JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 13, 2025

ORIGINAL RESEARCH

CORONARY

Randomized Comparison of Fractional Flow Reserve and Instantaneous Wave Free Ratio in Serial Disease

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ABSTRACT

BACKGROUND Fractional flow reserve (FFR) and the instantaneous wave-free ratio (iFR) identify arteries that benefit from percutaneous coronary intervention (PCI). FFR or iFR gradients on pullback are often used to predict the physiological result (FFR_{Δ} or iFR_{Δ}), but this approach is unvalidated.

OBJECTIVES The aim of this study was to compare the accuracy of FFR_{Δ}, iFR_{Δ} and FFR_{calc} (a mathematical solution incorporating interaction between lesions) for predicting post-PCI physiology in serial or diffuse disease.

METHODS Patients with a focal target lesion and either a second focal lesion or a diffusely diseased segment in the same vessel were randomized to FFR- vs iFR-guided PCI (ISRCTN18106869). FFR and iFR pullbacks were performed, with operators blinded to one modality. Following target lesion PCI, FFR and iFR were remeasured. The primary outcome was the error in predicted post-PCI physiology compared with actual values.

RESULTS A total of 87 patients were randomized to FFR (n = 45) or iFR (n = 42). Median FFR and iFR were 0.70 (Q1-Q3: 0.62 to 0.78) and 0.81 (Q1-Q3: 0.68 to 0.90) at baseline and 0.82 (Q1-Q3: 0.74 to 0.87) and 0.89 (Q1-Q3: 0.83 to 0.93) after target lesion PCI. The predictive errors were 12% (6% to 17%) for FFR_{Δ}, 4% (0% to 9%; $P < 0.001$) for iFR_{Δ}, and −5% (−18% to 8%; $P = 0.427$) for FFR_{calc}. Significant residual disease was missed in 36% of cases with FFR_{Δ}, 34% with iFR_{Δ}, and 14% with FFR_{calc}.

CONCLUSIONS FFR and iFR pullback gradients overestimate the benefit of target lesion PCI and can miss residual ischemia in one-third of patients. FFR or iFR should be routinely repeated post-PCI in serial disease.

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ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2025.05.033

ABBREVIATIONS AND ACRONYMS

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

PCI = percutaneous coronary intervention

PPG = pressure pullback gradient

Physiology-guided coronary revascularization in stable coronary artery disease improves patient outcomes and reduces costs compared with angiography guidance alone.[1-3] However, residual gradients after percutaneous coronary intervention (PCI) remain common[4,5] and are associated with both persistent angina and long-term adverse events.[6,7] Contemporary physiological assessment has therefore evolved to characterize the pattern of disease within an artery by performing a pullback of the pressure wire, in order to inform the revascularization strategy and anticipate the likely benefits from PCI.[8-10] This is most commonly done by visualizing the intracoronary pressure pullback trace during pharmacologic hyperemia (fractional flow reserve [FFR]) or without hyperemia (instantaneous wave-free ratio [iFR]) and using the gradient across a lesion (δFFR or δiFR) to predict the physiological impact of treating that lesion using PCI. The assumption inherent in this approach is that the whole-vessel FFR or iFR will increase by a value corresponding to δFFR or δiFR.

However, the validity of this assumption and the accuracy of this approach have not been systematically evaluated. This is particularly pertinent in arteries with serial lesions and/or diffuse disease, for which it can be difficult to predict post-PCI physiology,[11,12] as the pressure gradient across a proximal stenosis is affected by resistance from a distal stenosis and vice versa.[11] Recently, a mathematical calculation has been described that accounts for the hemodynamic interaction between diseased segments during hyperemia (FFR_{calc}) and has shown promising results in a single-center validation study.[12] The primary aim of our study was therefore to compare the accuracy of using δFFR and δiFR for predicting the physiological result after PCI to a single target lesion in coronary arteries with serial disease. Our secondary aim was to evaluate whether the novel parameter, FFR_{calc}, is associated with less error in predicting the final FFR and iFR compared with the translesional gradients currently used in clinical practice.

METHODS

STUDY DESIGN. SERIAL (Systematic Evaluation by Randomisation of Intracoronary Physiological Techniques for Assessing Tandem Lesions) is a prospective, blinded, randomized controlled trial conducted at 4 centers in the United Kingdom (ISRCTN18106869).

The study was approved by the National Health Service Health Research Authority in the United Kingdom (21/WA/0238), and all participants provided written informed consent. The study was overseen by an independent steering committee, coordinated by the King's College London Clinical Trials Unit and funded by an unrestricted educational grant from Abbott Vascular. The funder had no role in the design of the trial, data analysis, or decision to submit for publication. Angiographic and physiological data were analyzed by an independent core laboratory at King's College London blinded to treatment assignments and clinical outcomes. We vouch for the accuracy and completeness of the data and analyses and for fidelity to the trial protocol and statistical analysis plan.

