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FOCUS ON CORONARY ARTERY ASSESSMENT

Blinded Physiological Assessment of Residual Ischemia After Successful Angiographic Percutaneous Coronary Intervention

The DEFINE PCI Study

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ABSTRACT

OBJECTIVES This study sought to evaluate the incidence and causes of an abnormal instantaneous wave-free ratio (iFR) after angiographically successful percutaneous coronary intervention (PCI).

BACKGROUND Impaired coronary physiology as assessed by fractional flow reserve is present in some patients after PCI and is prognostically relevant.

METHODS DEFINE PCI (Physiologic Assessment of Coronary Stenosis Following PCI) was a multicenter, prospective, observational study in which a blinded iFR pull back was performed after angiographically successful PCI in 562 vessels in 500 patients. Inclusion criteria were angina with either multivessel or multilesion coronary artery disease with an abnormal baseline iFR. The primary endpoint of the study was the rate of residual ischemia after operator-assessed angiographically successful PCI, defined as an iFR <0.90. The causes of impaired iFR were categorized as stent related, untreated proximal or distal focal stenosis, or diffuse atherosclerosis.

RESULTS An average of 1.1 vessels per patient had abnormal baseline iFRs, with a mean value of 0.69 ± 0.22, which improved to 0.93 ± 0.07 post-PCI. Residual ischemia after angiographically successful PCI was present in 112 patients (24.0%), with a mean iFR in that population of 0.84 ± 0.06 (range 0.60 to 0.89). Among patients with impaired post-PCI iFRs, 81.6% had untreated focal stenoses that were angiographically inapparent, and 18.4% had diffuse disease. Among the focal lesions, 38.4% were located within the stent segment, while 31.5% were proximal and 30.1% were distal to the stent. Post-PCI vessel angiographic diameter stenosis was not a predictor of impaired post-procedural iFR.

CONCLUSIONS Blinded post-PCI physiological assessment detected residual ischemia in nearly 1 in 4 patients after coronary stenting despite an operator-determined angiographically successful result. Most cases of residual ischemia were due to inapparent focal lesions potentially amenable to treatment with additional PCI. (Physiologic Assessment of Coronary Stenosis Following PCI [DEFINE PCI]; NCT03084367) (J Am Coll Cardiol Intv 2019;12:1991–2001) © 2019 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

DS = diameter stenosis

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

PCI = percutaneous coronary intervention

QCA = quantitative coronary angiographic

The use of invasive physiological lesion assessment to guide coronary revascularization has been well established in multiple clinical trials (1,2), has been adopted in guidelines (3,4), and is increasing in use in clinical practice. The most frequently used index to determine the hemodynamic significance of a coronary stenosis is fractional flow reserve (FFR), which is calculated directly from hyperemic pressure measurements (5,6). FFR is used most frequently as a binary measure of ischemia in the distal coronary artery, and when FFR is abnormal, percutaneous coronary intervention (PCI) is guided by the angiographic vessel appearance. Moreover, FFR after an apparently successful angiographically guided PCI is rarely performed, even when FFR has been measured before PCI and the equipment is already in use (7).

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Accumulating evidence suggests that significant residual ischemia after angiographically successful PCI (defined as FFR ≤0.80) may occur in some patients (~10%) and is associated with a worse prognosis (8-11). Multiple studies have attempted to determine an optimal post-PCI FFR cutoff point that predicts future adverse events, and although that cutoff point has ranged on the basis of the study population from 0.86 to 0.96 (9-11), it is clear that there is an ischemic continuum such that higher post-PCI FFR values are associated with better long-term results (12). Despite this evidence, there are no specific guideline recommendations for routine post-PCI FFR assessment, and clinical adoption thus remains limited.

