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Prognostic Value of QFR Measured Immediately After Successful Stent Implantation

The International Multicenter Prospective HAWKEYE Study

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the potential role of post-percutaneous coronary intervention (PCI) quantitative flow ratio (QFR) measurements to predict clinical outcomes in patients with successful PCI.

BACKGROUND The prognostic value of QFR measured immediately after PCI has not been prospectively investigated.

METHODS Patients undergoing complete revascularization with successful PCI and stent implantation were eligible for acquisition of projections for QFR computation. At the end of the procedure, 2 angiographic projections for each vessel treated with PCI were acquired. Computation of QFR was performed offline by an independent core laboratory. The primary outcome was the vessel-oriented composite endpoint, defined as vessel-related cardiovascular death, vessel-related myocardial infarction, and ischemia-driven target vessel revascularization.

RESULTS Seven hundred fifty-one vessels in 602 patients were analyzed. The median value of post-PCI QFR was 0.97 (interquartile range: 0.92 to 0.99). Lesion location in the left anterior descending coronary artery, baseline SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score, lesion length, and post-PCI diameter stenosis were found to be predictors of lower post-PCI QFR. Altogether, 77 events were detected in 53 treated vessels (7%). Post-PCI QFR was significantly lower in vessels with the vessel-oriented composite endpoint during follow-up, compared with those without it (0.88 [interquartile range: 0.81 to 0.99] vs. 0.97 [interquartile range: 0.93 to 0.99], respectively; $p < 0.001$). Receiver-operating characteristic curve analysis identified a post-PCI QFR best cutoff of ≤0.89 (area under the curve 0.77; 95% confidence interval: 0.74 to 0.80; $p < 0.001$). After correction for potential confounding factors, post-PCI QFR ≤0.89 was associated with a 3-fold increase in risk for the vessel-oriented composite endpoint (hazard ratio: 2.91; 95% confidence interval: 1.63 to 5.19; $p < 0.001$).

CONCLUSIONS Lower values of QFR after complete and successful revascularization predict subsequent adverse events (Angio-Based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation [HAWKEYE]; NCT02811796) (J Am Coll Cardiol Intv 2019;12:2079–88) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

FFR = fractional flow reserve

IQR = interquartile range

IVUS = intravascular ultrasonography

MI = myocardial infarction

OCT = optical coherence tomography

PCI = percutaneous coronary intervention

%DS = percentage diameter stenosis

QFR = quantitative flow ratio

TVR = target vessel revascularization

VOCE = vessel-oriented composite endpoint

Thanks to the continuous refinement of techniques and materials, throughout recent decades the prognosis of patients undergoing percutaneous coronary intervention (PCI) has improved (1-3). However, a significant proportion of PCI patients continue to experience adverse events related to both stented segment and/or residual or diffuse disease (4). In daily practice, the adequacy of the PCI result is based on angiographic appearance only. Post-PCI fractional flow reserve (FFR) measurement could discriminate vessels with suboptimal results at higher risk for recurrence (5,6). FFR-guided optimization of PCI has been associated with a reduction of target vessel events (7). Nevertheless, this prognostic advantage remains theoretical because of the low penetration of post-PCI FFR measurement and the absence of randomized data (7,8). A recent nationwide survey showed that FFR measurement was performed in <10% of cases in which intracoronary physiology was used to guide revascularization (8). The quantitative flow ratio (QFR) is an angiographically derived FFR measurement recently developed as an alternative to invasive physiology (9-12). QFR measurement does not require pressure-wire use or hyperemia induction (13). QFR application in the post-PCI setting is not related to its use before PCI and can be used in both angiography- and physiology-guided procedures. In addition, like the FFR pull back curve, QFR permits the investigation of the entire vessel, which could be helpful to discriminate if issues are related or not to the stented segment. The theoretical advantage of QFR could be a wider implementation in clinical practice if compared with other PCI optimization tools.

Thus, the aim of the present study was to test whether QFR post-stenting is related to adverse events in follow-up in consecutive PCI patients undergoing complete revascularization and successful implantation of second-generation drug-eluting stents.

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METHODS

STUDY DESIGN. The multicenter, investigator-driven, prospective HAWKEYE (Angio-based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation) study investigated the ability to discriminate adverse events of QFR measured after successful PCI. The study was conducted at 7 centers in 2 countries (Italy and Spain). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Patients were informed that their participation was voluntary, and all gave informed written consent. This study was registered at ClinicalTrials.gov (NCT02811796) and approved by the ethical review boards at the participating hospitals.

PATIENTS. Patients ≥18 years of age who underwent PCI were eligible for the acquisition of projections for QFR computation if: 1) PCI was successful; 2) complete revascularization was achieved; and 3) second-generation drug-eluting stents were implanted. Successful PCI was defined as residual stenosis <20% by visual estimation and final TIMI (Thrombolysis In Myocardial Infarction) flow grade 3. Complete revascularization was defined as the treatment of all lesions showing diameter stenosis ≥50% (visual estimation) in major epicardial coronary arteries or their side branches with diameter ≥1.5 mm. The indication for PCI was left to the operator's discretion and was based on clinical and angiographic data. The operator was free to use invasive physiologic assessment to discriminate lesions requiring PCI. Exclusion criteria were: 1) ST-segment elevation myocardial infarction (MI); 2) clinical or angiographic features limiting QFR computation (left main or ostial right coronary artery, previous coronary artery bypass graft, atrial fibrillation, ongoing ventricular arrhythmias, or significant and persistent tachycardia); 3) inability to provide consent; and 4) life expectancy <1 year.

