ 1 minute). The distal boundary of the analyzed vessel segment was marked according to the original position of the

pressure-wire sensor during the staged FFR assessment (≈ 1 minute). After manual corrections of any gross deviation of the automatic vessel reconstruction from the true vessel contour (≈ 3 -5 minutes), 3D-QCA was automatically obtained. 3D-QCA-derived diameter stenosis (DS) was the parameter of choice to describe angiographic stenosis severity. Finally, the flow-correction based on TIMI frame count was added to obtain the final QFR value (≤ 1 minute) (Figure 2). As a reference, in FAVOR II Europe Study, time to complete QFR analysis was 5 minutes (interquartile range, 3.5–6.1), significantly shorter than time to perform FFR(10). However, QFR analysis was not achievable when available projections and image quality of the angiography didn't allow visual estimation of target segments in at least 2 valid projections (ie. overlapping, tortuosity) and/or TIMI frame count analysis (inadequate contrast opacification). Moreover, absence of healthy proximal reference diameter (ie. LM and RCA ostial lesion) limited QFR analysis because of lack of data in this scenario.

QFR analysis was performed by a recognized analyst who passed the certification process, strongly recommended for any aspiring QFR analyst and managed by Medis.

Finally, free license of QAngio-XA 3D software was provided by the company.

Statistics

Continuous variables are expressed as mean \pm standard deviation (SD) or median with interquartile ranges (IQR) as appropriate. Normality was tested with the Shapiro-Wilk test, P-P and box plots. Categorical variables are presented as numbers and percentages. Diagnostic performance of QFR was assessed with the area under the ROC curve (AUC), taking FFR as the reference. The relationship and agreement between QFR and FFR were assessed by Pearson correlation coefficient and Bland-Altman plot respectively. The ROC analysis was used to outline a grey zone in which a drop in diagnostic accuracy of QFR was noted, identifying an upper and lower QFR boundaries with a diagnostic accuracy $>95\%$. All

analyses were performed with Stata 13 software (StataCorp LP, College Station, TX, USA). A p-value <0.05 was considered statistically significant.

In order to have a reference of QFR diagnostic performance, a cohort of 172 patients with stable angina (206 target vessels) who underwent FFR assessment was used as a comparator. The control group was selected by propensity score matching, according to the same selection criteria of the study population, using a 1:1 nearest neighbor pairing based on a logistic regression model including the following co-variables: interrogated artery, diameter of the stenosis and reference vessel diameter. Propensity score matching was performed using the MatchIt package of R software. The diagnostic performance of QFR in the STEMI group was compared with that of the resultant matched control population as per comparison of AUC performed with DeLong test.

RESULTS

Baseline clinical and lesion characteristics

136 patients (159 vessels) fulfilled inclusion criteria and, after screening for inadequate image quality of the angiography (1 vessel), excessive vessel overlapping or tortuosity (36 vessels), diffuse disease (3) and absence of valid projections (28 vessels), 82 patients (91 vessels) were finally included. **Table 1** summarizes the baseline clinical characteristics of the STEMI population enrolled in the study. In all patients, the culprit lesion was treated with stent implantation.

The left anterior descending was the most commonly interrogated vessel (37 [41%]). On average, stenoses had intermediate angiographic severity (51.63 ± 9.76 %DS) (**Table 2**).

Fractional flow reserve

FFR values were normally distributed around a mean value of $0,82 \pm 0,09$ (**Table 2** and **Supplementary figure 1**). Minimal and maximal FFR values were 0.56 and 0.97. In a majority of cases (51%) FFR measurements were obtained within first 10 days, with a median of 8 days after the initial PCI procedure (IQR 5–43). All cases with $\text{FFR} \leq 0.80$ were treated with PCI.

Overall accuracy of quantitative flow ratio

Like FFR, QFR presented a normal distribution with a mean of $0,81 \pm 0,09$ (min-max 0.51-0.97), denoting intermediate stenosis severity (**Table 2** and **Supplementary figure 1**). Diagnostic performance of QFR in detecting ischemia-generating lesions ($\text{FFR} \leq 0.80$) was high as per ROC analysis (AUC 0.91 [95% CI, 0.85-0.97]), and significantly better than DS (AUC 0.73 [95% CI, 0.62-0.84], $p < 0.001$) as shown in **Supplementary figure 2**. The correlation ($r = 0.75$ [$p < 0.001$]) and agreement (mean difference -0.004 (CI 95% -0.032 to 0.023) between QFR and FFR were strong (**Figure 3**). Sensitivity and specificity of QFR to determine the FFR-based functional stenosis severity were 85.7% and 80.0% respectively, with a Youden index of 0.66 (**Supplementary table 1**). Negative and positive predictive values were 87.3% and 77.8% respectively. Classification agreement (i.e., diagnostic accuracy) between QFR and FFR was observed in 83.5% of the vessels.

QFR grey zone

The agreement in functional stenosis classification between QFR and FFR was above 95% for QFR values < 0.75 and > 0.85 . In that range of QFR values (56 vessels [61.5%]), the performance and accuracy of QFR were very high (AUC 0.98 (CI 95%: 0.95-1.00), classification agreement 95% (53/56) ($p < 0.001$ for comparison of accuracy). Alternatively, inside the QFR grey zone defined for values ≥ 0.75 and ≤ 0.85 (35 vessels [38.5%]),

performance and accuracy of QFR was modest (AUC 0.63 (CI 95%: 0.42-0.84), classification agreement 68.6%(**Supplementary figure 3**).

The use of a hybrid strategy combining decision making based solely on QFR when the values are out of the grey zone, and FFR only in cases with QFR values within the grey zone, would avoid the use of intracoronary physiology in 56 vessels (61.5%). In our study population, this hybrid QFR/FFR strategy would avoid repeat catheterization and FFR measurements in 48 patients (58.5%).

Comparison with stable CAD

The propensity-score model yielded 91 vessels from 69 patients with stable CAD (**Table 3**). Overall, patients and vessel characteristics of the reference group were similar to the STEMI study population, although significantly more patients with diabetes mellitus and less active smokers were noted in the control group. None of these clinical variables have been noted to influence QFR-FFR agreement in previous studies (15). Similarity, in the angiographic characteristics reflected a good adjustment of the propensity score model. Mean FFR and QFR values were also similar. The numerical diagnostic value of QFR compared to FFR as the reference standard improved slightly in the stable-CAD group, although the differences were not statistically significant (**Table 3** and **Figure 4**).

DISCUSSION

In this study, we found that functional assessment of NCL using QFR during primary PCI is feasible, with a classification concordance with FFR measurements similar to that observed in

stable patients. When QFR is used as part of a hybrid QFR-FFR strategy, adequate functional classification can be achieved at the time of primary PCI in 96.7% of NCL, and could have avoided further invasive testing in 58.5% of patients.

Recent studies on the management of MVD in patients presenting with STEMI have highlighted the potential value of FFR-guided revascularization applied to NCL. Like in stable patients, physiology may serve as a valuable gatekeeper for unneeded PCI. In this regard, the Compare-Acute trial (2) showed that FFR assessment of NCL in the acute phase of STEMI shifted more than 50% of angiography-based indications from PCI to PCI deferral. The potential of QFR as an alternative to FFR interrogation of NCL stems from the fact that it can be easily performed during or after primary PCI, does not require coronary instrumentation, and does not need administration of potent coronary vasodilators. The implications are that QFR might contribute to streamline the care of patients with STEMI and MVD, sparing additional invasive procedures, reducing risks, costs and length of hospital stay.