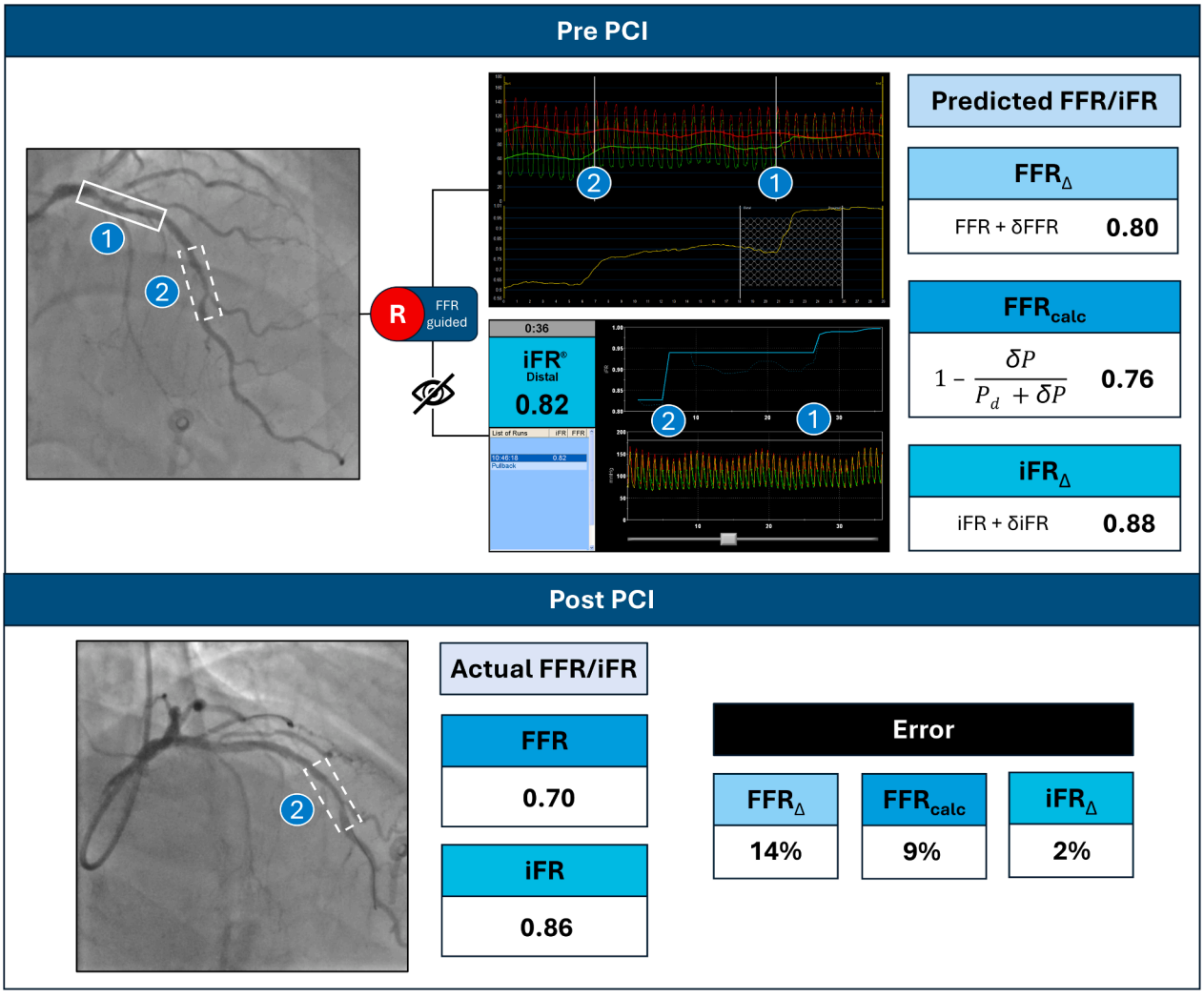
PARTICIPANTS AND RANDOMIZATION. Participants were eligible for inclusion if they had a focal lesion on coronary angiography causing ≥50% diameter stenosis by visual estimation, with either a second focal stenosis (that the operator would consider treating with separate non-overlapping stents) or a segment of diffuse disease. Exclusion criteria were a target vessel that was considered culprit for an acute coronary syndrome <72 hours prior to consent, an index ST-segment elevation myocardial infarction procedure, a target vessel protected by a coronary artery bypass graft, age <18 years, inability to provide written informed consent, and pregnancy or breastfeeding at the time of randomization. Eligible patients were randomized 1:1 to an FFR-guided or iFR-guided management strategy. The randomization sequence was computer generated with random block sizes and stratified by age and sex.

STUDY PROCEDURES AND BLINDING. Participants underwent physiological assessment with FFR and

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.

Manuscript received October 25, 2024; revised manuscript received April 28, 2025, accepted May 15, 2025.

FIGURE 1 **SERIAL Study Design and Example Case**



Two methods of predicting post-percutaneous coronary intervention (PCI) physiology were tested in this study. The first method uses the translesional pressure gradient: δFFR and δiFR indicate the gradients in fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) units across the treated segment. This is added to the whole-vessel FFR and iFR values to predict FFR and iFR (FFR_Δ and FFR_Δ) after PCI of the target lesion. The second method aims to account for the hemodynamic interaction between serial lesions: FFR_{calc} uses absolute pressure values in millimeters of mercury, δP indicates the gradient across the treated segment, and Pd indicates distal pressure measured at the beginning of the pullback trace. In this example, the patient has been randomized to FFR-guided treatment. Both FFR and iFR pullbacks are performed pre- and post-PCI, but the operator is blinded to the iFR results throughout. SERIAL = Systematic Evaluation by Randomisation of Intracoronary Physiological Techniques for Assessing Tandem Lesions.

iFR before and after treatment of a single lesion using PCI (**Figure 1**). Throughout the case, the operator was blinded to the data from one modality according to the randomized treatment assignment. These data were visible only to a member of the research team who advised the operator on the technical quality of the pressure trace and ensured standardized physiological measurements.