Recently, the instantaneous wave-free ratio (iFR), a resting physiological index that does not require vasodilator administration for maximal hyperemia, has been shown to correlate well with noninvasive ischemia testing (13) and to be noninferior to FFR in guiding revascularization decisions in patients with intermediate coronary artery disease (CAD) in 2 large randomized clinical trials (14,15). iFR is a measure of coronary lesion severity that can be rapidly performed and facilitates longitudinal vessel assessment to identify the hemodynamic contribution of individual lesions. However, the incidence and causes of an abnormal iFR after PCI are unknown. We therefore sought to prospectively evaluate the rate of abnormal post-stenting iFR and determine the pattern of residual ischemia as focal or diffuse in a blinded fashion after successful PCI on the basis of coronary angiography.

METHODS

STUDY DESIGN AND PROCEDURES. DEFINE PCI (Physiologic Assessment of Coronary Stenosis Following PCI) was a prospective, single-arm, blinded, multicenter study designed to assess the incidence and mechanisms of an abnormal distal vessel iFR after angiographically successful PCI. A total of 28 sites in the United States and Europe participated in the study. The study protocol was approved by the Institutional Review Board or ethics committee at each participating site. The study was supported by funding from Philips/Volcano (Amsterdam, the Netherlands) and conducted independently by the Cardiovascular Research Foundation. The funding source was uninvolved with the design of the protocol, the analysis and interpretation of the study results, and the preparation and decision to submit the manuscript.

Consented subjects presenting with stable or unstable CAD and angiographic criteria for physiological lesion assessment were eligible for participation. Among patients with unstable angina, non-ST-segment elevation myocardial infarction and prior ST-segment elevation myocardial infarction >7 days were included if TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 was present. Suitable

California; [l]Emory University Hospital, Atlanta, Georgia; [m]Royal Devon & Exeter NHS Foundation Trust, Exeter, United Kingdom; and the [n]Duke University Hospital, Durham, North Carolina. This study was supported by funding from Philips/Volcano Corporation. The funding source was uninvolved with the design of the protocol and the analysis and interpretation of the study results. Dr. Jeremias has received institutional funding (unrestricted education grant) from and serves as a consultant for Philips/Volcano, Abbott Vascular, Opsens Medical, and Boston Scientific. Dr. Davies has patents pertaining to the instantaneous wave-free ratio technology; and has received research funding from and is a consultant for Philips/Volcano. Dr. Shammas has received research and educational grants from Boston Scientific, Phillips, Intact Vascular, VentureMed Group, and Bard; and is a member of the Speakers Bureaus of Janssen, Boehringer Ingelheim, Novartis, and Zoll Medical. Dr. Sharp is a consultant for Philips Volcano. Dr. Ali has received grant support from Abbott Vascular; is a consultant for Abbott Vascular, Boston Scientific, Opsens Medical, Cardinal Health, and Cardiovascular Systems; and holds equity in Shockwave Medical. Dr. Patel has received research grants from Philips/Volcano, Bayer, Janssen, and the National Heart, Lung, and Blood Institute; and is an advisory board member for Bayer and Janssen. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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coronary anatomy included single-vessel CAD with a single lesion of ≥20 mm in length; multilesion CAD of a single vessel, defined as at least 2 separate lesions (≥10 mm apart) of ≥40% stenosis by visual estimation; or multivessel CAD, defined as at least 2 vessels with ≥40% stenosis. Exclusion criteria included ST-segment elevation myocardial infarction within the past 7 days, cardiogenic shock, sustained ventricular arrhythmias, prior coronary artery bypass surgery, chronic total occlusions, left ventricular ejection fraction ≤30%, severe mitral or aortic stenosis, TIMI flow grade <3 at baseline or post-PCI, intracoronary thrombus on baseline angiography, severe renal insufficiency (estimated glomerular filtration rate <30 ml/min/1.73 m^2), any medical comorbidity resulting in life expectancy <12 months, and major procedural complications, including coronary dissection or perforation requiring unplanned stents or additional procedures, no-reflow, or intra-procedural thrombus formation.