STUDY PROCEDURE. Invasive coronary angiography and PCI were performed following best local practices. Post-dilatation with a noncompliant balloon was strongly suggested. At the end of the procedure, 2 angiographic projections for each vessel treated with PCI were acquired for QFR computation. Angiographic projections were acquired after nitroglycerin (100 to 200 μg) administration at 15 frames/s during a single injection of 6 ml radiographic contrast medium at a flow rate of 4 ml/s and a pressure of 300 psi using a power injector system. Angiographic projections should be at least 25° apart, aiming for minimal vessel foreshortening and minimal vessel overlap. In agreement with previous studies, operators followed a table of recommended projection angles (Online Figure 1).

QFR. Computation of QFR was performed offline, using the software package QAngio XA 3D (Medis Medical Imaging Systems, Leiden, the Netherlands) (9-13). QFR computation was performed in agreement with the step-by-step procedure validated in previous

studies (9–13). In the present analysis, we considered contrast QFR values (12). QFR was calculated in the entire vessel, starting from the most proximal available segment until its diameter became <1.5 mm (12). In the second phase, the QFR curves of vessels with suboptimal result (QFR ≤0.89) were reanalyzed (post hoc analysis). In each curve, the localization of QFR drop was classified as: 1) in stent; 2) focal outside stent; 3) diffuse; or 4) a combination of these three locations. Some cases of optimal and suboptimal QFR values are reported in the Online Appendix (Online Figures 2 and 3). QFR computations were done in the core laboratory of the University Hospital of Ferrara. Two independent operators, blinded to outcomes, performed QFR computations. Both are certified operators for QFR computation. The inter-rater agreement between operators was very high in all cases ($\kappa > 0.95$). The median time to calculate QFR was 3.5 min (interquartile range [IQR]: 2 to 5.5 min).

QUANTITATIVE CORONARY ANGIOGRAPHY AND SYNTAX SCORE CALCULATION. Quantitative coronary analysis and SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score calculation were done in the core laboratory of the University Hospital of Ferrara by operators blinded to outcomes. Quantitative coronary analysis was performed using validated software (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). The following quantitative coronary angiographic values were measured before and after PCI: reference vessel size, lesion length, and percentage diameter stenosis (%DS) (14). The aforementioned values were measured at the level of the stented segment (14). The SYNTAX score was calculated from baseline coronary angiography, before PCI. For each patient, by scoring all coronary lesions with stenosis diameter ≥50% in vessels ≥1.5 mm, the baseline score value was calculated using the SYNTAX score algorithm available online.

DATA COLLECTION AND FOLLOW-UP. Patient demographic data, cardiovascular risk factors, clinical diagnoses, and procedural details were recorded at the time of PCI. Source data were collected online using dedicated electronic case report forms. Study angiograms were anonymized and submitted to core laboratory of the University Hospital of Ferrara. Clinical follow-up was performed at 30 days and then every 6 months. Follow-up was censored at the end of November 2018 or at the time of death. One-year follow-up was complete in all patients. Of note, 476 patients (79%) had longer follow-up. The median follow-up duration was 629 days (IQR: 584 to 746 days).

ENDPOINTS. In the present study we investigated the relationship between post-PCI QFR and clinical outcomes at the vessel level (5). The primary endpoint was the vessel-oriented composite endpoint (VOCE), defined as the composite of vessel-related cardiovascular death, vessel-related MI, and ischemia-driven target vessel revascularization (TVR) (5). Secondary endpoints were: 1) the cumulative occurrence of vessel-related cardiovascular death and MI; and 2) the cumulative occurrence of ischemia-driven TVR. All events were adjudicated by an independent clinical event committee (R.P., G.S.) blinded to QFR and quantitative coronary angiographic values. Events were designated as vessel related or not vessel related (5). All deaths were considered cardiac unless an unequivocal noncardiac cause could be established. Cardiovascular death in patients with multiple treated vessels was assigned to each vessel (5). The diagnosis of MI, as suggested by the fourth universal definition of MI (15), required a combination of symptoms, electrocardiographic changes, and significant increase in cardiac markers (troponin). Any MI without a clearly identifiable culprit vessel was counted as target vessel related (5). Ischemia-driven TVR was defined as any repeated revascularization of the target vessel in the presence of a lesion with %DS >50% and concomitant history of angina pectoris plus objective signs of ischemia at rest or during exercise test (or equivalent) or abnormal results of any invasive functional diagnostic test. In case of repeated adverse events in the same vessel, the first occurred was the one considered.

