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NEW RESEARCH PAPER

CORONARY

QFR-Based Virtual PCI or Conventional Angiography to Guide PCI

The AQVA Trial

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ABSTRACT

BACKGROUND Post-percutaneous coronary intervention (PCI) quantitative flow ratio (QFR) values ≥0.90 are associated with a low incidence of adverse events.

OBJECTIVES The AQVA (Angio-based Quantitative Flow Ratio Virtual PCI Versus Conventional Angio-guided PCI in the Achievement of an Optimal Post-PCI QFR) trial aims to test whether a QFR-based virtual percutaneous coronary intervention (PCI) is superior to a conventional angiography-based PCI at obtaining optimal post-PCI QFR results.

METHODS The AQVA trial is an investigator-initiated, randomized, controlled, parallel-group clinical trial. A total of 300 patients (356 study vessels) undergoing PCI were randomized 1:1 to receive either QFR-based virtual PCI or angiography-based PCI (standard of care). The primary outcome was the rate of study vessels with a suboptimal post-PCI QFR value, which was defined as <0.90. Secondary outcomes were procedure duration, stent length/lesion, and stent number/patient.

RESULTS Overall, 38 (10.7%) study vessels missed the prespecified optimal post-PCI QFR target. The primary outcome occurred significantly more frequently in the angiography-based group (n = 26, 15.1%) compared with the QFR-based virtual PCI group (n = 12 [6.6%]; absolute difference = 8.5%; relative difference = 57%; $P = 0.009$). The main cause of a suboptimal result in the angiography-based group is the underestimation of a diseased segment outside the stented one. There were no significant differences among secondary endpoints, although stent length/lesion and stent number/patient were numerically lower in the virtual PCI group ($P = 0.06$ and $P = 0.08$, respectively), whereas procedure length was higher in the virtual PCI group ($P = 0.06$).

CONCLUSIONS The AQVA trial demonstrated the superiority of QFR-based virtual PCI over angiography-based PCI with regard to post-PCI optimal physiological results. Future larger randomized clinical trials that demonstrate the superiority of this approach in terms of clinical outcomes are warranted. (Angio-based Quantitative Flow Ratio Virtual PCI Versus Conventional Angio-guided PCI in the Achievement of an Optimal Post-PCI QFR [AQVA]; NCT04664140) (J Am Coll Cardiol Intv 2023;16:783–794) © 2023 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAD = coronary artery disease

CCS = chronic coronary syndrome

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

LAD = left anterior descending

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiography

QFR = quantitative flow ratio

Several studies showed that successful angiography-based percutaneous coronary interventions (PCIs) are often suboptimal in terms of physiology, with negative implications on clinical outcomes.[1,2] Accordingly, many authors used post-PCI physiology to improve PCI outcomes with conflicting results.[1-4] The inherent limit of post-PCI physiology lies in the extra measurements needed and the consequent corrections (often of scarce benefit) at the end of the procedure. This leads to increased procedural time, radiations, contrast dye, and costs and consequent low use in clinical practice.[5,6] To overcome these limitations and improve the post-PCI outcome, several authors have suggested the application of pre-PCI physiology pull back to identify the best procedural plan.[2] Angiography-derived fractional flow reserve (FFR) (ie, quantitative flow ratio [QFR]) seems ideal for this purpose. In fact, QFR allows the generation of a pull back curve and the discrimination of the physiological contribution of every single segment/lesion as well as a diagnosis of diffuse disease. QFR computation before stenting allows the simulation of PCI results according to different treatment strategies (virtual PCI). Preliminary results showed the feasibility of a QFR-based virtual PCI,[7] but no randomized trial tested the effectiveness of this strategy versus the current standard of care. The AQVA (Angio-based Quantitative Flow Ratio Virtual PCI Versus Conventional Angio-guided PCI in the Achievement of an Optimal Post-PCI QFR) trial is the first step toward this direction.

METHODS

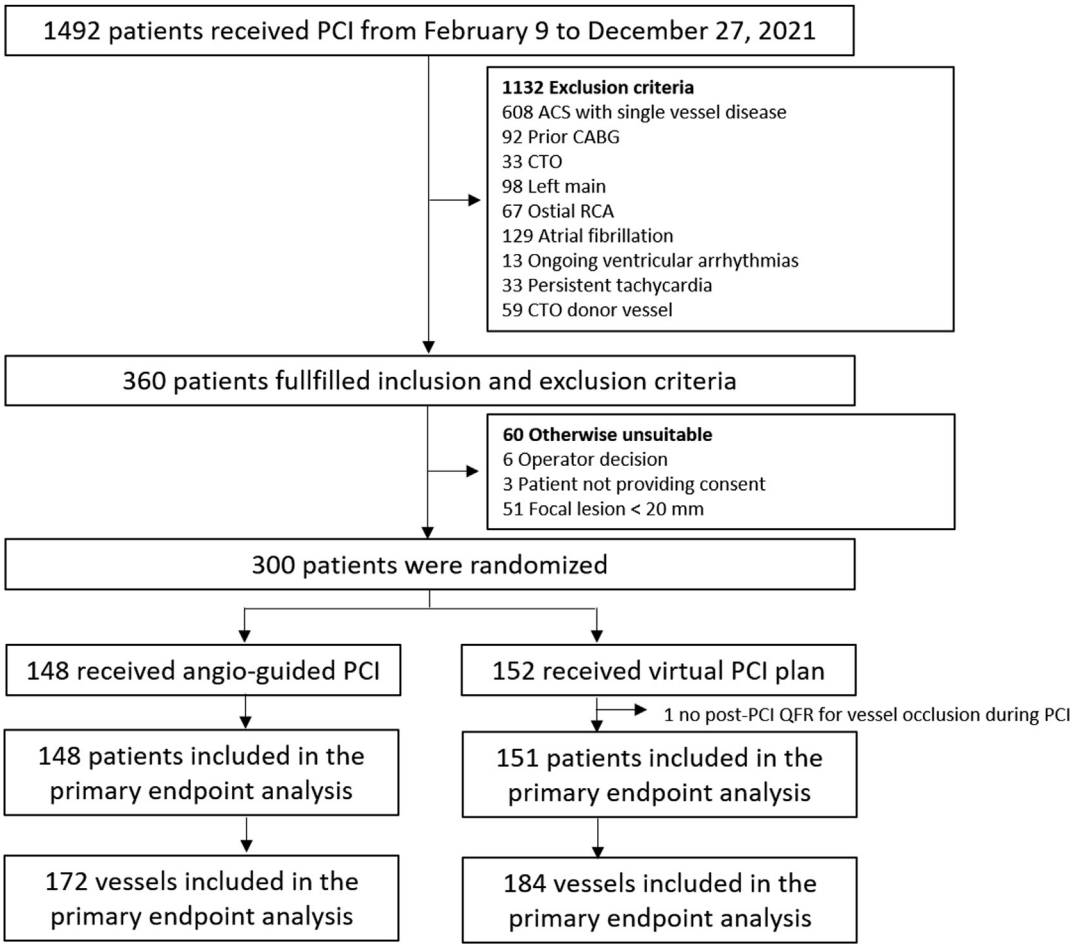
STUDY DESIGN. The AQVA was a multicenter, investigator-driven, randomized, controlled, parallel-group clinical trial (**Figure 1**). Briefly, patients with evidence of angiographically severe coronary lesions and indication to PCI were randomized 1:1 to either QFR-based virtual PCI or conventional angiography-based PCI. The study aimed to demonstrate the superiority of QFR-based virtual PCI over angiography-based PCI at obtaining an optimal post-PCI result (as defined as a post-PCI QFR value ≥0.90).[8] The study was conducted at 2 centers in Italy (Ferrara and Reggio Emilia) 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. The study was registered (NCT04664140) and approved by the ethical review boards at the participating hospitals. The 2 participating centers were activated at different time spans because of different approval procedures from the ethical committees.