STUDY PROCEDURES. All vessels in which a lesion of at least 40% angiographic severity by visual estimation was identified and deemed suitable for PCI had to be interrogated with the iFR (Prestige Guide Wire PLUS or Verrata guide wire, Philips/Volcano). Pressure normalization was performed in the aorta or the coronary ostia at baseline and was recorded for core laboratory confirmation. After administration of at least 200 μg of intracoronary nitroglycerin, the wire was positioned in the distal third of the vessel with angiographic documentation. An iFR measurement was obtained under resting conditions, and patients with iFRs <0.90 in at least 1 vessel were formally enrolled if all other inclusion and exclusion criteria were met. In patients with multivessel CAD, all vessels had to be interrogated, and those with abnormal iFRs had to be treated with PCI. Once significant ischemia in a myocardial territory was established by iFR, the wire was either removed or disconnected and used for the PCI. An iFR pull back with interrogation of individual lesions was not allowed at baseline. PCI was performed according to standard of care on the basis of angiographic guidance and local practice. Intravascular imaging was allowed according to the operator's preference. Once PCI was completed successfully and the operator was ready to terminate the procedure, the pressure wire was readvanced or reconnected, and a blinded iFR pull back was performed. Blinding was achieved by turning off the monitor in the procedure room. Guidance of the physiological measurements was provided by unblinded research staff members in the control room. After a distal vessel iFR was performed, a blinded iFR pull back recording was performed along the length of the vessel under resting conditions to determine residual transstenotic pressure gradients. The pull back was performed manually under continuous fluoroscopic guidance at a speed of ~2 mm/s and was continued until the pressure sensor reached the tip of the guiding catheter at the coronary ostium. Bookmarks were inserted 5 mm distal and proximal to the implanted stent and at the coronary ostium for core laboratory analysis. A final drift check was performed and recorded with the pressure wire located in the coronary ostium; if the measurement showed >0.02 units of drift, the wire was renormalized, and all measurements were repeated.

Unblinded research staff members documented the blinded physiologic data on specified study worksheets only. Blinded data were not documented in the catheterization laboratory procedure notes or in the patient's chart. Catheterization laboratory staff members were educated on the importance of ensuring that blinded study information was not shared with the investigators or blinded research staff members. The unblinded research staff members secured the blinded data, entered it into the electronic data collection system, and placed the written results into a sealed envelope to be opened only by study monitors for source document verification. All post-procedural patient contact and follow-up phone calls or visits were conducted by a blinded research staff member.

CORE LABORATORY ANALYSIS. All pressure tracings were sent to physiology and angiography core laboratories at the Cardiovascular Research Foundation for centralized independent review. The individual core laboratories were blinded to the physiological and angiographic data, respectively. All physiology tracings were reviewed on the Volcano s5 imaging system. The physiology core laboratory assessed each individual tracing for quality on the basis of pre-specified criteria that included evaluation of the aortic and coronary pressure signal for waveform distortion or loss, aortic pressure ventricularization, and arrhythmia as previously outlined (16). Each tracing received a binary decision regarding adequate quality for inclusion. Additionally, the quality of the iFR pull back was assessed along with the amount of drift. A range of 0.98 to 1.02 was considered acceptable. All tracings were overread by a physician experienced in physiology measurements to ensure data quality. Analyses were performed within a few days after patient enrollment, and immediate feedback was given to each site regarding data quality for continued education and quality assurance.

TABLE 1 Baseline Patient Demographics (n = 500)

Age, yrs	66.4 ± 9.9
Male	379 (75.8)
Body mass index, kg/m^2	30.8 ± 8.8
Diabetes mellitus	169 (33.8)
Current smoker	83 (16.6)
Hyperlipidemia	351 (70.2)
Hypertension	383 (76.6)
Renal disease	39 (7.8)
Prior PCI	227 (45.4)
Prior myocardial infarction	134 (26.8)
Left ventricular ejection fraction (%)*	56.3 ± 9.0
Clinical presentation	
Stable angina	212 (42.4)
Silent ischemia	27 (5.4)
Unstable angina	155 (31.0)
NSTEMI	85 (17.0)
Recent STEMI (>7 days)	21 (4.2)

Values are mean ± SD or n (%). *Available in only 346 patients.
NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Angiographic and Procedural Characteristics (562 Vessels)