Pressure wire assessment was performed according to a standard operating procedure specified in the trial protocol (Supplemental Figure S1). Pre-PCI FFR was measured using the PressureWire X (Abbott Laboratories), and pre-PCI iFR was measured using the Verrata or OmniWire (Philips Healthcare). If the operator elected to proceed to PCI, a single target lesion was treated with a drug-eluting stent and

optimized according to usual clinical practice. FFR and iFR were then both remeasured using the Verrata or OmniWire. After this, operators were free to further optimize the stented segment and/or treat the second serial lesion at their discretion.

PRESSURE WIRE ASSESSMENT. Following administration of intracoronary nitrates, a pressure wire was calibrated to aortic pressure and advanced to the distal vessel with the pressure wire sensor ≥15 mm beyond the most distal stenosis, in a portion of the target vessel >2 mm diameter by visual estimation. The position was recorded using fluoroscopy, and care was taken to record any subsequent measurements in the same location by reference to the stored fluoroscopy. Pd/Pa and whole-vessel FFR and iFR were measured followed by a continuous manual pullback of the pressure wire sensor to the tip of the guiding catheter. Markers were placed to indicate the position of lesions for offline coregistration with the coronary anatomy. If there was drift >0.02 units, repeat pressure wire measurements were recommended. For FFR measurements, hyperemia was induced by intravenous administration of adenosine in all cases.

CLINICAL DECISION MAKING. During the procedure, the operator was asked to declare their treatment strategy at each stage, as incremental physiological data became available. This included their intended treatment modality (optimal medical therapy, PCI, or coronary artery bypass grafting) and, if this was PCI, the target lesion (proximal, distal, or both). Responses were documented using a dedicated questionnaire, which was administered after initial angiography and on completion of the pre-PCI physiology assessment.

CORE LABORATORY ANALYSIS. Quantitative coronary angiography was performed using Medis QFR 2.2 Research Edition (Medis Medical Imaging). Physiology traces were assessed for technical quality, and in those meeting minimum standards, the treated segments were coregistered on the pullback trace (**Figure 1**). This was by combination of coronary angiography, presence of abrupt increases in FFR and iFR (in focal disease), and site placed markers. Any pullbacks submitted with drift >0.02 and <0.05 were considered suitable for analysis and were algorithmically corrected.

The pressure pullback gradient (PPG) is an index ranging from 0 to 1 that characterizes the pattern of pressure loss within an artery, with 0 indicating diffuse disease and 1 indicating focal disease.[8] This was automatically calculated from the pullback trace using Coroventis CoroFlow version 3.5.1 (Abbott Laboratories).

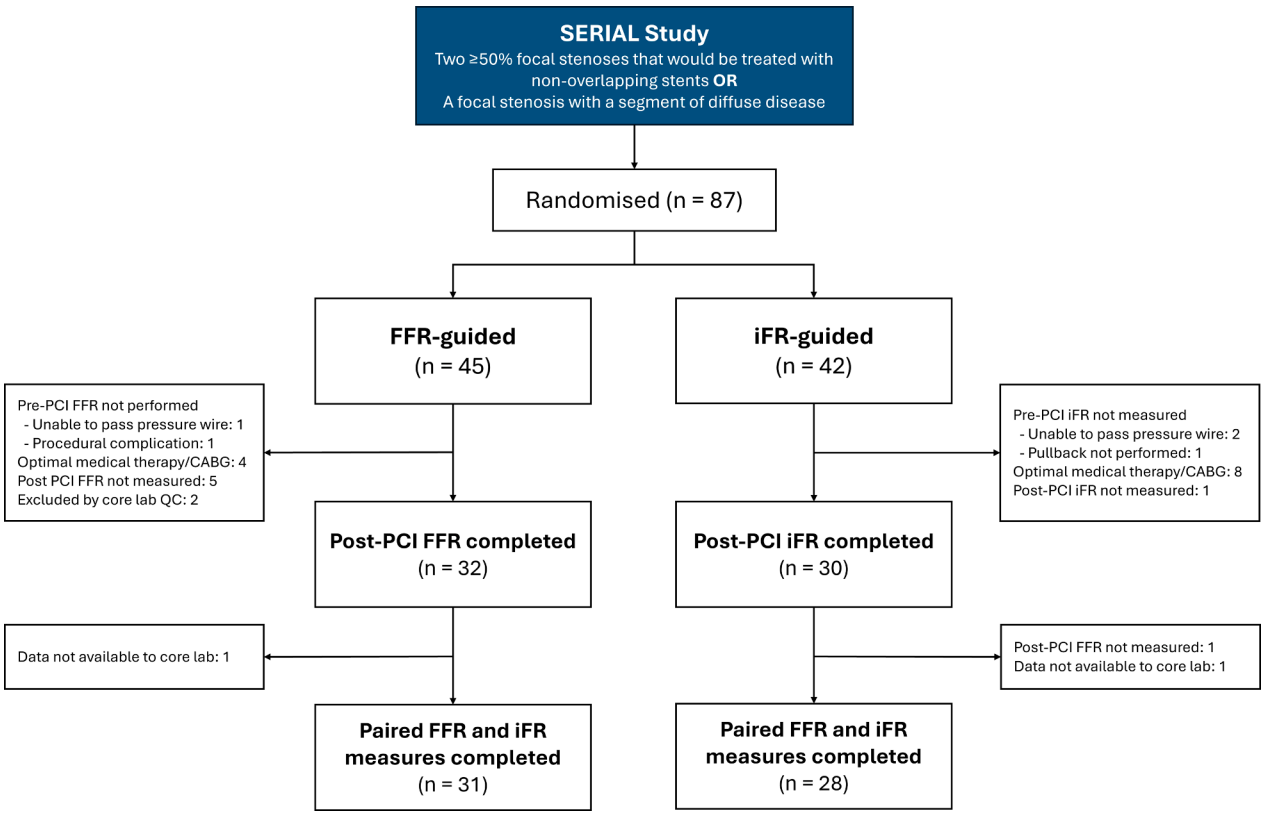
PREDICTION OF POST-PCI FFR AND iFR. Predicted post-PCI physiology after treatment of a single target lesion was calculated as follows (Supplemental Figure S2). First, the FFR gradient across the treated segment was measured (δFFR) and added to the whole-vessel FFR to estimate post-PCI FFR (FFR_{Δ}). The same process was applied to the iFR pullback to estimate post-PCI iFR (iFR_{Δ}). FFR_{calc}, which accounts for the interaction between serial lesions during hyperemia, was calculated as previously described (**Figure 1**).[12] In brief, this method assumes a linear relationship between translesional pressure and flow, where the resistance of stenoses and the distal circulation remains fixed, regardless of the number of stenoses. This allows post-PCI FFR to be calculated without the need for coronary occlusive pressure, which is impractical for routine clinical use.[13]