In our study, the diagnostic accuracy parameters of QFR when used in the acute setting of STEMI for discriminating functionally-significant NCL were high, although generally lower than those reported in previous studies including patients with stable CAD (**Supplementary table 2**) (4-10). This could be due to the intrinsic limitations of obtaining angiograms during an acute presentation that could potentially affect QFR accuracy in this clinical setting. Our data confirm the results obtained by Sejr-Hansen et al (15) who describe the same overall classification agreement with FFR (84%).

Use of a hybrid approach of QFR and FFR in clinical decision making

To date, the non-inferiority of QFR, compared to FFR, in terms of safety of clinical decision

making, has not been demonstrated. An alternative method of gathering evidence on the clinical utility of QFR is using a hybrid QFR-FFR approach, in which clinical decisions based on QFR are limited to values below and above a central “FFR zone”.

In our study, we found that applying a hybrid approach with QFR values <0.75 or >0.85 , limiting FFR interrogation to NCL with QFR values within these boundaries, would result in an overall classification agreement of 96.7% (**Figure 5**). These values are superior to those documented in the ADVISE II trial (12) applying an iFR/FFR hybrid approach which demonstrated classification agreement 94.2%. Of note, assuming that scheduled FFR in the subacute phase would be the routine practice to assess functional relevance of NCL in patients with STEMI and MVD, the use of a hybrid QFR/FFR approach, based on staged FFR interrogation only in non-culprit vessels with QFR within the grey zone (0.75-0.85), could be valuable in terms of reduction of healthcare costs. This is mainly due to avoidance of pressure wires and adenosine in patients with only very positive and/or very negative QFR values (58.5% of sample size) and even no need of a second procedure in patients with only very negative QFR values (35% of sample size).

Unfortunately, cost-effectiveness analysis was not possible as far as QAngio software license fee is still not definite due to the fact that software is still at its launch phase.

STUDY LIMITATIONS

Our study had several limitations. As a consequence of the retrospective design of this study, some vessels had to be excluded because of insufficient angiographic image quality, not suitable for QFR computation, and, in most of the cases, absence of calibration data of coronary angiography due to incompatibility of QAngio-XA 3D software with old X-ray software. Moreover, although nitrates are regularly administrated before coronary angiography, this could not be the case in the acute phase of STEMI due to potential

hemodynamic instability, leading to potential coronary diameters infra-estimation and consequently to lower values of QFR. However, positive predictive value of QFR in our study was high and comparable to previous studies therefore reassuring about the minor impact of this limitation. Moreover, a higher prevalence of microvascular dysfunction in non-culprit vessel of patients with STEMI is still matter of debate (9,13,14). Consequently, a reduced QFR accuracy due to microvascular dysfunction, as described elsewhere (9), cannot be excluded. Prospective studies with angiographic projections dedicated to QFR analysis are likely to overcome these limitations (in FAVOR II Europe[10], prospective QFR assessment was achievable in 296 of 302 vessels with the exclusion of 6 vessels only) and reproduce our findings. Finally, future trials randomizing strategies (FFR vs. hybrid QFR-FFR) with clinical follow-up should test the non-inferiority of this novel approach.

CONCLUSION

QFR has a high diagnostic accuracy in assessing the functional stenosis relevance of NCL, as judged by FFR, when applied to angiography acquired during primary PCI in patients with STEMI. A QFR-FFR hybrid approach for NCL, with need of invasive functional assessment only for QFR values ≥ 0.75 and ≤ 0.85 , could be safe and cost-effective. Prospective randomized trials including clinical follow-up data are needed to confirm QFR as a proper diagnostic tool and as a predictor of clinical events in this clinical situation.

Impact on daily practice

Functional assessment of non-culprit lesions (NCL) in patients presenting with STEMI and multivessel disease is underperformed due to practical consideration like financial reimbursement and additional burden to the operator. QFR, in particular within a QFR-FFR hybrid approach, has been shown to have an acceptable diagnostic performance in fast

assessing NCL without additional procedures and costs (besides the price of annual QFR software license), in a considerable number of patients.

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Appendix:

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Disclosures:

The Authors and Collaborators have not conflicts of interest to disclose.

References

- 1) Kelbæk H, Terkelsen CJ, Helqvist S, Lassen, JF, Clemmensen P, Kløvgaard L, Kaltoft A, Engstrøm T, Bøtker H, Saunamäki K, Krusell L, Jørgensen E, Hansen, Christiansen EH, Ravkilde J, Køber L, Kofoed KF, Thuesen L. Randomized comparison of distal protection versus conventional treatment in primary percutaneous coronary intervention: the drug elution and distal protection in ST-elevation myocardial infarction (DEDICATION) trial. *J Am Coll Cardiol* 2008; **51**: 899–905.
- 2) Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, Piroth Z, Horak D, Wlodarczak A, Ong PJ, Hambrecht R, Angerås O, Richardt G, Omerovic E; Compare-Acute Investigators. Fractional Flow reserve-guided multivessel angioplasty in myocardial infarction. *N Engl J Med*. 2017;**376**:1234–1244.
- 3) Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, Jørgensen E, Pedersen F, Saunamäki K, Clemmensen P, De Backer O, Ravkilde J, Tilsted HH, Villadsen AB, Aarøe J, Jensen SE, Raungaard B, Køber L. 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**:665–71.
- 4) 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; FAVOR II China Study Investigators. Diagnostic Accuracy of Angiography-Based Quantitative Flow Ratio Measurements for Online Assessment of Coronary Stenosis. *J Am Coll Cardiol*. 2017 Dec 26;**70**(25):3077-3087
- 5) Tu S, Barbato E, Köszegi Z, Yang J, Sun Z, Holm NR, ar B, Li Y, Rusinaru D, Wijns W, Reiber JH. 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 Jul;7(7):768–77.

- 6) 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. 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 Oct 10;9(19):2024–35.
- 7) Yazaki K, Otsuka M, Kataoka S, Kahata M, Kumagai A, Inoue K, Koganei H, Enta K, Ishii Y. Applicability of 3-Dimensional Quantitative Coronary Angiography-Derived Computed Fractional Flow Reserve for Intermediate Coronary Stenosis. *Circ J.* 2017 Jun 23;81(7):988–92.
- 8) 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, Böttcher M, Bøtker HE, Christiansen EH, 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 Mar;11(3):e007107.
- 9) Mejía-Rentería H, Lee JM, Lauri F, van der Hoeven NW, de Waard GA, Macaya F, Pérez-Vizcayno MJ, Gonzalo N, Jiménez-Quevedo P, Nombela-Franco L, Salinas P, Núñez-Gil I, Del Trigo M, Goto S, Lee HJ, Lontou C, Fernández-Ortiz A, Macaya C, van Royen N, Koo BK, Escaned J. Influence of Microcirculatory Dysfunction on Angiography-Based Functional Assessment of Coronary Stenoses. *JACC Cardiovasc Interv.* 2018 Apr 23;11(8):741-753.