PATIENTS. Patients ≥18 years old who underwent PCI were eligible for the trial if: 1) PCI was indicated for either acute (ACS) or chronic coronary syndrome (CCS); 2) there was evidence of at least 1 coronary vessel with an angiographically severe coronary lesion(s); and 3) informed consent was obtained. An angiographically severe coronary lesion was defined as a lesion with a visually estimated percent diameter stenosis ≥70%.[9] The inclusion of patients with a lesion length <20 mm was discouraged. The exclusion criteria were as follows: 1) vessel(s) representing the culprit lesion of patients with ST-segment elevation or non–ST-segment elevation myocardial infarction; 2) clinical or angiographic features limiting QFR computation (eg, left main or ostial right coronary artery, previous coronary artery bypass graft, atrial fibrillation, ongoing ventricular arrhythmias, and significant and persistent tachycardia); 3) planned surgical revascularization; 4) prior coronary artery bypass graft surgery; 5) revascularization of a chronic total occlusion; 6) PCI to a target artery providing Rentrop grade 2 or 3 collateral blood supply to another vessel; 7) noncardiovascular comorbidity reducing life expectancy to <1 year; and 8) the inability to provide consent.

RANDOMIZATION. Patients meeting all inclusion and exclusion criteria were eligible for randomization (QFR-based virtual PCI vs angiography-based PCI). Randomization was performed in the catheterization laboratory using a 1:1 variable block (2, 4, 6) randomization method generated through a web-based platform. Randomization was stratified by center (Ferrara vs Reggio Emilia), clinical presentation (ACS vs CCS), and study vessel (left anterior descending [LAD] artery vs other than LAD artery). Patients with more than 1 target vessel had all the vessels treated according to the randomization group.

STUDY PROCEDURES AND STUDY GROUPS. All procedures were performed by experienced operators in line with current guidelines and standards of care. All operators involved in the study were trained and certified for QFR analysis. The operator was free to use invasive physiology assessment only to discriminate lesions requiring PCI (pull back was not allowed) or

FIGURE 1 Study Flowchart



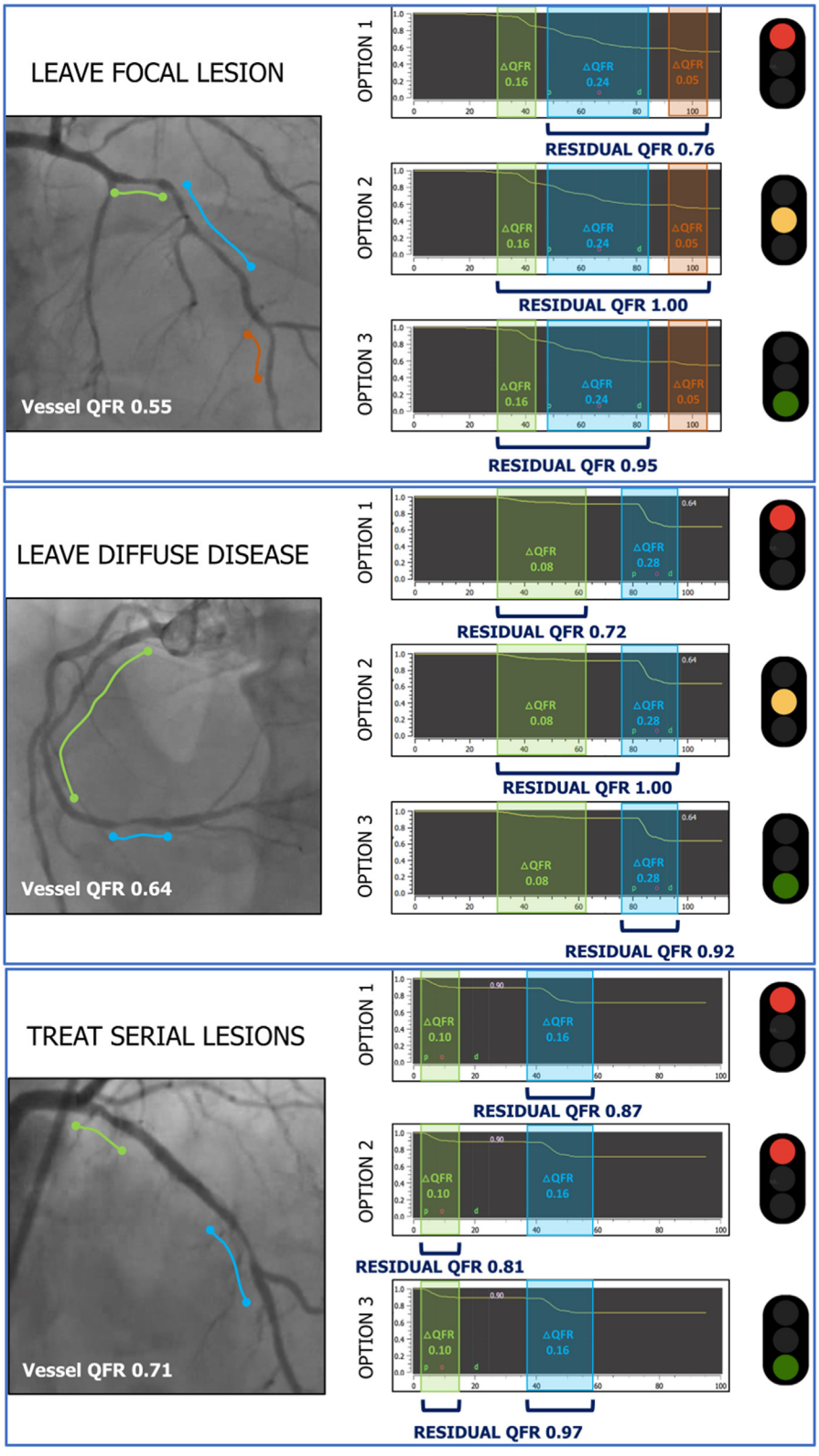
ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CTO = chronic total occlusion; PCI = percutaneous coronary intervention; QFR = quantitative flow ratio; RCA = right coronary artery.

intracoronary imaging for PCI optimization. Before randomization and PCI, the protocol mandated to acquire the angiographic projections for quantitative coronary angiography (QCA) and QFR computation in both groups. Only sirolimus-eluting ultrathin drug-eluting stents (Supraflex Cruz, Sahajanand Medical Technologies Ltd) were implanted. Postdilation with a noncompliant balloon was strongly suggested in all lesions and patients.