STATISTICAL ANALYSIS. Starting from previous similar studies (5–7), we expected a VOCE incidence ranging between 6% and 8% and a small number of predictors (about 5) from multivariate regression analysis. According to Peduzzi et al. (16), at least 600 patients and 740 vessels were needed. This estimate was consistent with the published research (5–7). Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. All variables showed skewed distributions and are reported as median and IQR. Comparisons between continuous variables were performed using the Mann-Whitney *U* test as appropriate. Categorical variables are reported as counts and percentages. Comparisons between categorical variables were carried out using Pearson chi-square or Fisher exact tests as appropriate. The predictive value of clinical and angiographic parameters on post-PCI QFR was determined by deriving the standardized β coefficients in a generalized linear mixed-effects multiple variable regression. Clinical and angiographic parameters plus

TABLE 1 Baseline Characteristics

Patients (n = 602)	
Age, yrs	68 (60-77)
Female	159 (26)
BMI, kg/m^2	26.5 (24.3-29.4)
CV risk factors	
Diabetes	139 (23)
Hypertension	444 (74)
Hyperlipidemia	336 (56)
Current smoker	114 (19)
Medical history	
MI	133 (22)
PCI	147 (24)
CVA	9 (1.5)
PAD	39 (6.5)
Chronic kidney disease*	47 (7.8)
Clinical presentation	
NSTEACS	402 (67)
SIHD	200 (33)
Angiographic disease severity	
Multivessel disease	125 (21)
SYNTAX score	14 (7-21)
Contrast media, ml	170 (136-220)
Vessels (n = 751)	
Location	
LAD	356 (48)
LCx	184 (24)
RCA	211 (28)
Quantitative coronary angiography	
Pre-PCI RVD, mm	2.8 (2.3-3.2)
Pre-PCI diameter stenosis, %	62 (55-76)
Pre-PCI lesion length, mm	21 (17-30)
Post-PCI diameter stenosis, %	11 (9-16)
Procedural data	
Number of stents	1 (1-2)
Diameter of stents, mm	3 (3-3.5)
Total length of stents, mm	30 (24-32)
Post-dilatation	627 (87)

Values are median (interquartile range) or n (%). *Defined as creatinine ≥2 mg/dl.

BMI = body mass index; CV = cardiovascular; CVA = cerebrovascular accident; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; NSTEACS = non-ST-segment elevation acute coronary syndrome; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; RCA = right coronary artery; RVD = reference vessel diameter; SIHD = stable ischemic heart disease; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

post-PCI QFR values were tested for predictive value by fitting a generalized linear mixed-effects multiple-variable regression model by backward elimination. To take into account the nonindependence of lesions, patient identification was introduced in the multilevel model as a random effect, and the model was fitted with random intercepts. Models were fitted by maximum likelihood, and Student's *t*-tests used Satterthwaite's method. Independent predictors ($p < 0.05$) were used in the time-to-event analysis, fitting a Cox regression model with robust variance to account for a possible lesion correlation. Tests for proportional hazards of each covariate were based on scaled Schoenfeld residuals. The optimal cutoff value of post-PCI QFR for predicting the VOCE was calculated by maximizing the sum of sensitivity and specificity, using receiver-operating characteristic curve analysis. Observations were grouped according to high and low levels of post-PCI QFR and were used in time-to-event analysis followed by proportional hazard tests after fitting a crude and adjusted Cox model. Finally, to evaluate the consistency of the findings, further analysis at the patient level was carried out. Methods and results of the patient-level analysis are available in the Online Appendix. One- or 2-tailed tests were used as appropriate, and statistical significance was defined as $p < 0.05$. All analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) by an independent statistician (M.M.).

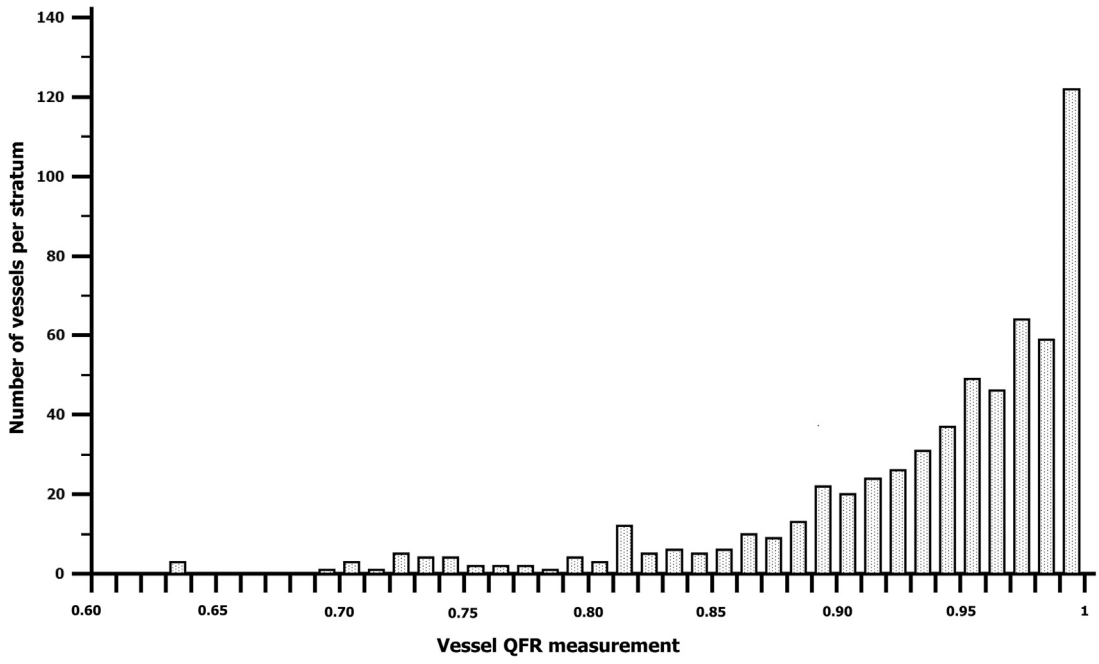
RESULTS

The study flowchart is depicted in Online Figure 4. From June 2016 to July 2017, 707 patients met the inclusion and exclusion criteria and had dedicated projections for QFR. Offline QFR computation was not feasible in 105 cases (15%). Therefore, 602 patients constituted the study population for the present analysis. Overall, 751 vessels were evaluated, of which 356 (47%) were left anterior descending coronary arteries, 211 (28%) were right coronary arteries, and 184 (25%) were circumflex arteries. Detailed patient, vessel, and procedural characteristics are reported in **Table 1**.