- 10) 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, Bøtker HE, Wijns W, Christiansen EH, 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 Jul 6;7(14)
- 11) Spitaleri G, Tebaldi M, Biscaglia S, Westra J, Brugaletta S, Erriquez A, Passarini G, Brieda A, Leone AM, Picchi A, Ielasi A, Girolamo DD, Trani C, Ferrari R, Reiber JHC, Valgimigli M, Sabatè M, Campo G. Quantitative Flow Ratio Identifies Nonculprit Coronary Lesions Requiring Revascularization in Patients With ST-Segment-Elevation Myocardial Infarction and Multivessel Disease. *Circ Cardiovasc Interv*. 2018 Feb;11(2):e006023.
- 12) Escaned J, Echavarría-Pinto M, García-García HM, van de Hoef TP, de Vries T, Kaul P, Raveendran G, Altman JD, Kurz HI, Brechtken J, Tulli M, Von Birgelen C, Schneider JE, Khashaba AA, Jeremias A, Baucum J, Moreno R, Meuwissen M, Mishkel G, van Geuns RJ, Levite H, Lopez-Palop R, Mayhew M, Serruys PW, Samady H, Piek JJ, Lerman A; ADVISE II Study Group. 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 May; 8(6):834-836
- 13) Prevalence of Microvascular and Endothelial Dysfunction in the Nonculprit Territory in Patients With Acute Myocardial Infarction. Díez-Delhoyo F, Gutiérrez-Ibañes E, Sanz-Ruiz R, Vázquez-Álvarez ME, González Saldívar H, Rivera Juárez A, Sarnago

F, Martínez-Sellés M, Bermejo J, Soriano J, Elízaga J, Fernández-Avilés F. Circ Cardiovasc Interv. 2019 Feb;12(2):e007257.

- 14) Microvascular obstruction in non-infarct related coronary arteries is an independent predictor of major adverse cardiovascular events in patients with ST segment-elevation myocardial infarction. Khorramirouz R, Corban MT, Yang SW, Lewis BR, Bois J, Foley T, Lerman LO, Herrmann J, Oh JK, Lerman A. Int J Cardiol. 2018 Dec 15;273:22-28.
- 15) Quantitative flow ratio for immediate assessment of nonculprit lesions in patients with ST-segment elevation myocardial infarction-An iSTEMI substudy. Sejr-Hansen M, Westra J, Thim T, Christiansen EH, Eftekhari A, Kristensen SD, Jakobsen L, Götberg M, Frøbert O, van der Hoeven NW, Holm NR, Maeng M. Catheter Cardiovasc Interv. 2019 Mar 25. doi: 10.1002/ccd.28208.

FIGURE LEGENDS

Figure 1. Study Flowchart.

FFR= Fractional Flow Reserve; QFR= Quantitative Flow Ratio; PCI= Percutaneous Coronary Intervention; STEMI= ST-elevated myocardial infarction

Figure 2. Non-culprit vessel acute QFR and staged FFR functional assessment.

A non-culprit lesion in circumflex artery assessed by QFR in the acute phase of STEMI (panels **A** and **B**). A 3-dimension reconstruction of the vessel with color-mapping of the pressure drop is shown in panel **C**. Panel **D** shows vessel diameter graph and QFR decrease along the vessel length. Panel **E** shows FFR pullback of the same vessel, obtained 5 days later. FFR= Fractional Flow Reserve; QFR= Quantitative Flow Ratio; STEMI= ST-elevated myocardial infarction

Figure 3. Relationship and agreement between QFR and FFR

Top panel: scatterplot showing the correspondence of QFR and FFR. Regression graph with confidence interval shows the correlation. **Bottom panel:** Bland Altman plot of differences between QFR and FFR. The majority of the values are included within ± 2 SD of the mean difference. FFR= Fractional Flow Reserve; QFR= Quantitative Flow Ratio; SD= Standard deviation

Figure 4. Comparison of QFR diagnostic performance in stable and STEMI populations.

QFR applied to non-culprit vessels at the time of primary PCI showed comparable diagnostic performance compared to QFR applied to stable coronary disease. AUC= area under the curve; QFR= Quantitative Flow Ratio; STEMI= ST-elevated myocardial infarction

Figure 5. QFR-FFR Hybrid Approach strategy

The QFR treatment (<0.75) and deferral (>0.85) values correctly classified 95% and 94.5% of stenoses, respectively. After including standard classification with FFR (virtual classification agreement 100%) in-between, the overall classification agreement of the proposed QFR-FFR Hybrid approach increased to 96.7%. FFR= Fractional Flow Reserve; QFR= Quantitative Flow Ratio

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TABLES

Table 1. Baseline Patient Characteristics.

Baseline Patient Characteristics (n=82)	Value
Age	62.2 ± 10.3
Male	63 (76.8%)
BMI (Kg/m2)	26.4 ± 4.3
Hypertension	54 (65.9%)
Diabetes mellitus	21 (25.6%)
Hypercholesterolemia	56 (68.3%)
Current Smokers	50 (61.0%)
Family History of Ischemic Heart Disease	9 (11.0%)
Prior myocardial infarction	20 (24.4%)
LVEF < 50%	24 (29.3%)
3-vessel disease	9 (11.0%)
Culprit vessel	
• Left anterior descending artery	33 (40%)
• Right coronary artery	32 (39%)
• Left circumflex artery	12 (15%)
• Obtuse marginal branch	3 (4%)
• Diagonal branch	1 (1%)
• Left Main	1 (1%)

Values are mean ± SD or n (%)

BMI= body mass index; LVEF= left ventricle ejection fraction; SD= Standard Deviation; STEMI= ST-elevated myocardial infarction

Table 2. Baseline Vessel Characteristics.

Baseline Vessel Characteristics	Value
Per-Vessel analysis (n= 91)	
Bifurcation	25 (27.5 %)
Target vessel	
• Left anterior descending artery	37 (41%)
• Left circumflex artery	25 (27%)
• Obtuse marginal branch	15 (17%)
• Right coronary artery	12 (13%)
• Diagonal branch	2 (2%)
Coronary segment target lesion	
• Proximal	29 (32%)
• Mid	39 (43%)
• Distal	6 (6%)
• Side branch	17 (19%)
• Serial stenoses	7 (8%)
3D-QCA results	
• Reference diameter, mm	2.63 ± 0.45
• Minimum lumen diameter, mm	1.28 ± 0.36
• Percent diameter stenosis	51.6 ± 9,8%
• Percent area stenosis	67.8 ± 11.4%
• Lesion length	19.2 ± 9.7 mm
• Vessel segment analyzed	72.7 ± 19.8 mm
Fractional Flow Reserve	
• Mean ± SD	0,82 ± 0,09
• ≤ 0.80	35 (38,5%)
• Median time to study (IQR), days	8 (5-43)
Quantitative Flow Ratio	
• Mean ± SD	0,81 ± 0,10
• ≤ 0.80	36 (39,6%)

Values are n (%) or mean ± SD or median ± IQR

IQR= Interquartile Range; SD= Standard Deviation; STEMI= ST-elevated myocardial infarction