In the angiography-based PCI group, the PCI procedure was undertaken according to the operator's judgment. The operator was free to plan the procedure (including predilatation, stenting techniques, number of stents, stent length, and so forth) according to their experience, daily routine, and available clinical and angiographic information.

In the QFR-based virtual PCI group, immediately after the randomization, the angiographic projections were sent to the software package QAngio XA 3D (Medis Medical Imaging System) for QFR computation.[10-12] The first operator hypothesized a procedural plan based on conventional angiography that was reported in the electronic case report form. The second operator would then proceed with QFR computation. The first operator, in collaboration with the second one, reviewed the pull back trace and simulated a PCI procedural plan by using the residual vessel QFR tool. The goal was to treat only the segment(s) to achieve a post-PCI QFR value ≥0.90 (**Figure 2,** Supplemental Methods and Figures 1 to 12). In particular, the operator moved the proximal (p) and distal (d) marker along the QFR pull back

FIGURE 2 **Examples of QFR-Based Virtual PCI Plans**



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(Figure 2) in order to obtain a residual QFR value ≥0.90 with the shortest stent length possible. After identifying the best procedural plan able to reach this result (including information regarding lesion length), the first operator followed it.

At the end of the procedure, in all patients, 2 angiographic projections for each study vessel were acquired for the assessment of the primary endpoint (blinded core lab).

DATA COLLECTION, ANGIOGRAPHIC CORE LAB, AND FOLLOW-UP. Patient demographic data, cardiovascular risk factors, clinical diagnoses, and procedural details were recorded at the time of the PCI. Source data were collected online using dedicated electronic case report forms. Angiographic projections for QCA and QFR analyses were acquired after nitroglycerin (100-200 μg) administration at 15 frames/s during a single injection of 6 mL radiographic contrast medium at a flow of 4 mL/s and a pressure of 300 psi using a power injector system. In agreement with previous studies, operators followed a table of recommended projection angles.[8] Study angiograms were anonymized and submitted to the core laboratory of the University Hospital of Ferrara. Core lab reviewers were blinded to randomization and outcome. QCA was performed with the validated software (CAAS II, Pie Medical System). The following QCA values were measured before PCI, including reference vessel diameter, lesion length, percent diameter stenosis, and percent area stenosis.[13] QFR computation was performed in agreement with the step-by-step procedure validated in previous studies.[10-12] Core lab QFR analyses included the computation in the study vessels of pre- and post-PCI QFR values and coronary artery disease (CAD) physiological patterns. CAD physiological patterns were defined according to previous studies[8,14] as follows: 1) focal (presence of single drop ≥ 0.05 in 10 mm); 2) serial lesions (presence of 2 or more focal drops separated at least by 3 times the reference vessel diameter in the same coronary vessel); 3) diffuse disease (progressive decline of the QFR value without clear evidence of a focal drop); and 4) a combination of previous patterns.

Clinical follow-up was performed at 30 days and then every 6 months. Follow-up is ongoing, and data will be reported separately.

ENDPOINTS. The primary endpoint was defined as the proportion of vessels with a final post-PCI QFR result <0.90 (Supplemental Methods). This prespecified target was associated with prognosis in previous studies.[8,15,16] The main secondary endpoints were the post-PCI QFR value, procedure duration, contrast media use, the dose area product, the number of stents, and the stent length. Other clinical secondary endpoints were the cumulative occurrence of vessel-related cardiovascular death and myocardial infarction and the cumulative occurrence of ischemia-driven target vessel revascularization; they will be reported in a dedicated analysis.

STATISTICAL ANALYSIS. In the HAWKEYE (Angio-based Fractional Flow Reserve to Predict Adverse Events After Stent Implantation) trial population, 16% of vessels presented a post-PCI QFR <0.90 after an angiography-based PCI.[8] In one-third of these lesions, low post-PCI QFR was caused by diffuse disease. Therefore, we can hypothesize that a QFR-based virtual PCI could reduce the rate of lesions with QFR <0.90 by two-thirds. Considering that some of the lesions with focal disease could also present diffuse disease, we estimated a reduction by 60% with QFR-based virtual PCI compared with the conventional strategy. Then, a cohort of at least 300 vessels was needed (β error = 80%, α error = 5%).

Continuous variables were reported as mean ± SD or median (IQR) according to their distribution. The Kolmogorov-Smirnov test was performed to verify the normality of the distribution. Comparisons between continuous variables were performed using the Student's *t*-test or the Mann-Whitney *U* test as appropriate. Categoric variables were reported as counts and percentages. Comparisons between

FIGURE 2 Continued

The analysis of the quantitative flow ratio (QFR) pull back allows estimation of the physiological impact of single segments (ΔQFR). The residual QFR tool allows estimation of the post-percutaneous coronary intervention (PCI) value after the treatment of 1 or more segments. The aim of the QFR-based virtual PCI is to treat the segments, allowing a post-PCI QFR value ≥0.90 (green light) and avoiding both undertreatment (red light) and overtreatment (yellow light) of coronary lesions/segments. **(Top)** The analysis suggests leaving a distal focal lesion (residual QFR = 0.95). **(Middle)** The plan suggests leaving diffuse proximal disease (residual QFR = 0.92). **(Bottom)** The preprocedural planning suggests treating both serial lesions (residual QFR = 0.97) because the treatment of just 1 lesion was not enough to achieve the optimal post-PCI goal.