POST-PCI QFR MEASUREMENT. The median value of post-PCI QFR was 0.97 (IQR: 0.92 to 0.99). The distribution of post-PCI QFR values is shown in **Figure 1**. By computing standardized coefficients in multiple regression analysis, left anterior descending coronary artery location (standardized $\beta = -0.156$; 95% confidence interval [CI]: −0.239 to −0.072; $p < 0.001$), baseline SYNTAX score (standardized $\beta = -0.124$; 95% CI: −0.208 to −0.040; $p = 0.004$), lesion length (standardized $\beta = -0.152$; 95% CI: −0.235 to −0.069; $p < 0.001$) and post-PCI %DS (standardized $\beta = -0.110$; 95% CI: −0.191 to −0.028; $p = 0.008$) were found to be significant predictors of a lower post-PCI QFR value.

CLINICAL FOLLOW-UP. At the vessel level, we observed 8 cardiovascular deaths in patients with 1 treated vessel, 1 in a patient with 2 treated vessels, and 2 in patients with 3 treated vessels. The numbers of vessels experiencing target vessel MI and TVR were 21 and 40, respectively. All vessels with target

FIGURE 1 Distribution of Post-Percutaneous Coronary Intervention Quantitative Flow Ratio Values

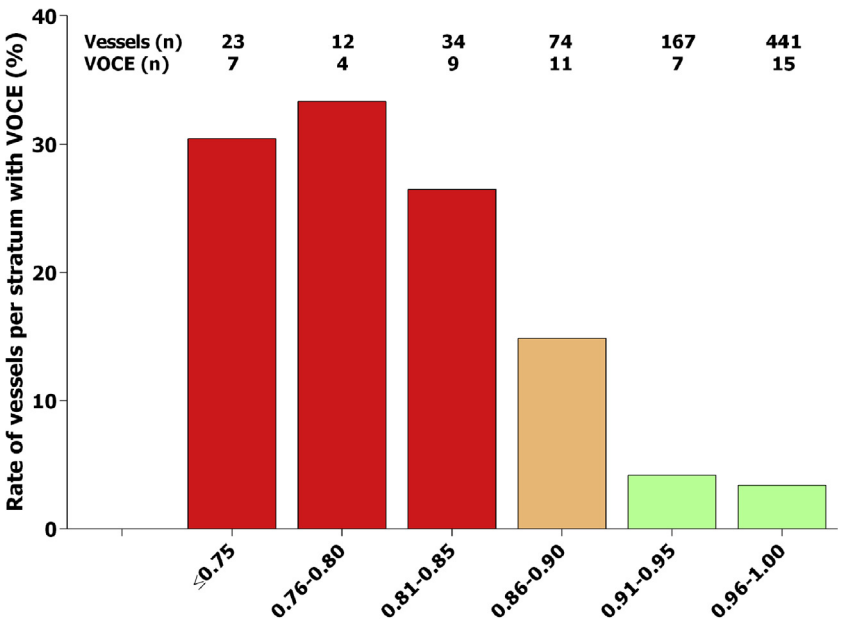


QFR = quantitative flow ratio.

vessel MI underwent concomitant TVR. Altogether, 77 events were detected in 53 treated vessels (7%) (Online Table 1). The occurrence of the VOCE stratified according to classes of post-PCI QFR values is shown in **Figure 2**. Post-PCI QFR was significantly lower in vessels with the VOCE during follow-up compared with those without (0.88 [IQR: 0.81 to 0.99] vs. 0.97 [IQR: 0.93 to 0.99], respectively; $p < 0.001$). Among the variables listed in **Table 1**, diabetes, prior MI, post-PCI %DS, and post-PCI QFR were independent predictors of the VOCE (**Table 2**). In the direct comparison with post-PCI %DS, post-PCI QFR showed better ability to discriminate vessels at risk for the VOCE (Online Figure 5). The time-to-event analysis confirmed the association among diabetes, prior MI, post-PCI QFR, and the VOCE (**Table 2**). Receiver-operating characteristic curve analysis identified a post-PCI QFR cutoff of ≤0.89 as having the best predictive accuracy for the VOCE, with 60% sensitivity and 87% specificity (area under the curve 0.77; 95% CI: 0.74 to 0.80; $p < 0.001$). Overall, 123 vessels (16%) had post-PCI QFR ≤0.89. Adverse events, stratified at the vessel level according to the ≤0.89 cutoff, are shown in Online Table 1. Vessels showing post-PCI QFR values ≤0.89 had a significantly higher VOCE rate compared with those with values >0.89 (25% vs. 3.5%, respectively; $p < 0.001$) (**Figure 3**, Online Table 1). After correction for potential confounding factors (diabetes, prior MI, lesion length, post-PCI %DS, left anterior descending coronary artery location, and baseline SYNTAX score), post-PCI QFR ≤0.89 remained associated with a 3-fold increase in the risk for VOCE (adjusted hazard ratio: 2.91; 95% CI: 1.63 to 5.19; $p < 0.001$). This finding was consistent also for secondary endpoints. The cumulative occurrence of vessel-related cardiovascular death and MI was higher in vessels with QFR values ≤0.89 (14.6% vs. 2.9%; $p < 0.001$; adjusted hazard ratio: 5.54; 95% CI: 2.46 to 12.5; $p < 0.001$), as well as that of ischemia-driven TVR (19.5% vs. 2.5%; $p < 0.001$; adjusted hazard ratio: 9.23; 95% CI: 4.3 to 19.7; $p < 0.001$). The patient-level analysis confirmed the finding of the vessel-level analysis (a detailed description is provided in Online Tables 2 to 4).