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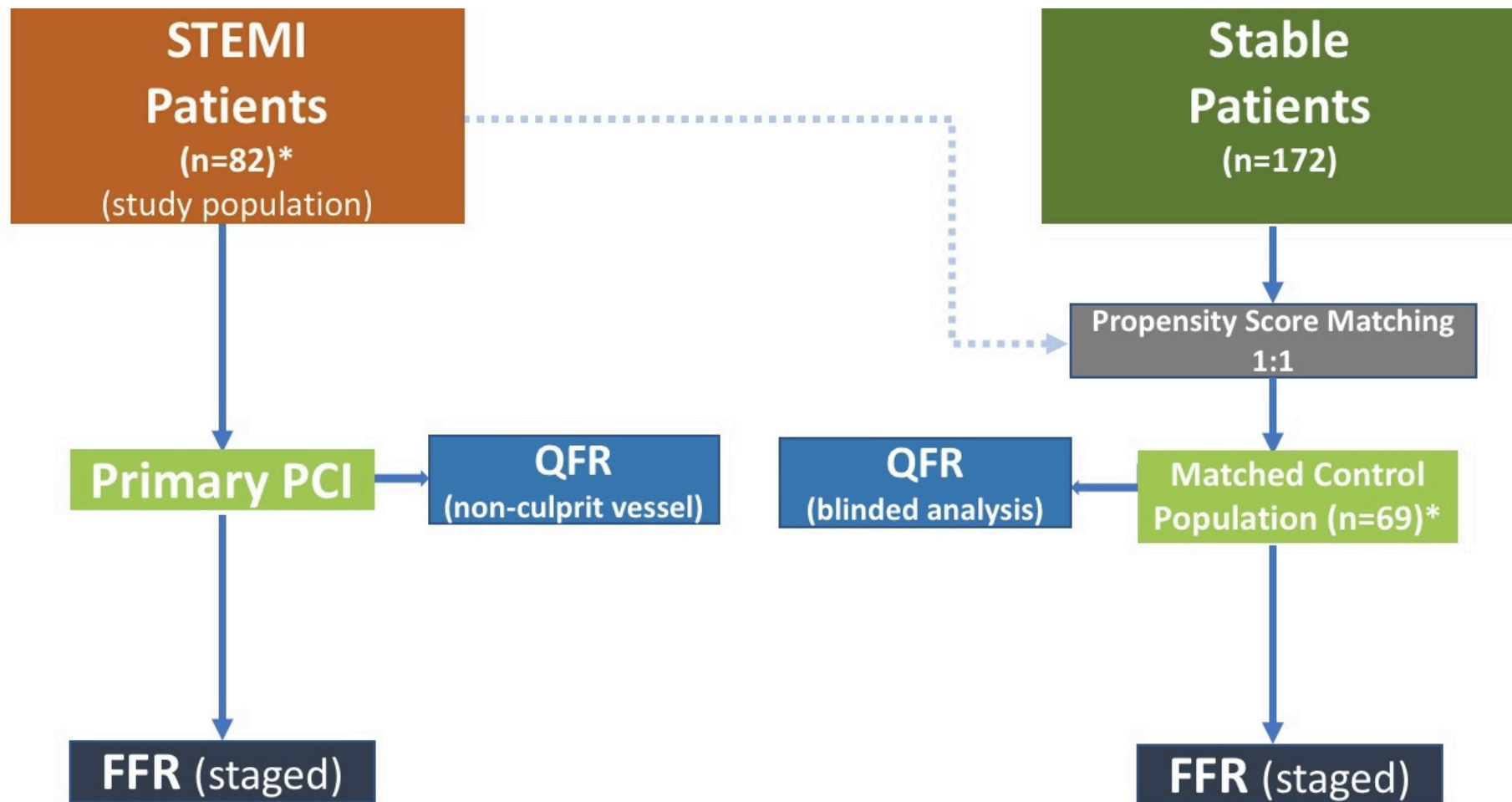
Table 3. Baseline characteristics, physiological parameters and diagnostic performance of QFR in STEMI population vs. the control matched group of stable patients.

Values are n (%) or mean \pm SD

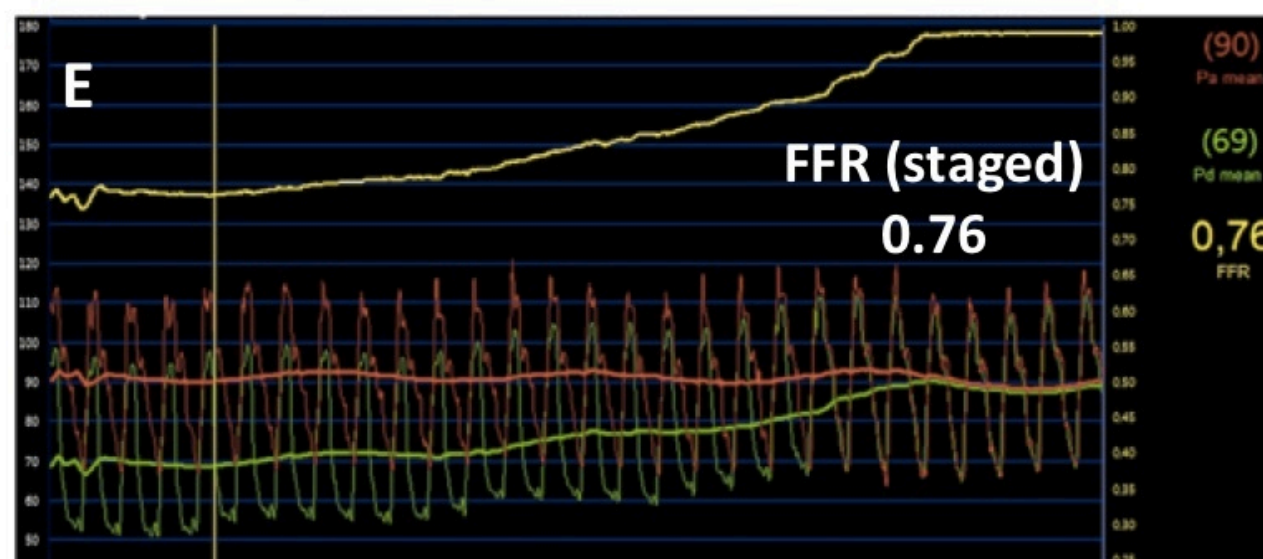
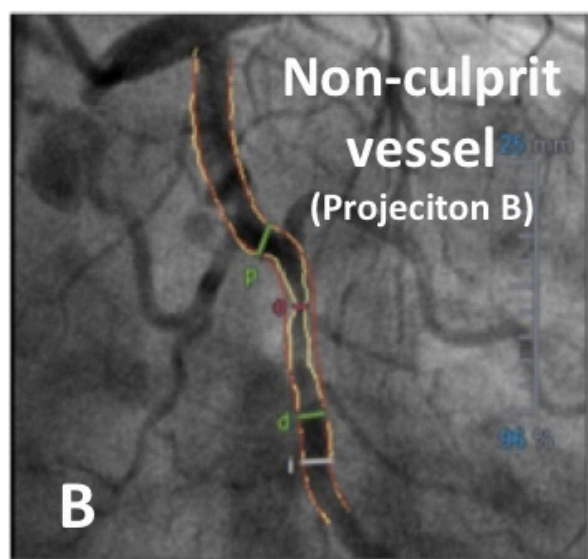
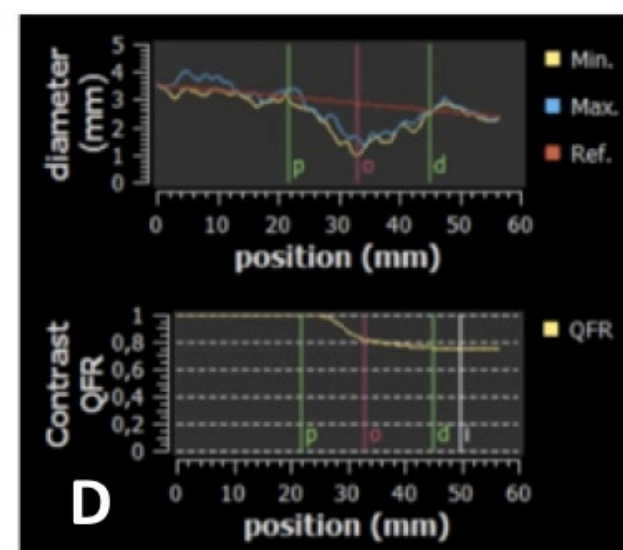
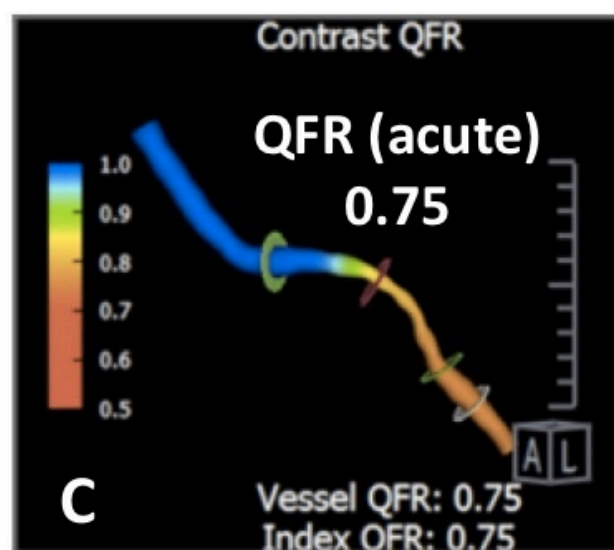
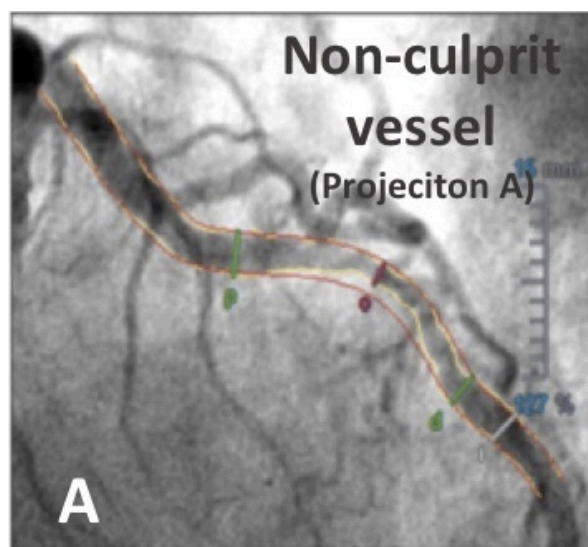
	Stable CAD (69 patients, 91 vessels)	STEMI patients (82 patients, 91 vessels)	p value
PATIENTS			
Age	64.8 \pm 10.1	62.0 \pm 10.2	0.104
Male	50 (72.5%)	63 (76.8%)	0.538
Smokers	11 (16.4%)	49 (61.3%)	<0.001
Diabetes Mellitus	31 (46.3%)	21 (25.6%)	0.008
Hypertension	46 (68.7%)	54 (65.9%)	0.717
Dyslipidemia	43 (64.2%)	56 (68.3%)	0.597
VESSELS			
LAD	39 (43%)	37 (41%)	0.764
Vessel diameter (mm)	2.59 \pm 0.55	2.62 \pm 0.45	0.701
DS %	51.6 \pm 13.1	51.6 \pm 9.8	0.516
FFR	0.81 \pm 0.11	0.82 \pm 0.09	0.787
QFR	0.80 \pm 0.12	0.81 \pm 0.10	0.543
DIAGNOSTIC ACCURACY PARAMETERS			
Pearson r	0.82	0.75	0.189
Accuracy	89.0%	83.5%	0.281
Sensitivity	87.2%	80.0%	0.403
Specificity	90.4%	85.7%	0.456
PPV	87.2%	77.8%	0.283
NPV	90.4%	87.3%	0.610
AUC	0.94 (0.89-0.99)*	0.91 (0.85-0.97)*	0.499