PPG has shown the ability to predict the final whole-vessel FFR (final FFR_{PPG}) after PCI.[8] We evaluated its performance against a δFFR-based prediction in this dedicated cohort of serial coronary disease (Supplemental Appendix).

OUTCOME MEASURES. The primary outcome measure was the error between predicted post-PCI FFR (FFR_{Δ}) or iFR (iFR_{Δ}) and actual post-PCI FFR or iFR (Supplemental Table S1). A significant residual gradient likely to be associated with ischemia was defined as post-PCI FFR ≤0.80 or iFR ≤0.89. The clinically relevant misclassification rate was therefore defined as the proportion of cases in which the pre-PCI prediction method incorrectly predicted post-PCI FFR >0.80 or iFR >0.89. Secondary outcomes were: 1) the change in decision making following baseline physiological assessment and after post-PCI physiological assessment; and 2) major adverse cardiovascular events (target vessel revascularization, myocardial infarction, stroke, and all-cause death) at 1 year. As clinical follow-up is ongoing, we report here the primary and intraprocedural secondary outcomes.

STATISTICAL ANALYSIS. The statistical analysis plan is available in the Supplemental Appendix. Previous work has shown a 20% error in iFR_{Δ} and 14% error in FFR_{calc} in predicting post-PCI physiology.[12] Sixty paired comparisons would be required to have 90% power to detect a difference in error rate of 6% between groups (at a significance level of 5%). Given that eligibility was based on angiographic criteria, we expected that a significant proportion of cases would not proceed to PCI (because of deferral based upon

FIGURE 2 Study Flowchart



CABG =coronary artery bypass grafting; QC = quality control; other abbreviations as in Figure 1.

treatment thresholds or physiologically diffuse disease that was unsuitable for PCI) and hence lack post-PCI physiological measurements. Accounting for a potential 50% loss after the initial physiological assessment, the target sample size was set at 120 patients. Recruitment was monitored by the trial steering committee with the intention to stop once 120 patients had been enrolled or 60 paired physiology data sets had been accrued, whichever occurred sooner.

Data are presented as mean ± SD or median (Q1-Q3) according to distribution and compared using Student's *t*-test or the Wilcoxon signed rank test. Categorical variables are presented as number (percentage). The primary outcome was assessed using the Wilcoxon signed rank test, and continuous agreement between predicted and measured pressure wire indexes was compared using the Bland-Altman method. A prespecified exploratory analysis was conducted to identify the determinants of error in FFR_{calc} using Pearson's correlation coefficients and univariate and multivariate regression. The secondary outcome was assessed using the McNemar-Bowker test. Applicable tests were 2 tailed, and a P value <0.05 was considered to indicate statistical significance. All analyses were performed using R version 4.4.1 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS. Between September 2021 and July 2024, 87 participants were randomized, with 45 assigned to FFR-guided treatment and 42 to iFR-guided treatment (Figure 2). Baseline characteristics were well matched and are shown in Table 1. The mean age was 67 ± 10 years, 28 patients (31%) had diabetes, and 64 (74%) presented with stable angina. Baseline angiographic and physiological characteristics are shown in Table 2.

Across the whole population, 72 patients (83%) were enrolled on the basis of the presence of 2 focal

TABLE 1 Baseline Demographics

	FFR Guided (n = 45)	iFR Guided (n = 42)
Demographics		
Age, y	67 ± 11	69 ± 10
Male	34 (76)	34 (81)
BMI, kg/m^2	27.7 ± 4.8	28.5 ± 5.4
Medical history		
Diabetes	12 (27)	15 (36)
Hypertension	25 (58)	23 (56)
Hypercholesterolemia	21 (50)	24 (63)
Current smoking	11 (31)	6 (18)
Chronic kidney disease (eGFR < 60 mL/min/1.73 m^2)	6 (15)	6 (16)
Peripheral vascular disease	2 (5)	1 (3)
Previous MI	13 (30)	19 (46)
Previous PCI	15 (36)	22 (52)
Presentation		
Stable angina	33 (77)	31 (78)
Unstable angina	5 (12)	4 (10)
NSTEMI/staged STEMI	5 (12)	5 (13)
LVEF, %	54 ± 8	53 ± 8
Symptoms		
CCS angina class		
1 or 2	23 (64)	18 (62)
3 or 4	13 (36)	11 (38)
NYHA functional class		
I or II	27 (84)	21 (78)
III or IV	5 (16)	6 (22)

Values are mean ± SD or n (%). Percentages may not total 100%, because of missing data.