TABLE 1 Baseline Patient Characteristics

	Total (N = 300)	Angiography Based (n = 148)	Virtual PCI (n = 152)	*P* Value
Age, y	70 (62-77)	71 (63-78)	69 (62-76)	0.43
Female	83 (27.7)	40 (27.0)	43 (28.3)	0.81
BMI, kg/m^2	27.5 (24.5-30.1)	27.6 (24.8-30.1)	27.4 (24.4-29.7)	0.75
Hypertension	250 (83.3)	125 (84.5)	125 (82.2)	0.61
Dyslipidemia	191 (63.7)	95 (64.2)	96 (63.2)	0.85
Diabetes	87 (29.0)	46 (31.1)	41 (27.0)	0.43
Current smoker	73 (24.3)	39 (26.4)	34 (22.4)	0.46
Prior MI	80 (26.7)	42 (28.4)	38 (25.0)	0.51
Prior PCI	80 (26.7)	41 (27.7)	39 (25.7)	0.69
COPD	29 (9.7)	15 (10.1)	14 (9.2)	0.79
CKD	52 (17.3)	27 (18.2)	25 (16.4)	0.68
PAD	67 (22.3)	35 (23.6)	32 (21.1)	0.59
CVA	16 (5.4)	8 (5.5)	8 (5.3)	0.93
LVEF, %	53 (47-60)	55 (48-60)	52 (45-60)	0.27
Clinical presentation				
STEMI	52 (17.3)	24 (16.2)	28 (18.4)	0.61
NSTEMI	104 (34.7)	51 (34.5)	53 (34.9)	0.94
CCS	143 (47.7)	72 (48.6)	71 (46.7)	0.74
SBP, mm Hg	134 (121-150)	137 (122-150)	132 (120-145)	0.35
HR, beats/min	72 (65-80)	73 (65-80)	72 (62-80)	0.40
Creatinine pre-PCI, mg/dL	1.04 (0.88-1.3)	1.05 (0.88-1.30)	1.04 (0.88-1.25)	0.18
eGFR, mL/min/1.73 m^2	87 (64-100)	84 (61-102)	89 (69-98)	0.41
Hemoglobin, g/dL	13.3 (12-14.1)	13.1 (12.2-13.9)	13.5 (12-14.3)	0.37

Values are median (IQR) or n (%).

BMI = body mass index; CCS = chronic coronary syndrome; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; eGFR = estimated glomerular filtration rate; HR = heart rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevated myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; STEMI = ST-segment elevated myocardial infarction.

categoric variables were performed with the Pearson chi-square or Fisher exact test as appropriate. One- or 2-tailed tests were used as appropriate, and the statistical significance was defined as $P < 0.05$.

The treatment effect was estimated by hierarchical modeling to account for within-subject correlation. In the estimated model, baseline predictors were fixed effects, and random effects were used to describe subject differences. No confounding variables were added to the model because no statistically significant differences at the baseline between the 2 treatment groups were observed. All analyses were performed with STATA (version 16.0, STATA Corporation) by an independent statistician (M.M.).

RESULTS

The study flow is reported in **Figure 1**. From February to December 2021, 300 patients met all inclusion and exclusion criteria and were randomized for a total of 356 study vessels. Clinical, vessel, and procedural characteristics were evenly distributed between the randomization groups (**Tables 1 and 2**). In the angiography-based PCI group (n = 148, 172 vessels), no major complications occurred. Invasive physiology and intracoronary imaging were used in 36 (24%) and 33 (22%) cases, respectively. In the virtual PCI group (n = 152, 184 vessels), 1 procedure was complicated by abrupt closure of the treated vessel. Invasive physiology and intracoronary imaging were used in 35 (23%) and 31 (20%) cases, respectively (no difference vs angiography-based PCI group). The operators were able to follow the QFR-based virtual PCI plan in 180 (97.8%) cases, modifying their initial prespecified strategy in 48 cases (26%; 95% CI: 20%-33%). In two-thirds of the cases (n = 32 [67%]), QFR-based virtual PCI suggested that a lesion that was deemed significant angiographically was not to be treated, whereas in one-third (n = 16 [33%]) it suggested that a lesion that was considered not significant should be treated. The Bland-Altman plot between estimated post-PCI QFR and measured post-PCI QFR in the virtual PCI arm is shown in Supplemental Figure 13.

PRIMARY ENDPOINT. Overall, 38 (10.7%) vessels missed the prespecified post-PCI QFR target (≥0.90). The primary outcome occurred significantly more frequently in the angiography-based PCI group (n = 26 [15.1%]) compared with the virtual PCI group (n = 12 [6.6%]; absolute difference = 8.5%, relative difference = 57%; 95% CI: 2.2%-15.0%; $P = 0.009$) (**Central Illustration, Figure 3**). The treatment effect was estimated as described in the Statistical Analysis section. Treatment was associated to the primary outcome (treatment group = 1; OR: 0.396; 95% CI: 0.192-0.817; $P = 0.012$). The mean value and distribution of post-PCI QFR values are reported in **Table 3** and **Figure 3** (right panel), respectively. The ΔQFR between pre- and post-PCI was higher in the virtual PCI groups compared with the angiography-based group with borderline statistical significance (median: 0.29 [IQR: 0.23-0.37] vs 0.27 [0.20-0.36]; $P = 0.05$) (**Table 3**). The results were consistent across all the major subgroups (Supplemental Figure 14).

LOCALIZATION OF QFR DROP IN VESSELS WITH SUBOPTIMAL PHYSIOLOGY. Analyzing the 26 vessels with a suboptimal result in the angiography-based PCI group, the site of QFR drop was in-stent in 2 (7.5%) cases, focal outside the stent in 22 (85%) cases, and diffuse in 2 (7.5%) vessels (**Central Illustration, Figure 4**). On the contrary, the mechanism of a suboptimal result in the virtual PCI group was mainly

related to diffuse disease (6 [50%]), whereas focal in or outside the stent was less frequent (2 [17%] vs 4 [33%], respectively; $P = 0.004$) (Supplemental Table 1, Figures 15 to 24).

SECONDARY ENDPOINTS. There were no significant differences among procedural secondary endpoints, such as procedural duration, contrast dye, and x-ray use (Table 3). Stent length/lesion and stent number/patient were numerically lower in the virtual PCI group (median: 1 [IQR: 1-2]; 1.4 ± 0.6 vs 1 [1-2] 1.6 ± 0.7; $P = 0.06$ and 40 [25-55]; 42.7 ± 20.1 vs 44 [28-60]; 46.1 ± 23.1; $P = 0.08$, respectively), whereas procedure length was numerically higher in the virtual PCI group (median: 66 [IQR: 51-82]; 69 ± 23.1 vs 67 [57-88]; 73.9 ± 23.9; $P = 0.06$).