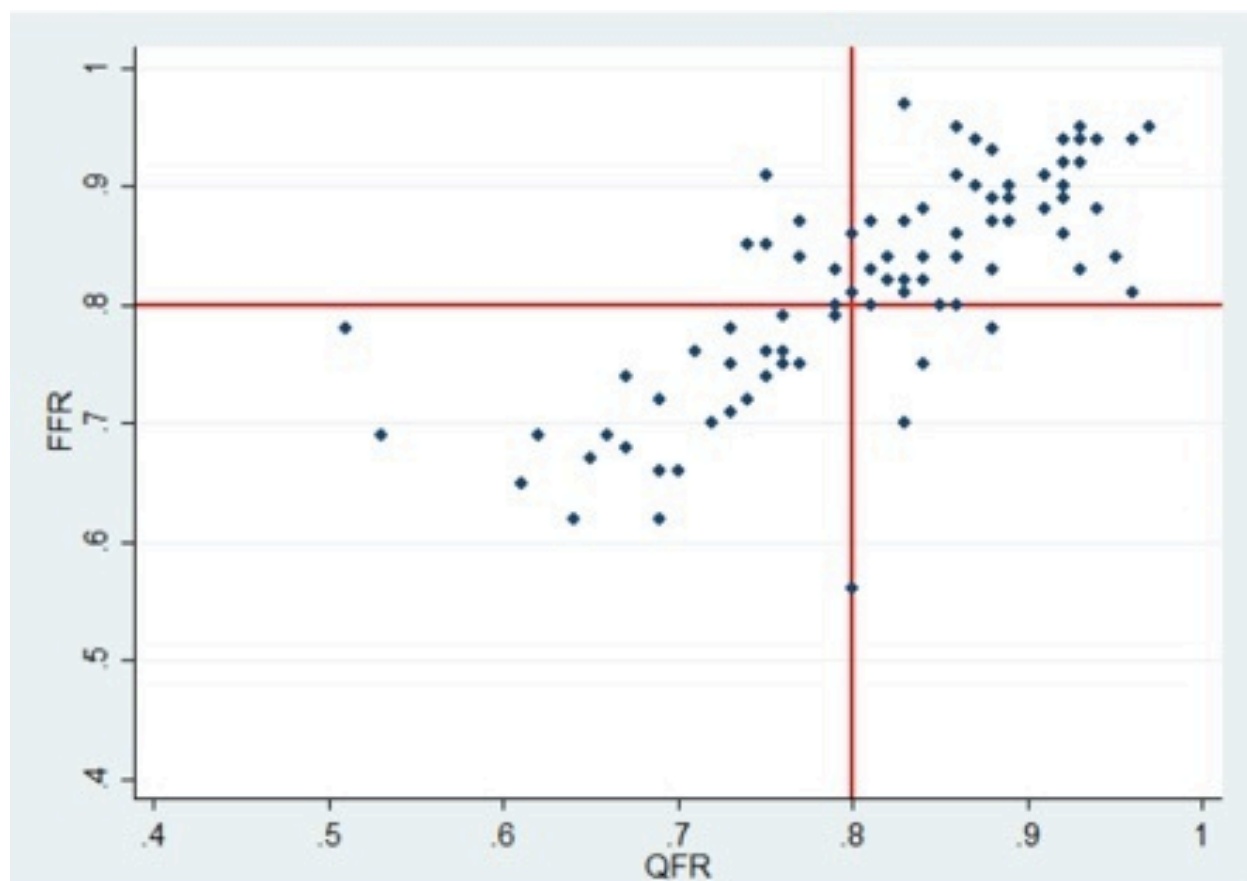
AUC= area under the ROC curve; CAD=coronary artery disease; DS= diameter stenosis; FFR= fractional flow reserve; IQR= Interquartile Range; LAD= left anterior descending artery; NPV= negative predictive value; PPV= positive predictive value; QFR=quantitative flow reserve; SD= Standard Deviation; STEMI= ST-elevated myocardial infarction.