BMI = body mass index; CCS = Canadian Cardiovascular Society; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

lesions. The target vessel was the left anterior descending coronary artery in 54 patients (64%) and the right coronary artery in 28 patients (33%). The operator-identified target lesion was more severely stenosed (57% ± 14% vs 46% ± 10%; $P < 0.0001$), was longer (29 mm [Q1-Q3: 22-38 mm] vs 18 mm [Q1-Q3: 15-26 mm]; $P < 0.0001$), and had a larger reference diameter (2.87 ± 0.57 mm vs 2.52 ± 0.47 mm; $P = 0.0002$) compared with the second lesion in the target vessel. Of the 74 patients who proceeded to PCI, intracoronary imaging was used in 61 (82%), with the target lesion being reduced to ≤20% diameter stenosis in 71 (96%) (mean post-PCI diameter stenosis 13% ± 9%). The mean trans-stent gradient within the FFR arm was 0.04 ± 0.03.

Drift leading to repeat pressure wire measurement was required for 27 of 264 (10%) pullbacks submitted to the core laboratory. Of the remaining 237 pullbacks, 33 (14%) showed drift >0.02 and <0.05 (the prespecified range requiring offline algorithmic correction). The median baseline whole-vessel pre-PCI FFR and iFR were 0.71 (Q1-Q3: 0.64-0.80) and 0.82 (Q1-Q3: 0.67-0.90), respectively. Baseline FFR and iFR discordance on the basis of binary thresholds of ≤0.80 for FFR and ≤0.89 for iFR was seen in 11 of 87 vessels (13%): 3 FFR−/iFR+ and 8 FFR+/iFR− (Supplementary Figure S3).

PERFORMANCE OF PREDICTED INDEXES. Using the translesional pullback gradient to predict the post-PCI FFR or iFR after treatment of a single target lesion, the median difference between FFR_{Δ} and the actual post-PCI FFR was 0.10 (Q1-Q3: 0.05 to 0.13) with 12% (Q1-Q3: 5.7% to 17.2%) error. The median difference between iFR_{Δ} and actual post-PCI iFR was 0.04 (Q1-Q3: 0 to 0.08) with 4% error (Q1-Q3: 0.0% to 9.0%; $P < 0.0001$ vs FFR_{Δ}). Using FFR_{calc}, the median difference was −0.05 (Q1-Q3: −0.15 to −0.06) with −5% (Q1-Q3: −18% to −8%; $P = 0.427$ vs FFR_{Δ}) error (**Figure 3**; Supplemental Figures S4 and S5). When binary thresholds are applied, a significant post-PCI gradient was misclassified in 23 of 64 vessels (36%) with FFR_{Δ}, 21 of 62 vessels (34%) with iFR_{Δ}, and 9 of 64 vessels (14%) with FFR_{calc} ($P = 0.002$ for FFR_{calc} vs FFR_{Δ}; $P = 0.008$ for FFR_{calc} vs iFR_{Δ}).

There was no significant difference in mean error for FFR_{calc} whether the target vessel was the left anterior descending or right coronary artery (−0.04 ± 0.15 vs −0.09 ± 0.18; $P = 0.43$). Distal pressure was weakly correlated ($R = 0.38$; 95% CI: 0.14 to 0.58), and the translesional pressure gradient was strongly negatively correlated ($R = -0.72$; 95% CI: −0.82 to 0.57) with the FFR_{calc} error (Supplemental Figure S6; Supplemental Table S2).

MANAGEMENT STRATEGY. After a management strategy was declared on the basis of angiography alone, pre-PCI physiological assessment altered the treatment modality in 9 of 82 patients (11%). There was no difference between the FFR (4 of 43 [9%]) and iFR (5 of 39 [13%]) treatment arms ($P = 0.91$). In the 67 cases in which the operator proceeded to PCI, physiological assessment changed the target lesion in 11 patients (16%), with no difference between the FFR (5 of 37 [15%]) and iFR (6 of 30 [20%]) arms ($P = 0.70$) (Supplemental Figures S7 and S8).

DISCUSSION

SERIAL is the first prospective, randomized, within-patient, head-to-head comparison of FFR vs iFR in serially diseased coronary arteries. First, we have found that in serial disease, performing coronary physiology with a pullback changes the target lesion in 1 in 6 cases. Second, conventional use of the translesional FFR or iFR gradient leads to overestimation of the post-PCI physiology result. Third, when binary treatment thresholds are applied, translesional FFR- or iFR-based predictions will