TABLE 2 Vessel Level Characteristics

	Total (N = 356)	Angiography Based (n = 172)	Virtual PCI (n = 184)	*P* Value
Coronary vessel (investigator)				0.13
RCA	98 (27.5)	40 (23.3)	58 (31.5)	
LAD	202 (56.7)	100 (58.1)	102 (55.4)	
LCx	56 (15.7)	32 (18.6)	24 (13.0)	
Percentage stenosis	80 (80-90)	80 (80-90)	80 (77.5-90)	0.43
Lesion length, mm	25 (16-38)	28 (16-40)	25 (18-38)	0.48
RVD, mm	3 (3-3.5)	3 (3-3.5)	3 (3-3.5)	0.71
Bifurcation	134 (37.6)	60 (34.9)	74 (40.2)	0.30
Severe calcification	94 (26.4)	48 (27.9)	46 (25.0)	0.53
Severe tortuosity	25 (7.0)	10 (5.8)	15 (8.2)	0.39
Predilation	326 (91.6)	160 (93.0)	166 (90.2)	0.34
Postdilation	349 (98)	168 (98)	181 (98)	0.67
Postdilation diameter, mm	3.5 (3-3.75)	3.5 (3-3.63)	3.5 (3-3.75)	0.57
QCA analysis (core lab)				
Diameter stenosis	50 (41-59)	51 (40-61)	48.5 (42-58)	0.42
Area stenosis	75 (65-83)	75 (64-85)	72 (65-82)	0.40
Lesion length, mm	21.4 (19-26)	21.4 (18.7-26.2)	21.6 (19-25.8)	0.99
RVD, mm	2.6 (2.2-2.9)	2.5 (2.2-2.8)	2.6 (2.2-3)	0.21
QFR pre-PCI (core lab)				
Value	0.69 (0.59-0.74)	0.69 (0.59-0.77)	0.68 (0.59-0.74)	0.10
QFR pattern (core lab)				0.07
Focal	138 (39.0)	78 (45.9)	60 (32.6)	
Serial	160 (45.2)	70 (41.2)	90 (48.9)	
Diffuse	12 (3.4)	4 (2.4)	8 (4.3)	
Combined[a]	44 (12.4)	18 (10.6)	26 (14.1)	

Values are median (IQR) or n (%). [a]Combination of focal or serial and diffuse patterns.

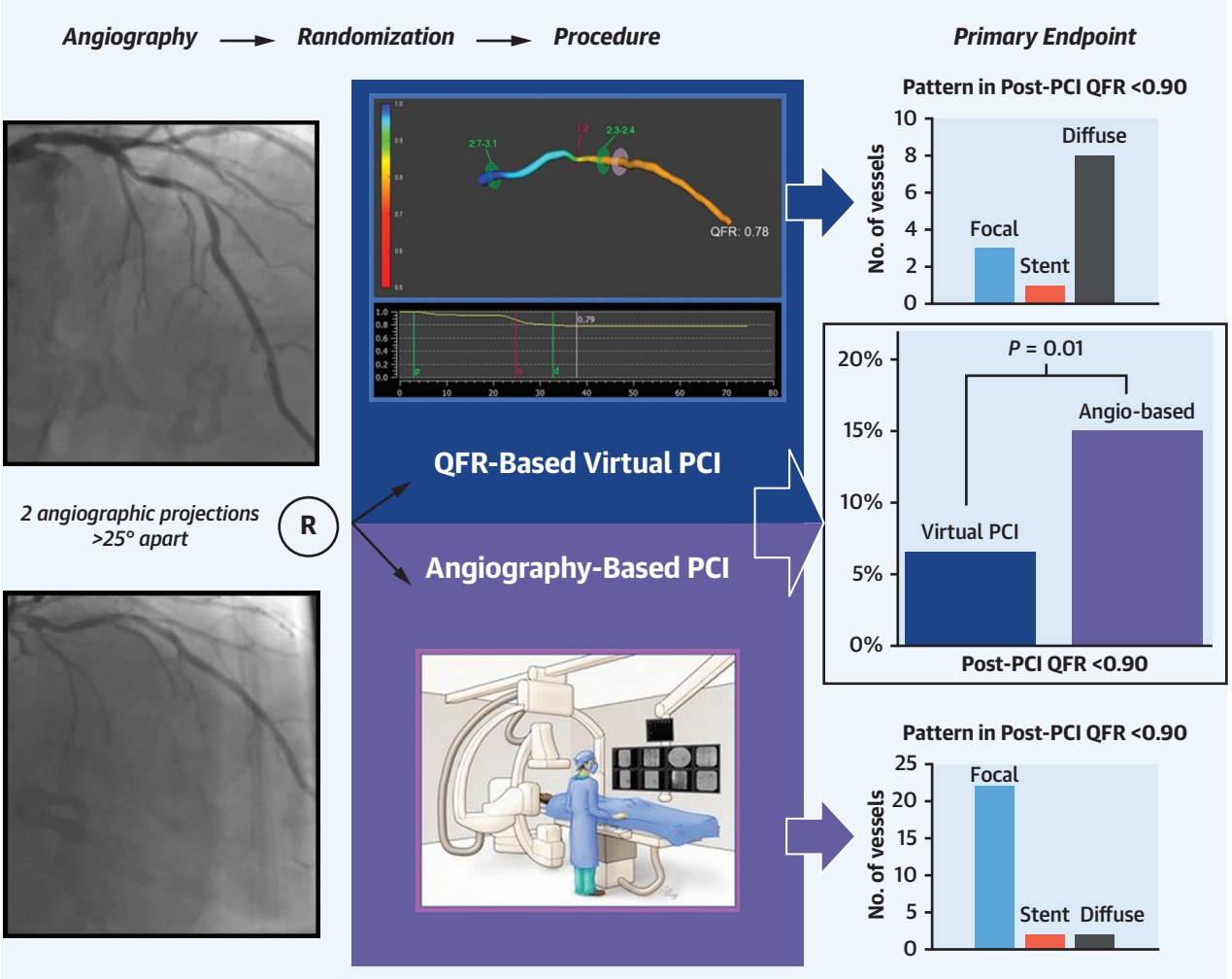
LAD = left anterior descending; LCx = left circumflex; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; QFR = quantitative flow ratio; RCA = right coronary artery; RVD = reference vessel diameter.

DISCUSSION

The main results of the AQVA trial can be summarized as follows: 1) QFR-based virtual PCI is superior to conventional angiography-based PCI at achieving optimal post-PCI physiology results; 2) QFR-based virtual PCI affects the procedural plan in more than one-quarter of patients; and 3) QFR-based virtual PCI application did not significantly increase procedural time, contrast dye, or x-ray use.