* 95% Confidence Interval

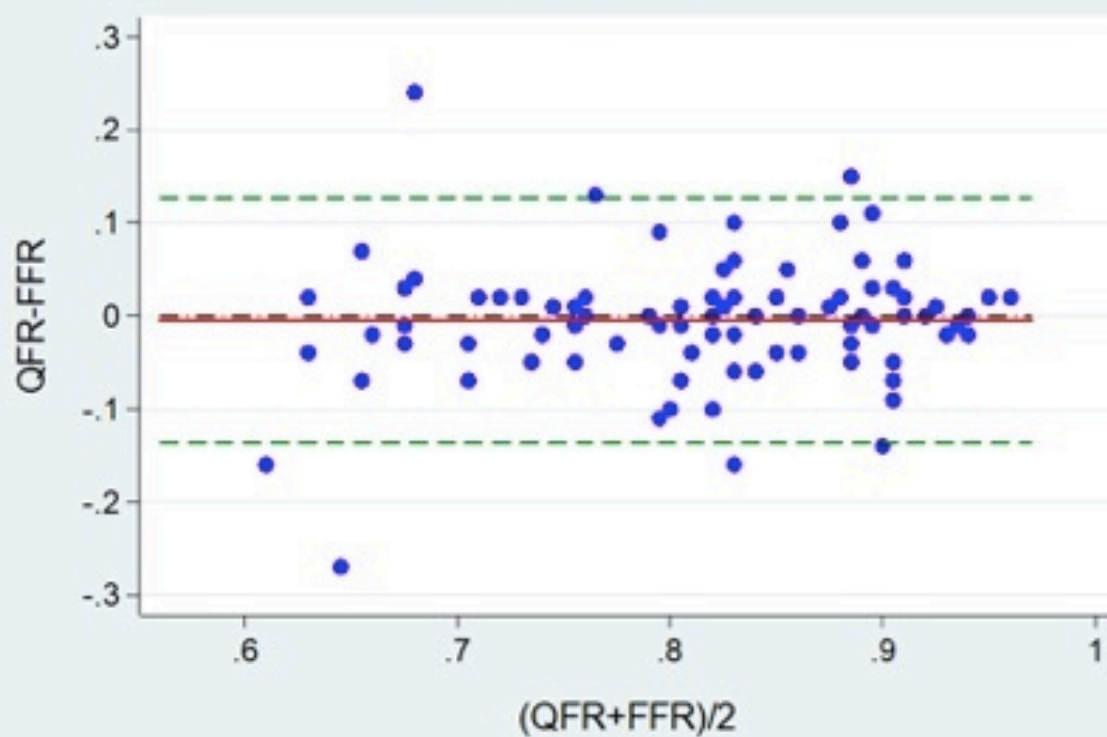


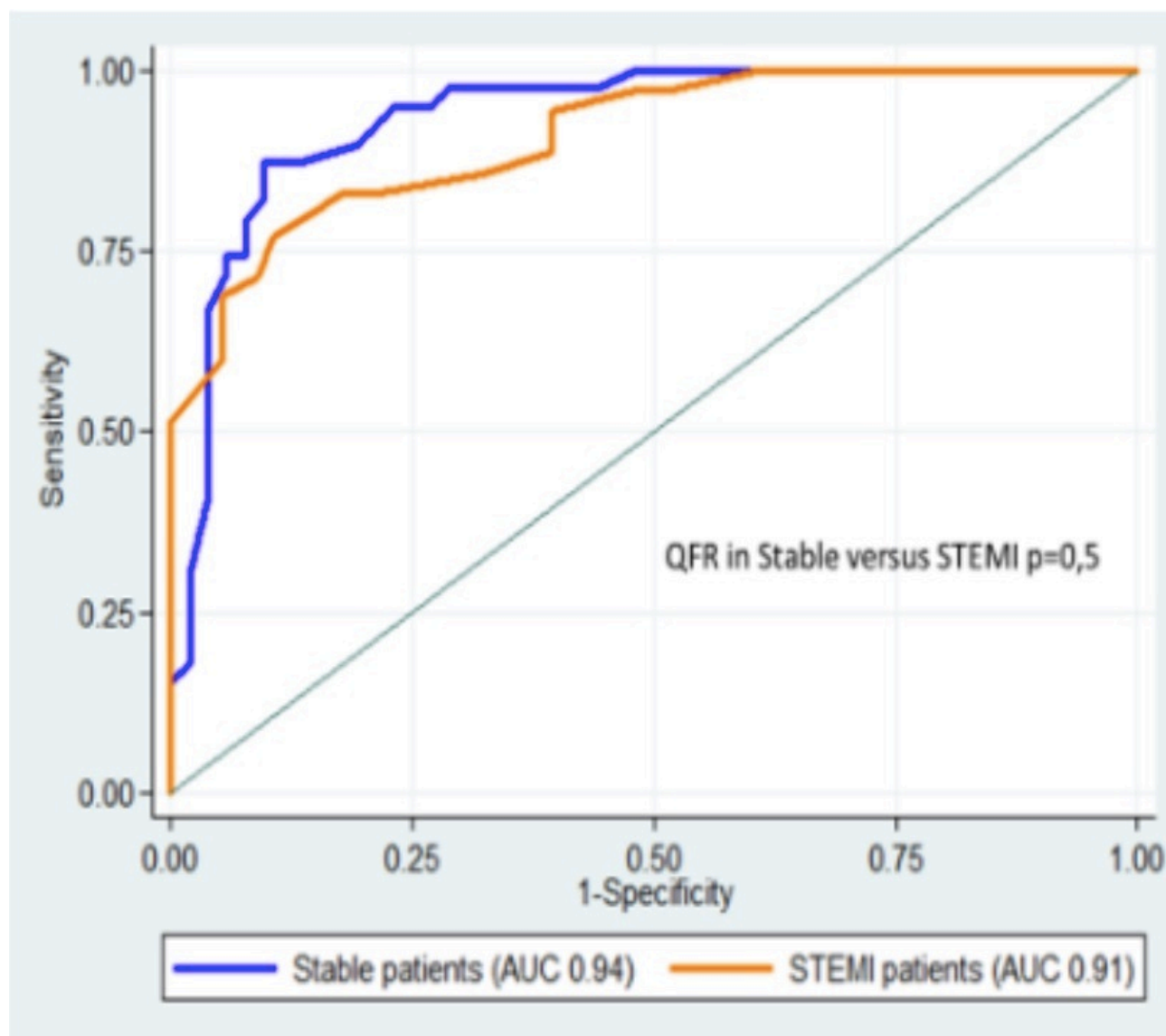
* 91 vessels

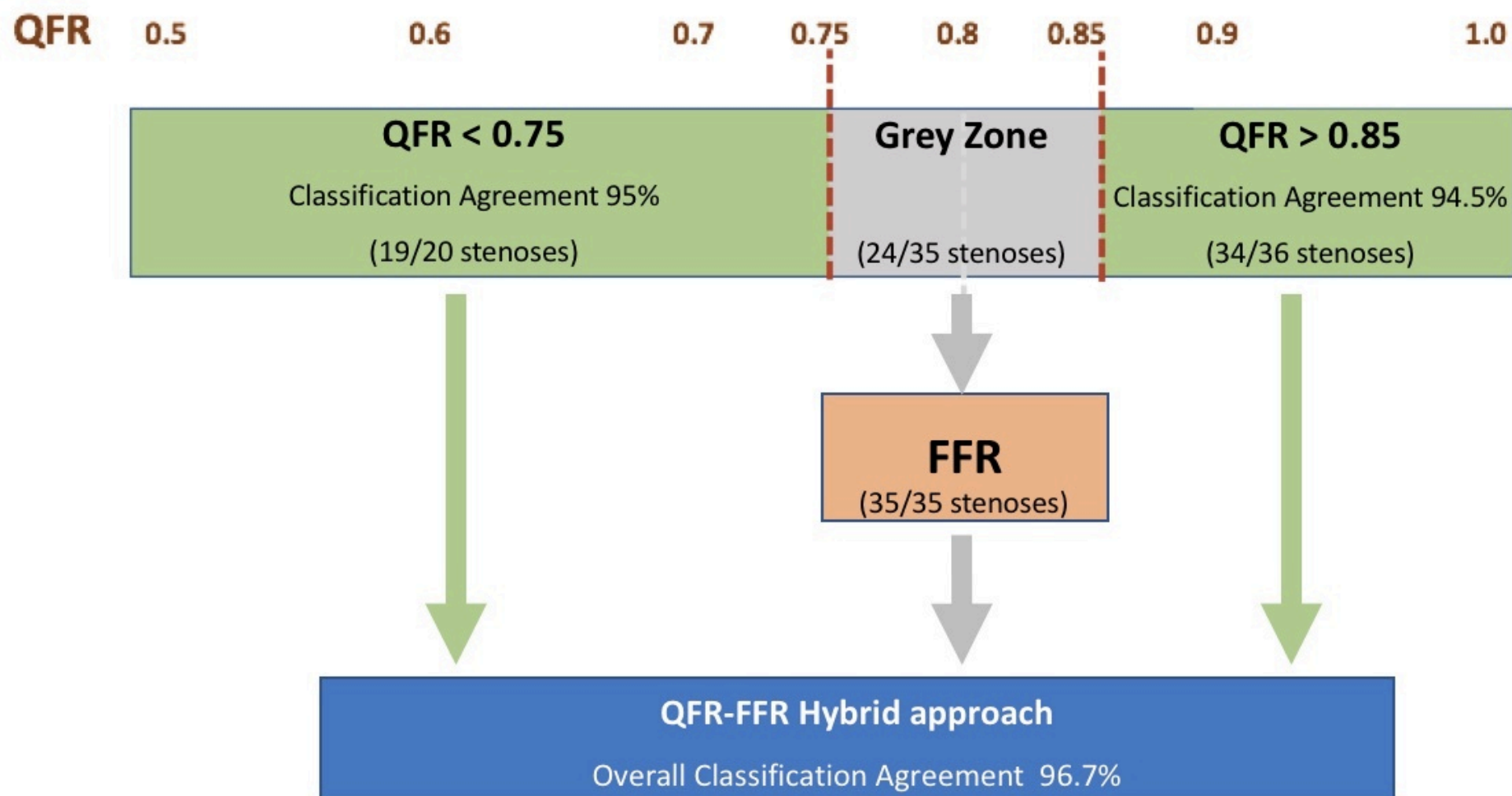