LOCALIZATION OF QFR DROP IN VESSELS WITH SUBOPTIMAL RESULTS. Analyzing the 123 vessels with suboptimal results, the site of QFR drop was limited to the stent in 16 cases (13%). A focal drop outside the stent was identifiable in 39 cases (32%).

FIGURE 2 Rate of Vessels With the Vessel-Oriented Composite Endpoint in the Different Post-Percutaneous Coronary Intervention Quantitative Flow Ratio Strata



Colors indicate the distribution according the best cutoff (≤0.89) for the prediction of the vessel-oriented composited endpoint (VOCE): **green** for values higher than the cutoff, **orange** for values near the cutoff, and **red** for values less than the cutoff.

Forty-two vessels (34%) showed a constant and progressive decrease of the QFR curve, suggestive of diffuse disease. Finally, 26 cases (21%) showed a combination of the aforementioned possibilities.

DISCUSSION

The HAWKEYE study was conducted to investigate the potential role of QFR computation after successful PCI with stent implantation in the prediction of adverse events. To minimize potential confounding factors, we selected patients undergoing complete and successful revascularization. Moreover, we performed QFR computation offline at an independent and blinded core laboratory, and we centrally adjudicated adverse events that were considered at the vessel level. The main findings are as follows.

First, post-PCI QFR values significantly varied, although the large majority of treated vessels was associated with higher and optimal functional result, as assessed by QFR measurement. Second, clinical (diabetes, prior MI), anatomic (lesion located in the left anterior descending coronary artery), and angiographic (lesion length, post-PCI residual diameter stenosis) variables influenced post-PCI QFR. Third, QFR identified a relatively small number of vessels (16%; 95% CI: 14% to 19%) with suboptimal results. Fourth, post-PCI QFR was an independent predictor of adverse events (**Central Illustration**).

These findings are consistent with those from studies with post-PCI measurement of FFR (5-7,14). The rationale for post-PCI FFR measurement was to evaluate residual disease burden, which cannot be fully assessed by angiographic assessment, and to integrate information obtained with intracoronary imaging (intravascular ultrasonography [IVUS] and optical coherence tomography [OCT]), which are

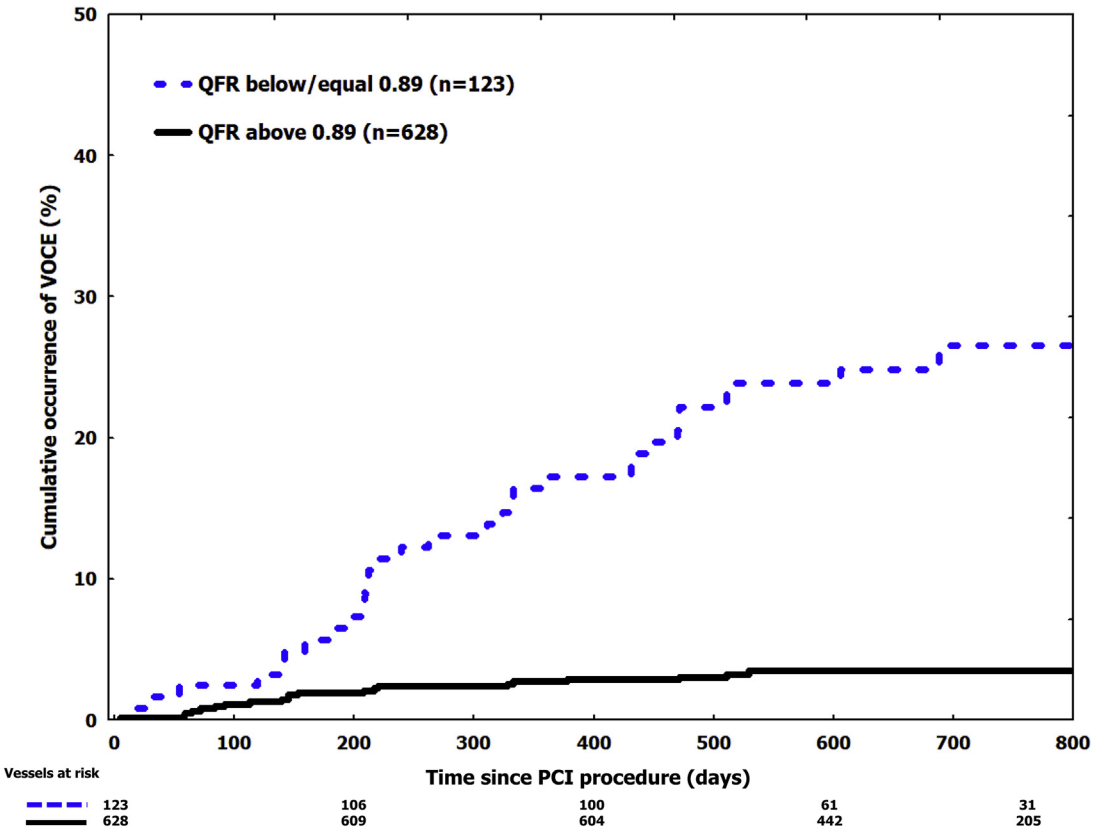
TABLE 2 Vessel-Level Analysis: Predictors of the Vessel-Oriented Composite Endpoint (751 Vessels)