Several efforts have been performed globally to optimize PCI results and outcomes.[2-4] These endeavors have been mainly focused on post-PCI physiology assessment, and their climax is represented by the TARGET-FFR (Trial of Angiography vs. pressure-Ratio-Guided Enhancement Techniques-Fractional Flow Reserve) study.[5] After angiography-based PCI, 260 patients were randomized 1:1 to receive either the FFR-guided incremental optimization strategy or blinded coronary physiology assessment. In the study group, only 30.5% underwent further intervention, whereas in 15% of the cases, the operator declined to perform optimization even if FFR was below the threshold of 0.90. There was no significant difference in the primary endpoint of the proportion of patients with final post-PCI FFR ≥0.90 between groups ($P = 0.099$). In addition, procedure length, contrast media, and x-ray dose were all significantly higher in the FFR-optimized group.[5] Thus, a post-PCI FFR-based approach does not seem to be so rewarding for a systematic application in clinical practice, and the attention has shifted from optimization based on post-PCI physiology value to a better procedural plan based on pre-PCI physiology pull back.[17,18] Pull back pressure gradient, ΔFFR/Δt, and instantaneous wave-free ratio (iFR) pull back are the best examples of this field of research. The first 2 were both able to discriminate between focal and diffuse disease. However, these measurements share some of the same limitations of post-PCI FFR, require expertise, and are mainly indicated in the discrimination of lesions suitable for PCI rather than in guiding PCI in complex settings. iFR does not require adenosine administration and enables a quick and easy pull back to investigate the entire vessel and to discriminate the site of pressure drop. iFR has been tested in the post-PCI setting in the DEFINE-PCI (Physiologic Assessment of Coronary Stenosis Following PCI) study. An ischemic post-PCI iFR (≤0.89) was present in 24% of patients. A post-PCI iFR <0.95 was present in 61% of patients, and it was associated with a significantly higher occurrence of adverse cardiovascular events.[19,20] An iFR-guided PCI optimization is currently being tested in the DEFINE GPS (Distal Evaluation of Functional Performance

CENTRAL ILLUSTRATION **Study Flow and Main Results of the AQVA Trial**



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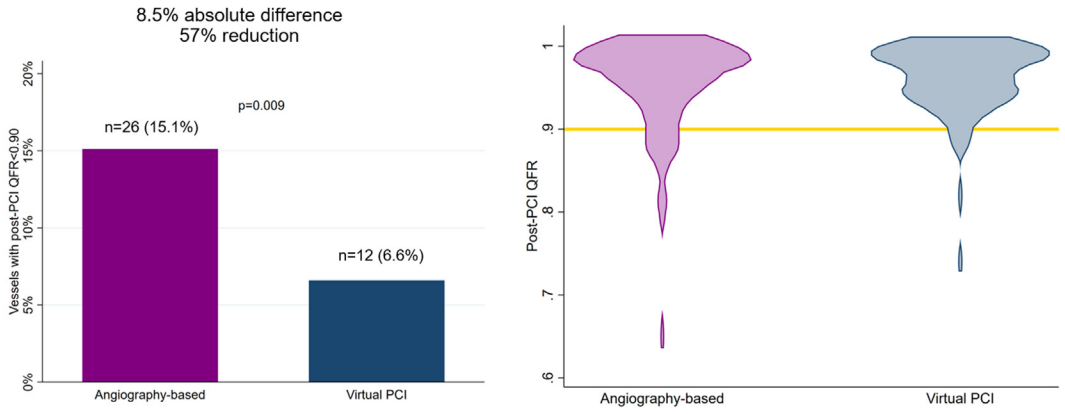
Patients with indication for percutaneous coronary intervention (PCI) of at least 1 vessel according to international guidelines, after coronary artery angiography, were randomized to either a quantitative flow ratio (QFR)-based virtual PCI plan or angiography-based PCI. The virtual PCI plan application was able to significantly reduce the number of vessels with suboptimal post-PCI physiology (defined as post-PCI QFR <0.90) compared with angiography-guided PCI. In those patients with suboptimal post-PCI physiology, the residual pattern of disease was mainly diffuse in the virtual PCI plan group, whereas it was mainly focal in the angiography-guided one.

with Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting) trial that is going to enroll more than 3,000 patients with a clinical endpoint. However, its use, as for FFR, is unlikely to be systematic, especially in complex settings caused by costs and the length of the procedure.

Angiography-derived FFR seems to be promising in overcoming wire-based physiology intrinsic features that limit its penetration because it enables the performance of physiology evaluation without the need of wire and adenosine and post-PCI values are related to the outcome.[8,15,16] Another advantage of angiography-derived FFR is the automatic availability of a full-vessel pull back with point-by-point detailed information of the functional impact of given stenosis. In fact, the same approach of discrimination of CAD pattern through pull back pressure gradient and ΔQFR/Δt has been demonstrated for QFR along with

FIGURE 3 Primary Endpoint



(Left) The rate and percentage of primary endpoint occurrence between the 2 groups. **(Right)** A violin plot showing the distribution of post-percutaneous coronary intervention (PCI) quantitative flow ratio (QFR) values among the 2 groups. The **gold line** represents a post-PCI QFR value of 0.90 (threshold).

the use of the automatically generated pull back trace for the simulation of different procedural plans (virtual PCI) with the aim to estimate the final functional value postintervention.[7,14,21]

A further appealing alternative, especially in the CCS setting, is represented by coronary computed tomography angiography and CT-FFR-based procedural planning in the prediction of functional outcomes. Recent evidence showed a strong correlation between QFR and CT-FFR values ($R = 0.759$; $P < 0.001$)[22] and that the CT-FFR-derived revascularization planner is accurate and precise for predicting FFR after PCI.[23] Studies directly comparing FFR-CT and QFR plans are warranted.

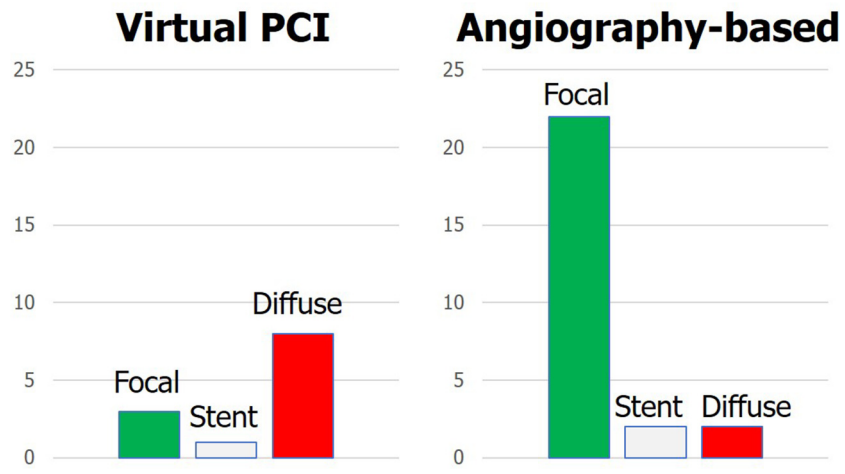
The results of the AQVA trial represent a relevant step forward. They confirm the feasibility and reliability of a QFR-based virtual PCI, which has been recently shown in a subanalysis of the PANDA III (Comparison of BuMA eG Based BioDegradable Polymer Stent With EXCEL Biodegradable Polymer Sirolimus-eluting Stent in "Real-World" Practice) trial.[24] They also show its superiority in comparison with a conventional angiography-based strategy at achieving an optimal physiological PCI result. Interestingly, the QFR-based virtual PCI plan changed the a priori reported operators' plan in 26% (95% CI: 20%-33%) of the cases. The change in procedural plans was mainly conservative. In fact, the QFR-based virtual PCI suggested that lesions deemed angiographically significant (67% of the cases) were not to be treated. This is associated with overtreatment in the angiography-based arm, which is probably not related to outcome but rather to resource waste, procedural lengthening, and a higher probability of post-PCI complications. However, in one-third of the cases, it suggested to treat lesions that otherwise would not have been treated angiographically. A consistent message comes from the analysis of the residual pattern of disease in suboptimal post-PCI QFR. Although in the virtual PCI group the pattern is mainly diffuse, in the angiography-based group the main one is focal disease. This is probably caused by lesions not deemed significant angiographically but that would have been considered significant with physiology. This