TABLE 2 Baseline Angiographic and Physiological Characteristics

	All (N = 87)	FFR Arm (n = 45)	iFR Arm (n = 42)
Target vessel			
LAD	54 (64)	28 (64)	26 (63)
LCx	3 (4)	3 (7)	0 (0)
RCA	28 (33)	13 (30)	15 (37)
Abbott pressure wire			
Pd/Pa	0.87 (0.80-0.93)	0.86 (0.76-0.91)	0.88 (0.83-0.95)
FFR	0.70 (0.62-0.78)	0.70 (0.55-0.75)	0.72 (0.65-0.83)
PPG	0.59 (0.51-0.72)	0.60 (0.50-0.73)	0.58 (0.53-0.72)
Phillips pressure wire			
Pd/Pa	0.86 (0.77-0.92)	0.86 (0.76-0.90)	0.88 (0.80-0.93)
iFR	0.82 (0.67-0.90)	0.78 (0.67-0.86)	0.84 (0.70-0.92)
Pre-PCI QCA			
Lesion 1 diameter stenosis	57 ± 14	60 ± 14	53 ± 12
Lesion 1 length	29 (22-38)	29 (20-38)	30 (24-37)
Lesion 1 RVD	2.87 ± 0.57	2.79 ± 0.57	2.97 ± 0.56
Lesion 2 diameter stenosis	46 ± 10	47 ± 10	46 ± 11
Lesion 2 length	18 (15-26)	19 (15-26)	17 (15-23)
Lesion 2 RVD	2.52 ± 0.47	2.48 ± 0.42	2.58 ± 0.53
Post-PCI QCA			
Lesion 1 diameter stenosis	13 ± 9	13 ± 11	14 ± 6
Pullback Analysis			
δFFR	0.18 (0.12-0.27)	0.21 (0.12-0.30)	0.17 (0.13-0.22)
δiFR	0.12 (0.06-0.23)	0.14 (0.07-0.23)	0.11 (0.07-0.23)
δPressure, mm Hg	17 (10-23)	19 (12-24)	17 (10-23)
Distal pressure, mm Hg	54 (45-62)	42 (44-55)	58 (50-64)
Predicted post-PCI physiology			
FFR_{Δ}	0.90 (0.85-0.93)	0.90 (0.84-0.94)	0.91 (0.86-0.93)
iFR_{Δ}	0.93 (0.90-0.96)	0.93 (0.91-0.96)	0.94 (0.90-0.97)
FFR_{calc}	0.76 (0.68-0.85)	0.73 (0.59-0.84)	0.79 (0.71-0.85)
Actual post-PCI physiology			
FFR	0.82 (0.74-0.87)	0.79 (0.70-0.87)	0.83 (0.75-0.88)
iFR	0.89 (0.83-0.93)	0.89 (0.82-0.94)	0.88 (0.84-0.92)

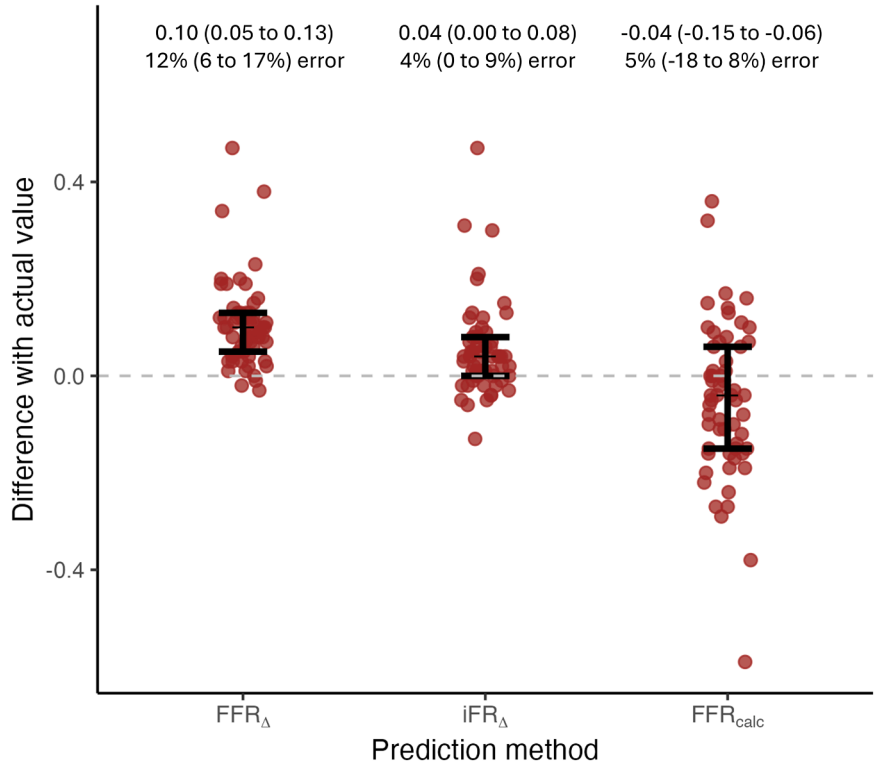
Values are n (%), median (Q1-Q3), or mean ± SD. Lesion 1 refers to the operator-determined target lesion for PCI. Post-PCI physiology refers to the predicted values after treatment of this single target lesion only. Comparisons between treatment arms for Pd/Pa (Abbott), $P = 0.037$; distal pressure, $P = 0.044$; baseline iFR, $P = 0.043$; and lesion 1 diameter stenosis, $P = 0.035$. All other comparisons were nonsignificant.

FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; RCA = right coronary artery; RVD = reference vessel diameter.

misclassify residual ischemia in more than one-third of cases (**Central Illustration**). Finally, although a calculation that accounts for the hemodynamic interaction between serial lesions is associated with a lower rate of misclassification, the spread of error is appreciable.