	GLM Effects*		Cox Regression†	
	Standardized β (95% CI)	p Value	HR (95% CI)	p Value
Diabetes	0.037 (0.013 to 0.061)	0.002	2.59 (1.39 to 4.81)	0.002
Prior MI	0.046 (0.022 to 0.070)	<0.001	2.79 (1.52 to 5.13)	<0.001
Post-PCI diameter stenosis	0.036 (0.017 to 0.058)	<0.001	1.24 (0.99 to 1.56)	0.055
Post-PCI QFR	−0.067 (−0.087 to −0.047)	<0.001	0.56 (0.46 to 0.68)	<0.001

*Variables able to predict the vessel-oriented composite endpoint were identified by fitting a generalized linear mixed-effects multiple-variable regression model by backward elimination. †Independent predictors of the previous analysis were used in time-to-event analysis fitting a Cox regression model with robust variance.

CI = confidence interval; GLM = generalized linear mixed; HR = hazard ratio; QFR = quantitative flow ratio; other abbreviations as in Table 1.

FIGURE 3 Cumulative Occurrence of the Vessel-Oriented Composite Endpoint in Vessels Stratified According the Best Cutoff

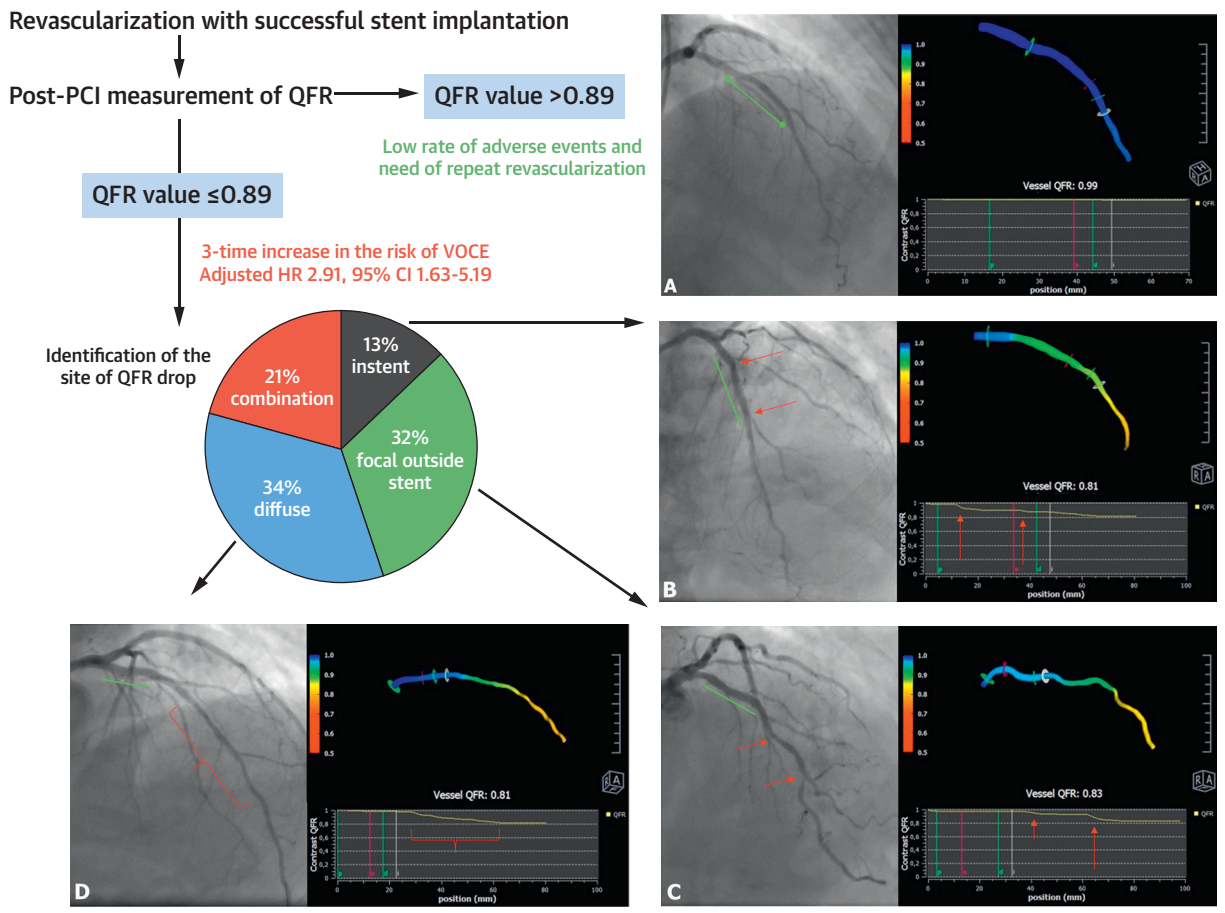


Black continuous line = vessels with values of post-percutaneous coronary intervention (PCI) quantitative flow ratio (QFR) ≤0.89. **Blue dotted line** = vessels with values >0.89. The cutoff of 0.89 was obtained by receiver-operating characteristic curve analysis for the best prediction of the vessel-oriented cardiac endpoint (VOCE).