Bland-Altman Agreement

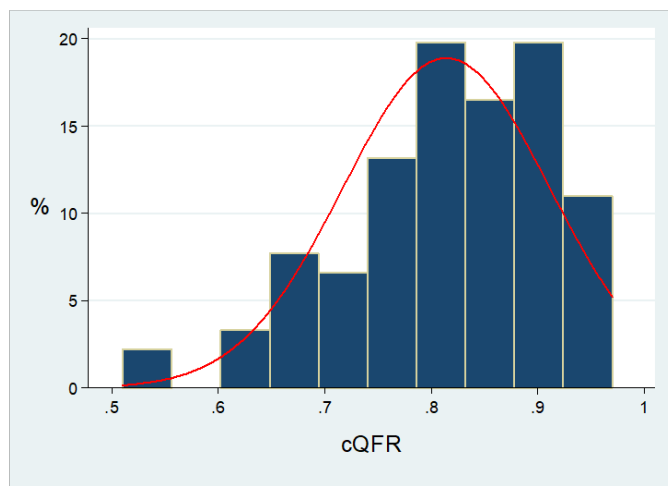
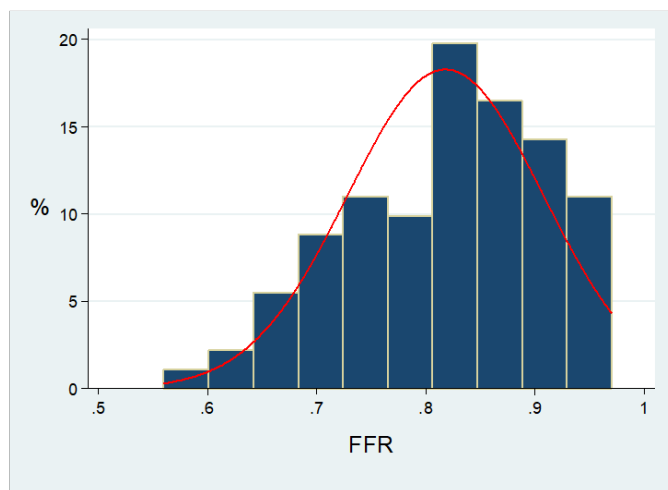
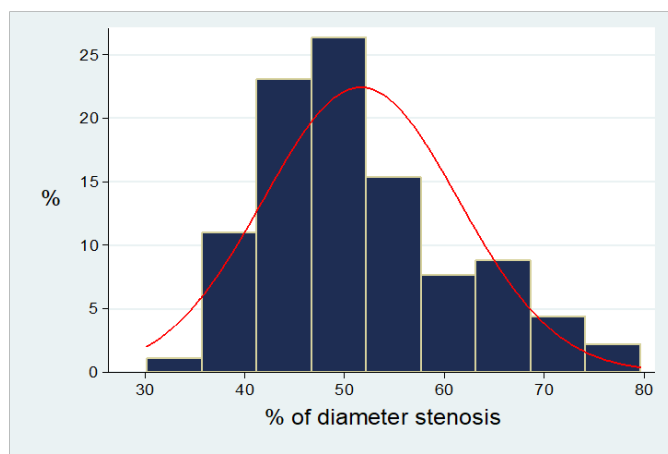