Target vessel	
Left anterior descending coronary artery	342 (60.9)
Left circumflex coronary artery	103 (18.3)
Right coronary artery	107 (19.0)
Left main coronary artery	2 (0.4)
Ramus intermedius	8 (1.4)
Multivessel PCI performed (≥2 vessels)	60 (12.0)
Bifurcation lesion	188/557 (33.8)
Calcification (moderate/severe)	213/558 (38.2)
Lesion length, mm*	23.6 ± 13.6
Pre-PCI diameter stenosis, %*	67.4 ± 11.1
Post-PCI diameter stenosis, worst lesion in the target vessel, %*	24.3 ± 15.0
Post-PCI residual stenosis ≥50%*	39/560 (7.0)
Total number of stents used	1.4 ± 0.8
Total stent length, mm	32.9 ± 19.5
Maximum device size, mm	3.3 ± 2.2
Maximum balloon pressure, atm	17.8 ± 4.0
Post-dilatation performed	324/553 (58.6)

Values are n (%) or mean ± SD. *By quantitative coronary angiography.
PCI = percutaneous coronary intervention.

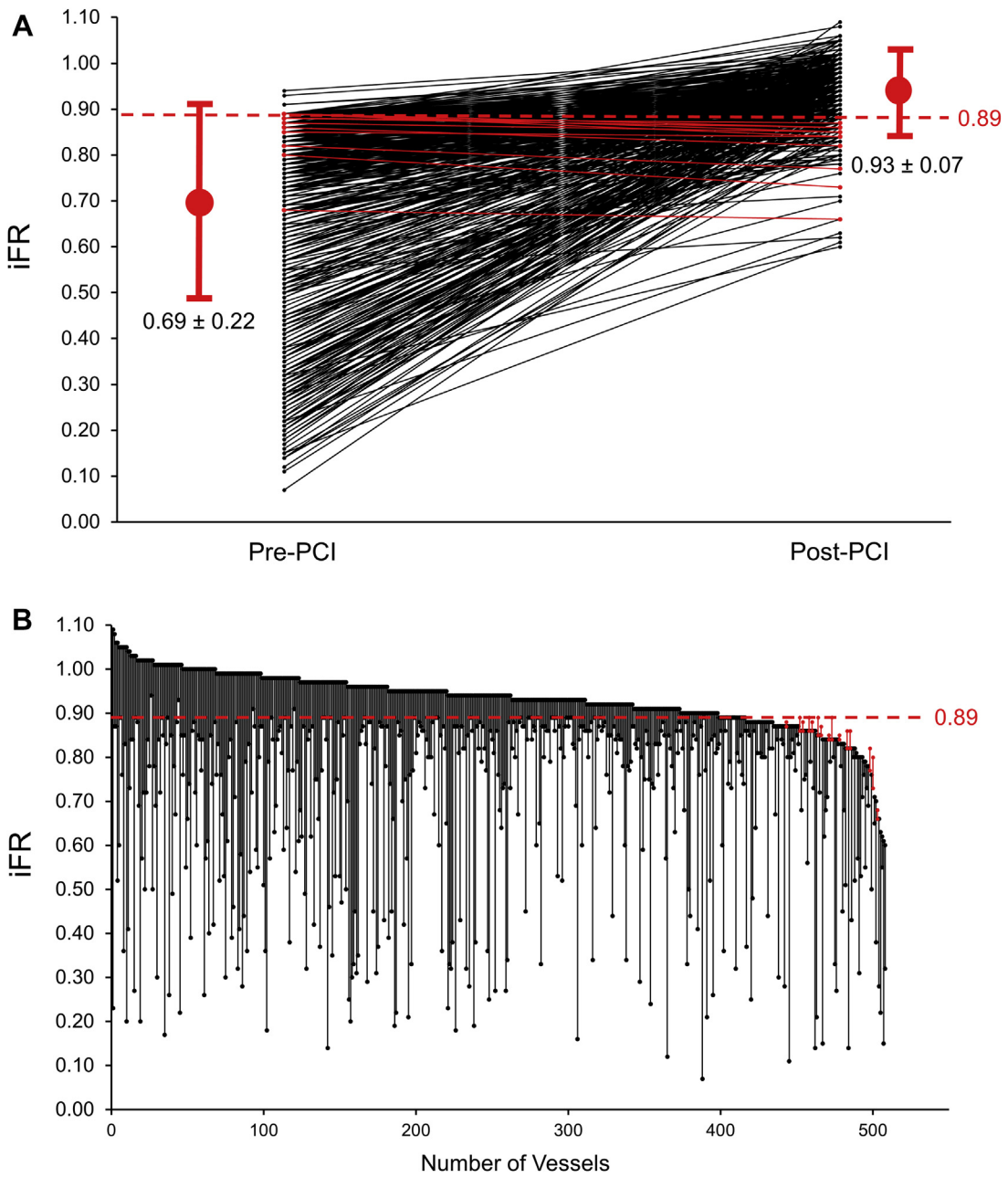
The blinded post-PCI iFR pull back was analyzed for transstenotic pressure gradients, which were categorized according to their location (distal vessel; stented segment, which included 5 mm of proximal and distal stent edge; or proximal vessel) and classified into focal lesions or diffuse disease. The location was determined by the bookmarks on the iFR pull back tracings, which also allowed an estimation of lesion length on the basis of the known stent length. Transstenotic pressure gradients of ≥0.03 were categorized as focal lesions when their length was ≤15 mm and as diffuse disease when their length exceeded 15 mm. Focal lesions and diffuse disease could occur in the same vessel in which case it was categorized as mixed disease.