more detailed regarding stent apposition. Despite there being a consistent and reliable association between low post-PCI FFR and increased risk for clinical events (5-7,14,17,18), the use of post-PCI FFR in daily practice is negligible (8). Several factors and drawbacks can explain this issue. First, its predictability was reported to be low (5). Second, optimal cutoff values ranged widely and should be integrated with information from pre-PCI values (5-7,14,17,18). Third, post-PCI FFR measurement is generally performed only in patients in whom invasive physiology was used to guide revascularization (8). Recently, Kikuta et al. (19) confirmed the accuracy and effectiveness of the instantaneous wave-free ratio in the presence of tandem and diffuse coronary disease. Compared with FFR, the instantaneous wave-free ratio does not require adenosine administration and permits a quick and easy pull back to investigate the entire vessel and to well discriminate the site of pressure drop. These features make the instantaneous wave-free ratio appealing also for post-PCI assessment, and preliminary evidence confirms this (NCT03084367).

QFR is a novel approach to estimate coronary physiology, based on the elaboration by dedicated software of angiographic projections. After adequate training, the acquisition of appropriate images and the computation are relatively easy and quick. QFR does not require maximal epicardial vasodilation or the use of dedicated materials. We found that QFR measurement after optimal PCI was feasible. The presence of lower QFR values predicted an increased risk for adverse events (**Central Illustration**). The increase in events was in terms of both vessel-related cardiac death and MI and repeated TVR. This is the largest study showing a relationship between QFR and outcomes. Previous studies were focused on the concordance between QFR and invasive physiologic assessment (i.e., FFR)

CENTRAL ILLUSTRATION **Final Angiographic Projection, Reconstruction of the Vessel With Vessel Contrast Quantitative Flow Ratio, and the Quantitative Flow Ratio Pullback**



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The **green line** shows the stented segment. The **red arrows** show the points with the major quantitative flow ratio (QFR) drop. **(A)** Optimal result, QFR value near to 1, no drops. **(B)** Two focal drops inside the stent. **(C)** Two focal drops in the distal portion of the vessel, outside the stent. **(D)** Long diffuse disease distally to the stent. PCI = percutaneous coronary intervention; VOCE = vessel-oriented composite endpoint.

and on feasibility of online assessment (9-11). The HAWKEYE study adds evidence that QFR can work also as gatekeeper for the discrimination of future events. Obviously, the evidence is preliminary, limited to the post-PCI scenario, and generated by a small number of vessels (n = 123) with a limited number of adverse events (n = 31) and should be confirmed in larger studies.

As shown by the analysis of the QFR drop localization, the mechanisms underlying lower QFR values and poor outcomes are different (**Central Illustration**). Even though this analysis should be considered only hypothesis generating, it enables us to speculate about the potential clinical implications of post-PCI QFR measurement. As expected, suboptimal stent deployment is among the causes of low post-PCI QFR. In the present study, all patients underwent second-generation drug-eluting stent implantation by experienced operators, with post-dilatation in more than 85% of cases. The current gold standard for stent optimization is intracoronary imaging (IVUS or OCT) (20-24). Recent studies confirmed that imaging-guided PCI is associated with better outcomes (20-24). Nevertheless, the systematic application of the imaging-guided approach is far from being achieved. IVUS and OCT are used for guidance in <10% and 2% of cases, respectively (24). In our study population, left main PCI was an exclusion criterion,

median lesion length was about 20 mm, and only 35% of patients underwent implantation of stents in overlap. Therefore, it is not surprising that we found a relatively small number of patients with QFR drop limited to stented segment (13% [95% CI: 8% to 19%] of the cases with suboptimal QFR results). In these patients, we can speculate that intracoronary imaging and further stent optimization might improve the results. In other cases, QFR could help physicians unravel unnoticed lesions or quantify diffuse disease burden. Additional lesions can be successfully treated with PCI, whereas the quantification of diffuse disease may help explain residual symptoms or persistently abnormal noninvasive functional studies. Similarly, whether more aggressive medical strategies (i.e., longer dual-antiplatelet therapy regimen, PCSK9 inhibitors, etc.) can improve the outcomes of patients with lower QFR value and diffuse disease is unknown.

STUDY LIMITATIONS. First, only patients undergoing complete and successful revascularization were eligible.

Second, the protocol did not recommend the acquisition of projections for QFR computation before revascularization. In addition, because the indication for PCI was left to operator's discretion, we did not capture in the dataset the rate and value of preprocedural physiological assessment. This is the major limitation of our study. Indeed, recent studies, based on wire-based physiological assessment, showed that the pre-PCI value is important to better understand the post-PCI value and to better stratify the prognosis (14). In our study, the lack of pre-PCI values did not permit the replication of findings regarding the prognostic role of pre-PCI versus post-PCI values or of the percentage of increase of the value before and after PCI (14). Similarly, we cannot exclude that a systematic assessment of QFR before PCI could change the revascularization strategy, the rate of adverse events, and the proper identification of hemodynamically significant untreated lesions.

Third, QFR computation was performed offline. Previous studies showed good agreement between offline and online measurements (9,10). The reproducibility of our findings in a real-life scenario, with online assessment, should be properly investigated. We observed slightly lower QFR feasibility compared with previous FAVOR II trials (9,10). We cannot exclude that this issue may be related to direct feedback on the quality of angiographic projections given during online computation. In addition, the distal point for QFR computation was arbitrarily located in the distal portion of the vessel, when the diameter becomes <1.5 mm. This was an arbitrary decision, and we are unable to estimate if it influenced the findings of the study.