PREDICTING POST-PCI PHYSIOLOGY. Clinical coronary physiology has evolved from assessing hemodynamic significance at the vessel level to longitudinally mapping pressure loss within a vessel by pullback of the pressure wire. Although hyperemia lends the FFR pullback a higher spatial resolution, which is desirable in complex disease (as pressure loss is distributed over a wider range than iFR), there is a well-documented phenomenon of hemodynamic interaction between lesions, whereby a proximal lesion affects the distal lesion's FFR and vice versa.[13] Although it has previously been suggested that coronary autoregulation maintains constant flow at rest, and therefore nonhyperemic indexes such as iFR are less vulnerable to this interaction,[10,14,15] systematic assessment across a range of serial stenoses has shown that iFR is not immune. Indeed, for more proximal and severe coronary disease, iFR (with its calculation exclusively in diastole) is paradoxically affected to a greater degree than Pd/Pa or FFR.[16,17] In the present study, we observed that iFR performs no better than FFR in when using binary classification thresholds. The absolute error

FIGURE 3 Difference Between Predicted and Actual FFR and iFR



Comparison of FFR$_\Delta$, iFR$_\Delta$, FFR$_{calc}$, and the actual measured indexes for the 59 participants with paired FFR and iFR measurements made pre- and post-PCI. A positive value indicates overestimation, and a negative value indicates underestimation of the post-PCI FFR and iFR. Abbreviations as in Figure 1.

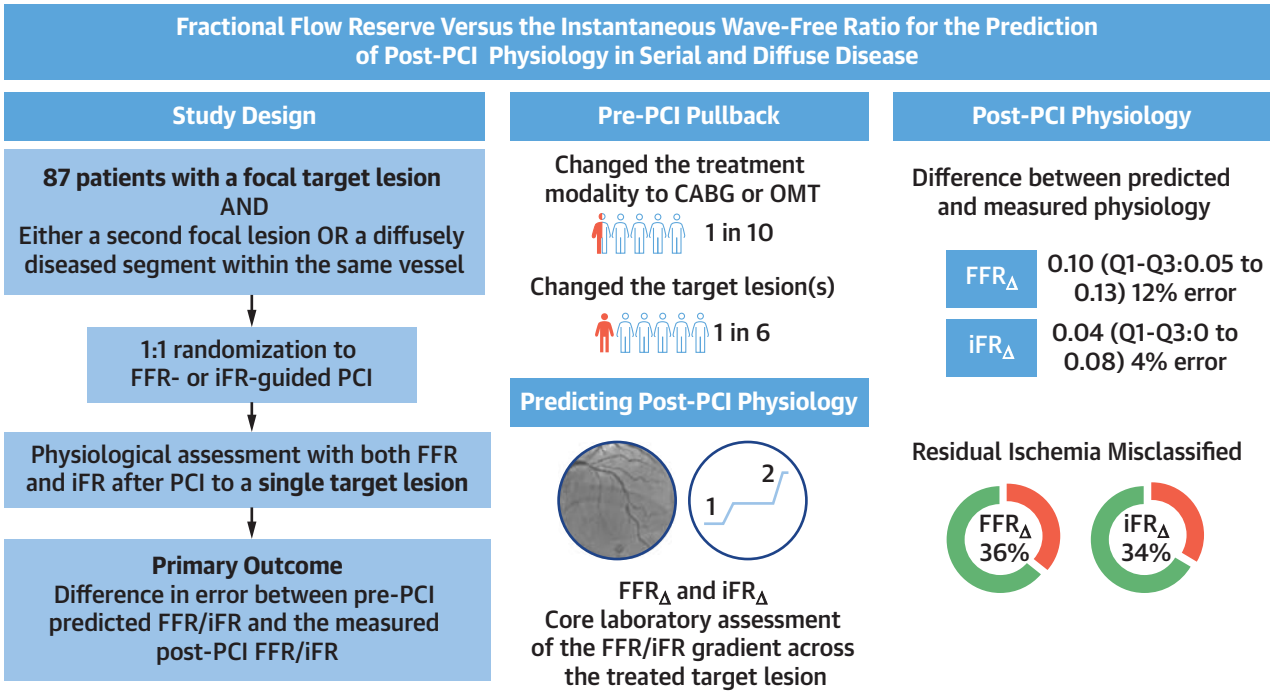
rate is greater than reported recently by Matsuo et al[14] (0.036 ± 0.037) and markedly higher than earlier descriptions of the technique.[9,15]

Both FFR$_\Delta$ and iFR$_\Delta$ tend to overestimate the hemodynamic benefit of PCI to a single target lesion in serial and diffuse disease. This is consistent with previous work, although we found that FFR$_{calc}$ underestimates post-PCI FFR in contrast to the initial validation study.[12] This may be explained by the inclusion of more severe and longer lesions in the present study. Although FFR$_{calc}$ performs better than FFR$_\Delta$ or iFR$_\Delta$ on average, the larger spread of error suggests that this simple correction fails to account for the hemodynamic nuances that apply in more severe and complex disease.

Therefore, we advise caution when attempting to predict the physiological result after PCI in serial disease, particularly when the post-PCI result by FFR$_\Delta$ or iFR$_\Delta$ is predicted to be borderline. We would strongly recommend reassessment of physiology after target lesion PCI, with a view to further stent optimization or treatment of additional segments of vessel as required. In cases in which further PCI would be either undesirable or not feasible, surgical revascularization or medical therapy should be considered from the outset.