The angiographic core laboratory analyzed all angiograms before and after PCI using standard methods (17). Post-PCI analysis consisted of quantification of all residual lesions of 30% severity or greater as well as the stented segment.

STUDY ENDPOINTS AND STATISTICAL ANALYSIS. The primary endpoint of the present study was the rate of residual ischemia, defined as a distal vessel iFR <0.90 after operator-assessed angiographically successful PCI (residual diameter stenosis [DS] <50% in all treated lesions in the target vessel). Secondary physiology endpoints included: 1) categorization of residual ischemia as stent related, focal stenosis in the proximal or distal vessel (in relation to the stent), or diffuse disease; 2) the proportion of cases in which optimizing stent-related issues or stenting untreated residual focal disease could theoretically improve iFR to ≥0.90; and 3) the correlation between post-PCI quantitative coronary angiographic (QCA) assessment and residual iFR as continuous measures as well as in a dichotomous fashion with an iFR cut point of <0.90 and a QCA DS of ≥50%. In addition, all patients will be followed for 1 year to examine the relationship between post-PCI iFR values and clinical outcomes. Follow-up is ongoing in this phase of the study.

Data were summarized using descriptive statistics. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as counts and percentages. The associations between post-PCI iFR <0.90 and DS ≥50% were tested using generalized estimating equations for logistic regression to account for the correlation of observations from the same subject. Multivariate logistic regression models predicting post-PCI iFR <0.90 were performed using generalized estimating equations, including pre-PCI reference vessel diameter, post-PCI DS, pre-PCI iFR, total stent length per vessel, left anterior descending coronary artery location, calcification, and diabetes as covariates. A 2-sided p value < 0.05 was considered to indicate statistical significance for all tests. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

FIGURE 1 Pre- and Post-Percutaneous Coronary Intervention Instantaneous Wave-Free Ratio After Angiographically Successful Percutaneous Coronary Intervention