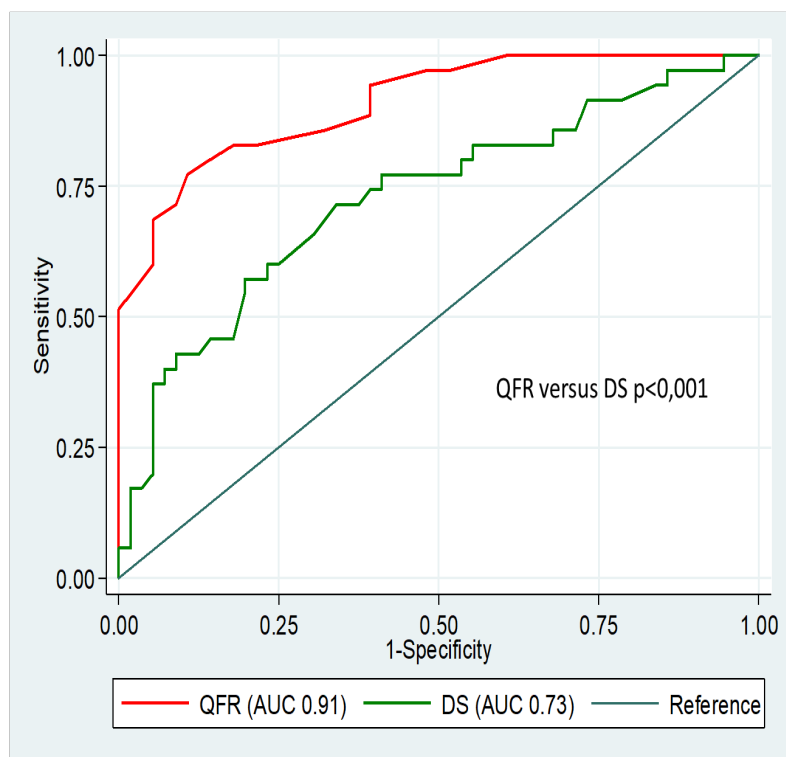
SUPPLEMENTARY MATERIAL

Supplementary figure 1. Distribution of angiographic percentage diameter stenosis and values of FFR and QFR.



cQFR= contrast quantitative flow reserve; FFR= fractional flow reserve

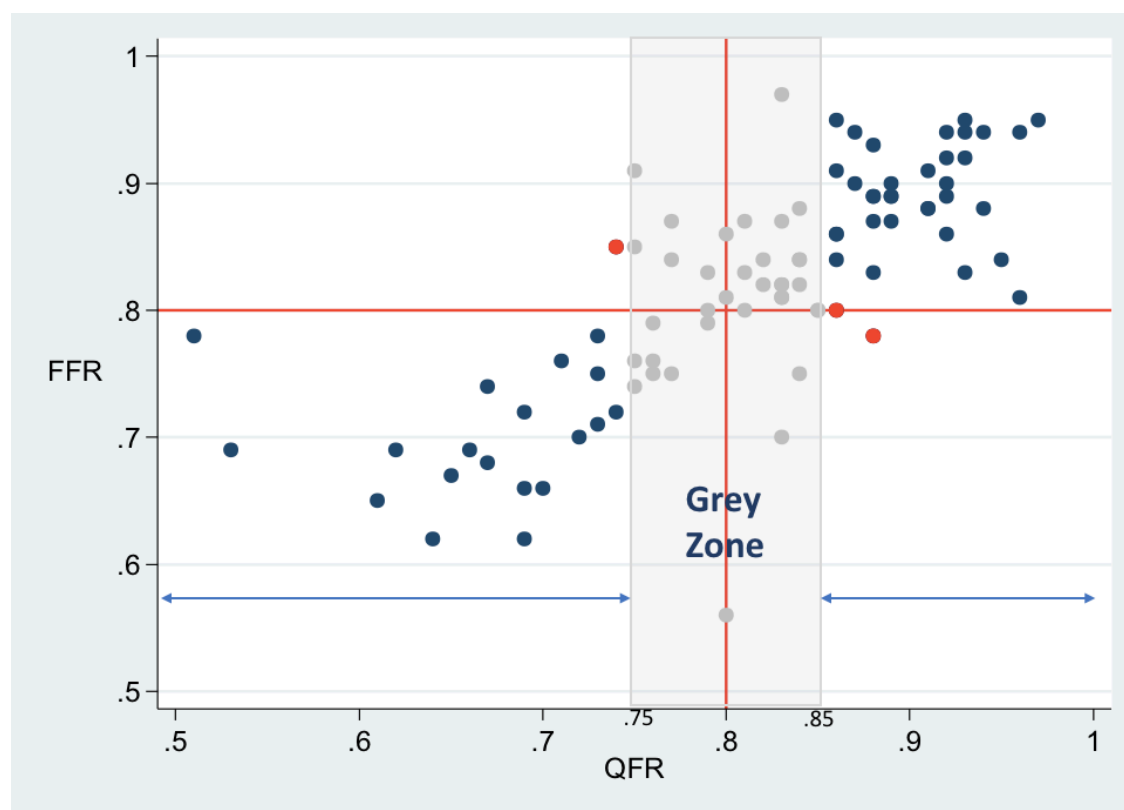
Supplementary figure 2. Diagnostic performance of QFR and angiographic diameter stenosis in assessing functional relevance of non-culprit lesions in STEMI patients.



QFR showed a good diagnostic performance compared to FFR and significantly better than %DS.

%DS= percent diameter stenosis; QFR=quantitative flow reserve; STEMI= ST-elevated myocardial infarction

Supplementary figure 3. QFR Grey zone.



Outside of the grey zone, QFR values <0.75 and >0.85 (**blue bidirectional arrows**) are associated with $>95\%$ concordance with FFR in discriminating flow-limiting stenoses, reassuring the QFR-FFR hybrid approach. Furthermore, within the “safety zone” (**green bidirectional arrow**), QFR had a 100% negative predictive value permitting safe deferral of PCI without need of pressure wire functional assessment.

FFR= Fractional Flow Reserve; QFR= Quantitative Flow Ratio

Supplementary table 1. Diagnostic performance of QFR and DS (3D-QCA) in detecting an FFR ≤ 0.80 in non-culprit vessels at the time of primary PCI (n= 91).

Parameters	QFR ≤ 0.80	DS $\geq 50\%$
Sensitivity	85.7%	74.3%
Specificity	80.0%	60.7%
PPV	77.8%	54.2%
NPV	87.3%	79.1%
Overall diagnostic accuracy	83.5%	65.9%
AUC	0.91 (0.85-0.97) *	0.73 (0.62-0.84) *

AUC = area under the curve; DS= diameter stenosis; NPV = negative predictive value; FFR= fractional flow reserve; PPV = positive predictive value; QFR= quantitative flow ratio; 3D-QCA= 3-dimensions quantitative coronary angiography

* 95% Confidence Interval

Supplementary table 2. Diagnostic performance of QFR reported in previous studies including patients with stable coronary disease.

Parameters	FAVOR Pilot Study (6)	Yazaki K. (7)	FAVOR II China Study (4)	WIFI II Study (8)	Mejia-Renteria H. (9)	FAVOR II Europe-Japan Study (10)	Our Study (stable patients)	Our Study (STEMI patients)
Year	2016	2017	2017	2018	2018	2018	2018	2018
Prospective Design	Yes	No	Yes	Yes	No	Yes	No	No
Sample size (vessels)	n =84	n =151	n =328	n =240	n =300	n =317	n =91	n =91
Correlation	r =0.77	r =0.80	r =0.86	r =0.70	r =0.83	r =0.83	r =0.82	r =0.75
Overall Accuracy	86%	88%	93%	83%	88%	87%	89%	84%
Sensibility	74%	89%	95%	77%	89%	86.5%	87%	86%
Specificity	91%	89%	92%	86%	87%	87%	90%	80%
NPV	88%	95%	97%	75%	91%	93%	90%	78%
PPV	80%	77%	86%	87%	85%	76%	87%	87%
AUC	0.92	0.93	0.96	0.88	0.93	0.92	0.94	0.91

AUC = area under the curve; NPV = negative predictive value; PPV = positive predictive value; QFR= quantitative flow ratio; STEMI= ST-elevated myocardial infarction