TABLE 3 Secondary Endpoints

	Total	Angiography Based	Virtual PCI	*P* Value
Post-PCI QFR value	0.97 (0.94-1)	0.97 (0.94-1)	0.97 (0.94-0.99)	0.23
ΔQFR	0.28 (0.22-0.37)	0.27 (0.20-0.36)	0.29 (0.23-0.37)	0.053
Stent mm/vessel	40 (28-58)	44 (28-60)	40 (25-55)	0.08
Number of stent/patient[a]	1 (1-2)	1 (1-2)	1 (1-2)	0.06
Procedure length, min[a]	67 (54-86)	66 (51-82)	67 (57-88)	0.06
Contrast media, mL[a]	177 (137-222)	180 (144-217)	170 (135-239)	0.59
DAP, cGy/cm^2[a]	5,576 (3,276-6,789)	5,450 (3,487-6,501)	5,612 (3,577-6,702)	0.79
Creatinine peak post-PCI, mg/dL[a]	1.05 (0.90-1.31)	1.05 (0.90-1.39)	1.05 (0.90-1.3)	0.74
Hospitalization length, d[a]	4 (3-6)	4 (3-6)	4 (3-6)	0.86

Values are median (IQR). [a]Data presented at the patient level.
DAP = dose area product; other abbreviations as in Table 2.

FIGURE 4 Number of Vessels With Suboptimal Post-PCI Physiology Result Stratified According to the Different Pattern of Suboptimal Results Between the 2 Study Groups



In the angiography-guided group, the main mechanism underlying a suboptimal result is represented by focal disease outside the stented segment. In the virtual percutaneous coronary intervention (PCI) group, the main mechanism was represented by residual diffuse disease not amenable to improvement with further PCI.

undertreatment in the angiography-based arm can be hypothesized to be the one related to the outcome. The benefit shown in the present study also could have been partially diluted for the presence of a nonsignificant trend toward simpler (more focal) patterns in the pre-PCI pull back in the angiography-guided group.

Recently, a randomized trial showed that QFR applied as a gatekeeper to PCI was superior to angiography thanks to a significant reduction of myocardial infarction.[12] Interestingly, the reduction was not only related to stent-related events in the angiography-guided group but also to lesions deemed nonsignificant by angiography and leading to myocardial infarction in the follow-up. The AQVA trial is complementary to these findings and shows that QFR is superior also in the guidance and optimization of the PCI procedure in a complex setting by reducing the occurrence of suboptimal physiological post-PCI results.

At the same time, the AQVA trial confirmed some substantial differences between FFR and QFR in the post-PCI setting. The first one is the mean higher value of angiography-derived FFR (0.96) post-PCI compared with FFR (0.86)[5] as well as a lower incidence of a suboptimal post-PCI physiology result (15% vs 38%) after angiography-based PCI using a threshold of 0.90.[5] These results have been consistently shown in all studies on angiography-derived FFR in the post-PCI setting,[8,15,16] but the reasons remain to be fully elucidated. Hydrostatic factors related to coronary anatomy and the height of the pressure wire sensor above or below the aortic pressure transducer as well as higher flow rates across long segments of residual mild diffuse atheroma can result in large pressure gradients in these vessels, especially the LAD artery.[5] Most of these factors are not accounted for in the angiography-derived FFR reconstruction and can, at least in part, explain these differences.

It is noteworthy that the systematic application of QFR-based virtual PCI did not significantly increase the administration of contrast material or radiation exposure. Our results differ from what was previously reported for FFR in which a full physiology-guided procedure was associated with a significantly increased procedural time, radiation exposure, and administration of contrast media.[5]

Finally, it is important to highlight that the QFR-based virtual PCI plan should always be combined with intravascular imaging, especially after PCI to check stent apposition and expansion because pre-PCI QFR-based virtual assessment cannot predict the in-stent status. The importance of an integrated approach has been confirmed recently by the result of the FFR-REACT (FFR-Guided PCI Optimization Directed by High-Definition IVUS Versus Standard of Care) trial.[25]

STUDY LIMITATIONS. The first limitation of this study is that it only involved 2 centers with wide experience in QFR analysis and interpretation as well as with a dedicated organization to systematically apply QFR in clinical practice. Therefore, it cannot be applied to centers at different stages of experience and organization with this technology. In addition, the extensive list of exclusion criteria may limit the widespread applicability of our findings. Second, FFR use may have generated treatment differences among the 2 groups, although the proportion of use was not different among them. IVUS use was around 20%, which is lower than optimal, but, at the same time, higher than in our previous study on post-PCI QFR (3%),[8] similar to the one of the TARGET-FFR trial (16%)[5] and in line with the use in real practice, which is around 9% in Italy and around 11% in the United Kingdom.[5] Third, the low number of vessels with suboptimal results limits the advantage of our approach to a niche of patients. Fourth, although the inclusion of lesions <20 mm was discouraged, 64 (18%) of the included lesions were <20 mm, partially diluting the advantage of the tested strategy. Fifth, we applied one system of angiography-based FFR, and dedicated studies are needed for the other available systems. Finally, the AQVA trial is not powered to show any difference in clinical endpoints. Based on our hypothesis-generating findings, a bigger, international trial including only patients undergoing PCI of complex lesions powered for a clinical endpoint is warranted.

CONCLUSIONS

The AQVA trial demonstrated that QFR-based virtual PCI was superior to conventional angiography-based PCI at achieving an optimal post-PCI physiology result, which was defined as a post-PCI QFR value ≥0.90. The QFR-based virtual PCI strategy changed the operators' procedural plan in one-quarter of the cases and was not associated with either longer procedures or a higher amount of contrast or radiation dose.

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PERSPECTIVES

WHAT IS KNOWN? Post-PCI QFR values ≥0.90 are associated with a low incidence of adverse events.

WHAT IS NEW? The systematic application of a QFR-based virtual PCI plan was able to significantly reduce the number of vessels with suboptimal physiology after PCI compared with an angiography-guided strategy.

WHAT IS NEXT? A randomized clinical trial aimed at the demonstration of QFR virtual PCI plan superiority compared with angiography-guided PCI with a hard clinical endpoint is warranted.