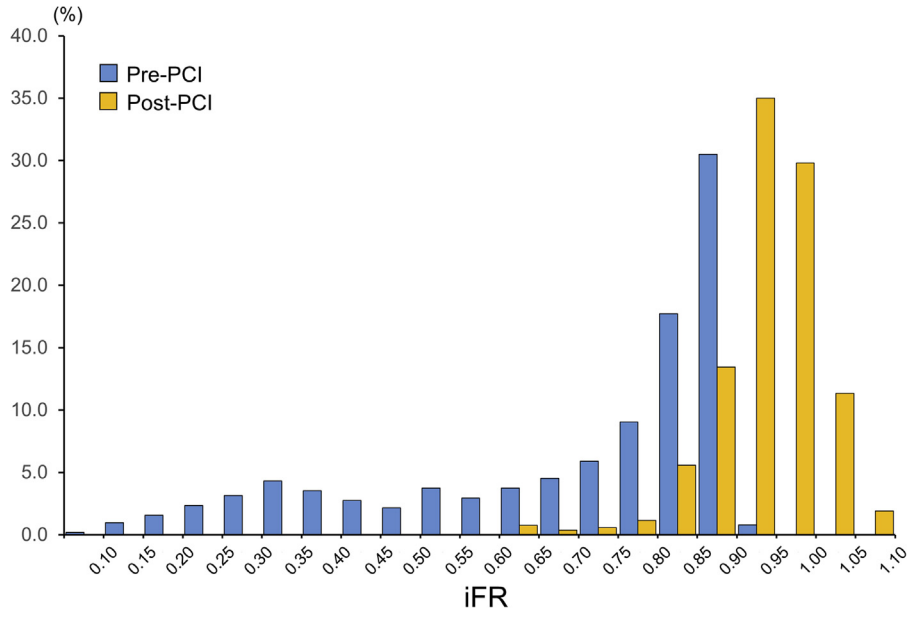


(A) Pre- and post-percutaneous coronary intervention (PCI) instantaneous wave-free ratio (iFR) values in individual vessels and mean iFR **(red circle)** with 95% confidence interval (CI) **(error bar)**. **Black lines** depict improved iFR values after PCI; **red lines** represent lower iFR values after PCI. **(B)** Distribution of post-PCI iFR values in all vessels sorted by magnitude of iFR improvement from **left to right**. Pre-PCI iFR values are displayed at the **bottom** and post-PCI iFR values at the **top**. **Black and red lines** as in **A**.

RESULTS

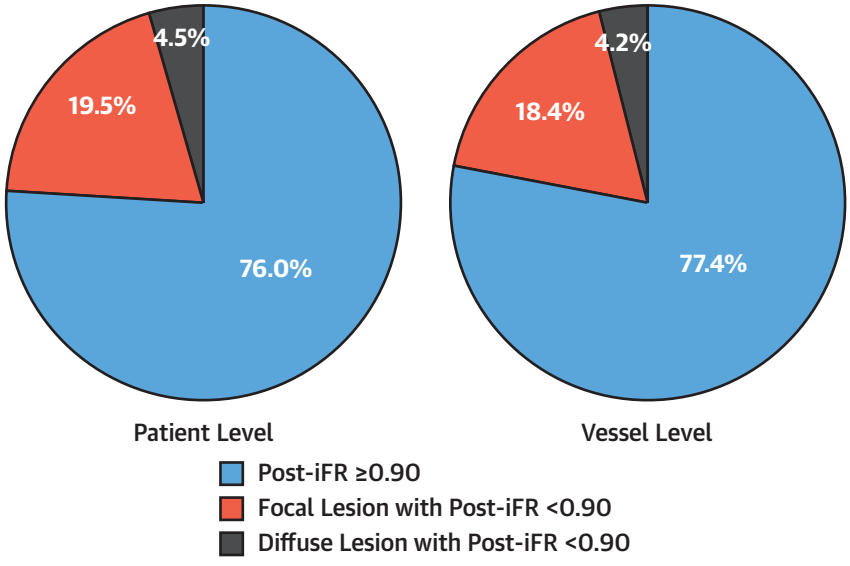
PATIENT DEMOGRAPHICS AND PROCEDURAL DATA. A total of 500 patients undergoing PCI in 562 vessels (1.1 vessels per patient) were included in the study. Among those, 562 and 560 vessels were available for angiography core laboratory review pre-PCI and post-PCI, respectively. Baseline patient

FIGURE 2 Instantaneous Wave-Free Ratio Frequency Distribution



Frequency distribution of pre-percutaneous coronary intervention (PCI) **(blue)** and post-PCI **(yellow)** instantaneous wave-free ratio (iFR) values.