HOW COMMON IS SERIAL DISEASE? The angiographic or physiological definition of serial disease varies widely,[11] with previous studies largely defining disease distribution and serial anatomy by a visual estimation of severity and lesion separation. In contrast, we pragmatically enrolled patients on the basis of the presence of a lesion that the operator judged to be suitable for treatment with a stent, with either a second lesion or a segment of diffuse disease. Furthermore, we report the treated segment length, which is invariably longer than the angiographic lesion length reported in other studies of serial disease.[11] Given that even mild diffuse atheroma can cause pressure loss within a vessel[18] and that truly normal coronary segments outside of the target

CENTRAL ILLUSTRATION **FFR vs iFR in Serial and Diffuse Disease**



Li Kam Wa ME, et al. JACC Cardiovasc Interv. 2025;18(13):1617–1627.

The SERIAL (Systematic Evaluation by Randomisation of Intracoronary Physiological Techniques for Assessing Tandem Lesions) study was a randomized, within-patient comparison of fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) in serial and diffuse coronary disease. It evaluated the ability of the pre-percutaneous coronary intervention (PCI) FFR or iFR pullback to predict physiology after treatment of a single target lesion.

segment are uncommon, the incidence of physiological serial disease is bound to be higher than reported in historical angiographic series. Recent efforts have been made to recognize that flow-limiting atheroma exists on a spectrum and that we should be moving to a physiological classification, whereby relative focality is expressed using an objective continuous index, the PPG.[8] Derived from the hyperemic pullback trace, the PPG has also been shown to predict the hemodynamic response to PCI. Although a model incorporating PPG (FFR_{PPG}) was less accurate at predicting final FFR in the present study compared with the initial validation cohort, it nonetheless performs better than a δFFR-based estimation (Supplemental Figures S9 and S10).

FUTURE DIRECTIONS. Functional coronary angiography (coronary physiology derived from angiography only) has proliferated in recent years, with ostensibly clear advantages in avoiding pressure wire use or the need for hyperemia, while offering implicit coregistration with angiography and reduced costs. Although multiple studies have suggested that functional coronary angiography indexes are able to predict their own value post-PCI, or FFR post-PCI, this has not yet been systematically tested in serially diseased arteries.[19-22] With recent advances in ultrahigh coronary computed tomography angiography resolution, combined with its ability to generate a true 3-dimensional coronary model (as opposed to extrapolation from 1 or more views), it is

possible that the effects of "virtual" PCI may be best assessed from noninvasive data.[23]

STUDY LIMITATIONS. First, assessment of hyperemic physiology is imprecise without the automated coregistration of angiographic anatomy and physiology pullback traces, such as with iFR Scout (Philips Healthcare) and SyncVision (Philips Healthcare). This potential error is amplified with manual pullback, where the pullback speed may be inconsistent, and in diffuse disease, where clear physiological "plateaus" may be absent. Nonetheless, most patients in this study were enrolled on the basis of 2 focal lesions.

Second, pressure wire drift <0.02 was not corrected in this study. Although representative of real-world clinical practice, in this population in which the post-PCI indexes lie close to binary cutoff values, small changes can significantly shift misclassification rates.[24]

Third, although all these techniques assume complete removal of the pressure gradient across a diseased segment, stent optimization techniques such as intracoronary imaging were not mandated (although this was performed as the standard of care in 82%). Conversely, the frequent use of intracoronary imaging optimized stents may dilute the impact of post-PCI physiology on clinical decisions.[25]

Fourth, this study was conducted at 4 experienced coronary physiology centers, but in wider practice coronary physiology is used in only 20% of patients with intermediate lesions.[24] Although the use of a core laboratory ensures objective analysis, it is uncertain whether these results can be replicated in real time in a broader setting.

Fifth, microcirculatory function and the degree of hyperemia present during post-PCI physiological assessment were not systematically quantified in this study. Finally, SERIAL was not powered to assess change in decision making, ischemia classification, or clinical outcomes.

CONCLUSIONS

Using pre-PCI FFR or iFR translesional gradients to predict the physiological impact of PCI in serially diseased coronary arteries overestimates the benefit and often leads to the misclassification of residual ischemia. This can be improved using a technique that accounts for the hemodynamic interaction between stenoses, but until validated in large studies, direct measurement of post-PCI physiology is strongly recommended.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This trial was funded by an unrestricted grant from Abbott Vascular. Drs Li Kam Wa, Ezad, and Perera are supported by British Heart Foundation grants FS/CRTF/22/24342, FS/CRTF/21/24118, and RE/18/2/34213. Dr Collet has received research grants from Coroventis Research and Abbott; and has received consultancy fees from Abbott and Philips. Dr O'Kane has received honoraria and speaker fees from Philips. Drs Collison and Perera have received speaker fees from Abbott. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Pre-PCI FFR or iFR pullbacks are commonly used to predict the physiological effects of PCI, but this approach has not been systematically evaluated in serial and diffuse disease.

WHAT IS NEW? Conventional use of pre-PCI FFR or iFR pullbacks systematically overestimates the benefit of PCI. Patients with residual stenoses post-PCI should undergo repeat measurement of coronary physiology for definitive assessment of its hemodynamic significance.

WHAT IS NEXT? Additional work is needed to understand the factors associated with error in the prediction of post-PCI physiology, with solutions to be tested in larger cohorts.

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KEY WORDS coronary physiology, fractional flow reserve, instantaneous wave-free ratio, percutaneous coronary intervention

APPENDIX For SERIAL sites and investigators, trial steering committee membership, Supplemental Methods, figures, tables, and a video of the interactive Central Illustration, please see the online version of this paper.