REFERENCES

1. Hakeem A, Uretsky BF. Role of postintervention fractional flow reserve to improve procedural and clinical outcomes. *Circulation*. 2019;139(5):694–706. https://doi.org/10.1161/CIRCULATIONAHA.118.035837

2. Biscaglia S, Uretsky B, Barbato E, et al. Invasive coronary physiology after stent implantation: another step toward precision medicine. *J Am Coll Cardiol Intv*. 2021;14(3):237–246. https://doi.org/10.1016/j.jcin.2020.10.055

3. Ding D, Huang J, Westra J, et al. Immediate post-procedural functional assessment of percutaneous coronary intervention: current evidence and future directions. *Eur Heart J*. 2021;42(27):2695–2707. https://doi.org/10.1093/EURHEARTJ/EHAB186

4. van Zandvoort LJC, Ali Z, Kern M, van Mieghem NM, Mintz GS, Daemen J. Improving PCI outcomes using postprocedural physiology and intravascular imaging. *J Am Coll Cardiol Intv*. 2021;14(22):2415–2430. https://doi.org/10.1016/J.JCIN.2021.08.069

5. Collison D, Didagelos M, Aetesam-ur-Rahman M, et al. Post-stenting fractional flow reserve vs coronary angiography for optimization of percutaneous coronary intervention (TARGET-FFR). *Eur Heart J*. 2021;42(45):4656–4668. https://doi.org/10.1093/eurheartj/ehab449

6. 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;11:1482–1491. https://doi.org/10.1016/j.jcin.2018.04.037

7. Rubimbura V, Guillon B, Fournier S, et al. Quantitative flow ratio virtual stenting and post stenting correlations to post stenting fractional flow reserve measurements from the DOCTORS (Does Optical Coherence Tomography Optimize

Results of Stenting) study population. *Catheter Cardiovasc Interv*. 2020;96(6):1145–1153. https://doi.org/10.1002/ccd.28615

8. Biscaglia S, Tebaldi M, Brugaletta S, et al. Prognostic value of QFR measured immediately after successful stent implantation: the International Multicenter Prospective HAWKEYE Study. *J Am Coll Cardiol Intv*. 2019;12(20):2079-1088. https://doi.org/10.1016/j.jcin.2019.06.003

9. Mehta SR, Wood DA, Storey RF, et al. Complete revascularization with multivessel PCI for myocardial infarction. *N Engl J Med*. 2019;381(15). https://doi.org/10.1056/nejmoa1907775, 1411-1121.

10. Westra J, Tu S, Campo G, et al. Diagnostic performance of quantitative flow ratio in prospectively enrolled patients: an individual patient-data meta-analysis. *Catheter Cardiovasc Interv*. 2019;94(5):693-701. https://doi.org/10.1002/ccd.28283

11. 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. https://doi.org/10.1161/CIRCINTERVENTIONS.117.006023

12. Xu B, Tu S, Song L, et al. Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China): a multicentre, randomised, sham-controlled trial. *Lancet*. 2021;398(10317):2149–2159. https://doi.org/10.1016/s0140-6736(21)02248-0

13. 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(20):2099-2109. https://doi.org/10.1016/j.jcin.2018.07.031

14. Biscaglia S, Uretsky BF, Tebaldi M, et al. Angio-based fractional flow reserve, functional pattern of coronary artery disease, and prediction of percutaneous coronary intervention result: a proof-of-concept study. *Cardiovasc Drugs Ther*. 2022;36(4):645–653. https://doi.org/10.1007/s10557-021-07162-6

15. Kogame N, Takahashi K, Tomaniak M, et al. Clinical implication of quantitative flow ratio after percutaneous coronary intervention for 3-vessel disease. *J Am Coll Cardiol Intv*. 2019;12(20):2064–2075. https://doi.org/10.1016/j.jcin.2019.08.009

16. Masdjedi K, van Zandvoort LJC, Balbi MM, et al. Validation of novel 3-dimensional quantitative coronary angiography based software to calculate fractional flow reserve post stenting. *Catheter Cardiovasc Interv*. 2021;98(4):671–677. https://doi.org/10.1002/CCD.29311

17. Lee SH, Shin D, Lee JM, et al. Automated algorithm using pre-intervention fractional flow reserve pullback curve to predict post-intervention physiological results. *J Am Coll Cardiol Intv*. 2020;13(22):2670–2684. https://doi.org/10.1016/J.JCIN.2020.06.062

18. Collet C, Sonck J, Vandeloo B, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. *J Am Coll Cardiol*. 2019;74(14):1772–1784. https://doi.org/10.1016/J.JACC.2019.07.072

19. Jeremias A, Davies JE, Maehara A, et al. Blinded physiological assessment of residual ischemia after successful angiographic percutaneous coronary intervention: the DEFINE PCI study. *J Am Coll Cardiol Intv*. 2019;12(20):1991–2001. https://doi.org/10.1016/j.jcin.2019.05.054

20. Patel MR, Jeremias A, Maehara A, et al. 1-year outcomes of blinded physiological assessment of residual ischemia after successful PCI: DEFINE PCI trial. *J Am Coll Cardiol Intv*. 2022;15:52–61. https://doi.org/10.1016/J.JCIN.2021.09.042

21. Shin D, Dai N, Lee SH, et al. Physiological distribution and local severity of coronary artery disease and outcomes after percutaneous coronary intervention. *J Am Coll Cardiol Intv*. 2021;14(16):1771–1785. https://doi.org/10.1016/j.jcin.2021.06.013

22. Kawashima H, Kogame N, Ono M, et al. Diagnostic concordance and discordance between angiography-based quantitative flow ratio and fractional flow reserve derived from computed tomography in complex coronary artery disease. *J Cardiovasc Comput Tomogr*. 2022;16(4):336–342. https://doi.org/10.1016/J.JCCT.2022.02.004

23. Sonck J, Nagumo S, Norgaard BL, et al. Clinical validation of a virtual planner for coronary interventions based on coronary CT angiography. *J Am Coll Cardiol Img*. 2022;15(7):1242–1255. https://doi.org/10.1016/J.JCMG.2022.02.003

24. Zhang R, Xu B, Dou K, et al. Post-PCI outcomes predicted by pre-intervention simulation of residual quantitative flow ratio using augmented reality. *Int J Cardiol*. 2022;352:33–39. https://doi.org/10.1016/J.IJCARD.2022.01.054

25. Neleman T, van Zandvoort LJC, Tovar Forero MN, et al. FFR-guided PCI optimization directed by high-definition IVUS versus standard of care: the FFR REACT trial. *J Am Coll Cardiol Intv*. 2022;15(16):1595–1607. https://doi.org/10.1016/J.JCIN.2022.06.018

KEY WORDS angiography-derived fractional flow reserve, percutaneous coronary intervention, quantitative flow ratio, virtual percutaneous coronary intervention

APPENDIX For an expanded Methods section and a supplemental table and figures, please see the online version of this paper.