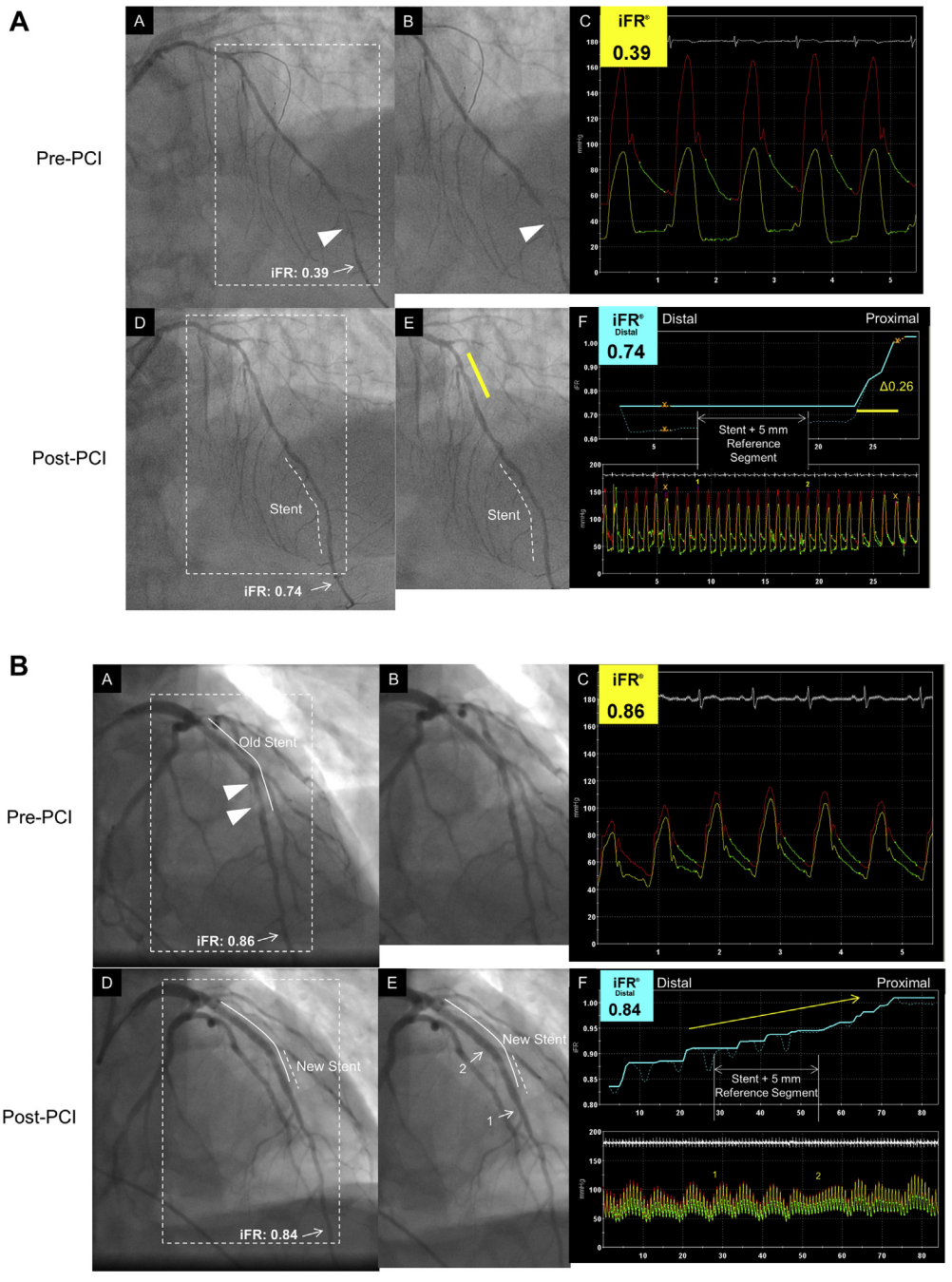
CENTRAL ILLUSTRATION Post-Percutaneous Coronary Intervention Coronary Physiology



Jeremias, A. et al. J Am Coll Cardiol Intv. 2019;12(20):1991–2001.