Fourth, the strict inclusion and exclusion criteria limit the generalizability of our results.

Finally, advanced intracoronary imaging (IVUS and/or OCT) was left to the operator's discretion and was performed in <4% of the cases. Information from IVUS and/or OCT would have been helpful to better understand the mechanisms underlying low QFR values and recurrence of events.

CONCLUSIONS

The measurement of QFR after complete and successful revascularization with PCI and stenting is feasible. Post-PCI QFR values were suboptimal in about 15% of cases. Lower values of post-PCI QFR were independent predictors of adverse events and identified a subgroup of patients at higher risk for poor outcomes.

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PERSPECTIVES

WHAT IS KNOWN? QFR showed good agreement and concordance with FFR in the invasive hemodynamic evaluation of intermediate coronary stenoses. The prognostic value of QFR, measured after successful PCI with stent implantation, is unknown.

WHAT IS NEW? QFR values after successful PCI showed significant variability, being suboptimal in about 15% of the treated vessels. Clinical (diabetes, prior MI), anatomic (lesion located in the left anterior descending coronary artery), and angiographic (lesion length, post-PCI residual diameter stenosis) variables were related to post-PCI QFR. Lower post-PCI QFR is associated with worse clinical outcomes at the vessel level.

WHAT IS NEXT? Future studies are clearly needed to investigate how to optimize outcomes in vessels with suboptimal QFR values.

REFERENCES

1. von Birgelen C, Zocca P, Buiten RA, et al. Thin composite wire strut, durable polymer-coated (Resolute Onyx) versus ultrathin cobalt-chromium strut, bioresorbable polymer-coated (Orsiro) drug-eluting stents in all comers with coronary artery disease (BIONYX): an international, single-blind, randomized non-inferiority trial. Lancet 2018;392:1235–45.

2. Sabaté M, Brugaletta S, Cequier A, et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. Lancet 2016;387:357–66.

3. Taniwaki M, Stefanini GG, Silber S, et al. 4-Year clinical outcomes and predictors of repeat revascularization in patients treated with new-generation drug-eluting stents: a report from the RESOLUTE all-comers trial (A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention). J Am Coll Cardiol 2014;63:1617–25.

4. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226–35.

5. 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:e005233.

6. Kasula S, Agarwal SK, Hacioglu Y, et al. Clinical and prognostic value of poststenting fractional flow reserve in acute coronary syndromes. Heart 2016;102:1988–94.

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. J Am Coll Cardiol Intv 2016;9:1022–31.

8. Tebaldi M, Biscaglia S, Fineschi M, et al. Evolving routine standards in invasive hemodynamic assessment of coronary stenosis: the nationwide Italian SICI-GISE cross-sectional ERIS study. J Am Coll Cardiol Intv 2018;11:1482–91.

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:e009603.

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;70:3077–87.

11. 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. J Am Coll Cardiol Intv 2016;9:2024–35.

12. 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:e006023.

13. Cesaro A, Gragnano F, Di Girolamo D, et al. Functional assessment of coronary stenosis: an overview of available techniques. Is quantitative flow ratio a step to the future? Expert Rev Cardiovasc Ther 2018;16:951–62.

14. Lee JM, Hwang D, Choi KH, et al. Prognostic implications of relative increase and final fractional flow reserve in patients with stent implantation. J Am Coll Cardiol Intv 2018;11:2099–109.

15. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237–69.

16. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373–9.

17. Nam CW, Hur SH, Cho YK, et al. Relation of fractional flow reserve after drug-eluting stent implantation to one-year outcomes. Am J Cardiol 2011;107:1763–7.

18. 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;7:917–23.

19. Kikuta Y, Cook CM, Sharp ASP, et al. Pre-angioplasty instantaneous wave-free ratio pullback predicts hemodynamic outcome in humans with coronary artery disease: primary results of the international multicenter iFR GRADIENT registry. J Am Coll Cardiol Intv 2018;11:757–67.

20. Zhang J, Gao X, Kan J, et al. Intravascular ultrasound versus angiography-guided drug eluting stent implantation: the ULTIMATE trial. J Am Coll Cardiol 2018;72:3126–37.

21. Di Mario C, Koskinas KC, Räber L. Clinical benefit of IVUS guidance for coronary stenting: the ULTIMATE step toward definitive evidence? J Am Coll Cardiol 2018;72:3138–41.

22. Ali ZA, Maehara A, Généreux P, et al. Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III: OPTIMIZE PCI): a randomised controlled trial. Lancet 2016;388:2618–28.

23. Di Mario C, Mattesini A. Will optical coherence tomography become the standard imaging tool for percutaneous coronary intervention guidance? J Am Coll Cardiol Intv 2018;11:1322–4.

24. Jones DA, Rathod KS, Koganti S, et al. Angiography alone versus angiography plus optical coherence tomography to guide percutaneous coronary intervention: outcomes from the Pan-London PCI Cohort. J Am Coll Cardiol Intv 2018;11:1313–21.

KEY WORDS angiography-based fractional flow reserve, outcome, percutaneous coronary intervention, quantitative flow ratio, second-generation drug-eluting stent, vessel-oriented composite endpoint

APPENDIX For supplemental methods and results, tables, and figures, please see the online version of this paper.