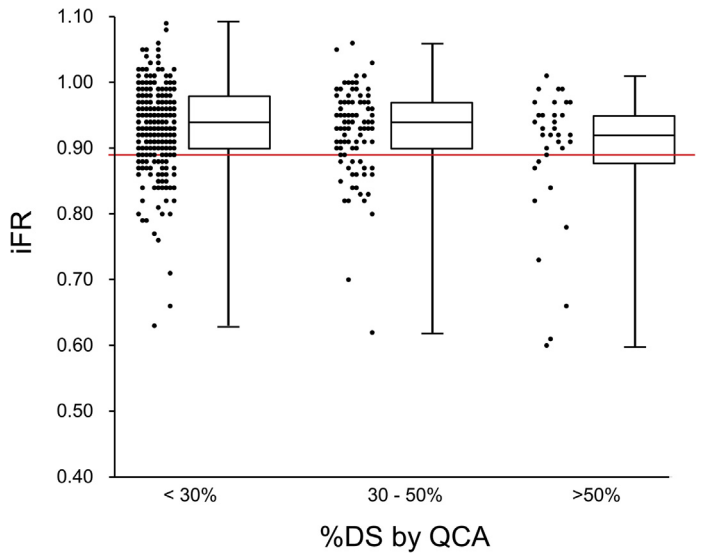
Percentage of vessels with post-percutaneous coronary intervention (PCI) ischemia, defined as an instantaneous wave-free ratio (iFR) of <0.90 on patient level **(left)** and vessel level **(right)** after angiographically successful procedure. A total of 24% of patients and 22.6% of vessels had residual ischemia. The majority of vessels with iFR <0.90 contained focal lesions versus diffuse disease, potentially amendable to further optimization with additional PCI.

FIGURE 3 **Case Examples**



(Top, A) Significant residual ischemia after percutaneous coronary intervention (PCI) due to an angiographic inapparent focal lesion proximal to an implanted stent. Coronary angiography **(A,B)** demonstrated a severe distal stenosis of the left anterior descending coronary artery (LAD) with a pre-PCI instantaneous wave-free ratio (iFR) of 0.39 **(C)**. After angiographically successful stent implantation of the distal LAD **(D,E)**, the post-PCI iFR improved to 0.74 but remained lower than the ischemic threshold of 0.90. An iFR pull back **(F)** demonstrated no significant pressure gradient within the stent segment but a 0.33 iFR gradient in the mid-LAD proximal to the stent at the site of an angiographic mild stenosis (quantitative coronary angiographic diameter stenosis 42.8%) **(yellow bar)**, the cause of the residual ischemia. **(Bottom, B)** Significant residual ischemia after PCI due to diffuse disease. Coronary angiography **(A,B)** demonstrated in-stent restenosis of the LAD with a pre-PCI iFR of 0.86 **(C)**. Despite angiographically successful stent implantation in the mid-LAD **(D,E)**, the post-PCI iFR decreased to 0.84. An iFR pull back **(F)** demonstrated diffuse disease of the new stent segment and proximal LAD in the old stent segment without a focal gradient.

FIGURE 4 Post-Percutaneous Coronary Intervention Physiology in Various Angiographic Subgroups



Mean post-percutaneous coronary intervention instantaneous wave-free ratio (iFR) values (95% confidence interval) and iFR distribution in various angiographic subgroups on the basis of diameter stenosis (DS) by quantitative coronary angiography (QCA). **Red line** depicts ischemic threshold of <0.90.

characteristics are presented in Table 1. The mean age of the population was 66.4 ± 9.9 years, and 75.8% were male. Clinical presentation was predominantly stable or unstable angina (78.8%), with the remainder being non-ST-segment elevation myocardial infarction or recent ST-segment elevation myocardial infarction.

Procedural characteristics are summarized in Table 2. Most lesions were located in the left anterior descending coronary artery (60.9%), and 12.0% of patients underwent multivessel PCI. Approximately one-third of vessels contained lesions with moderate or severe calcification or that were located at a bifurcation. Mean lesion length per vessel was 23.6 ± 13.6 mm, and mean QCA pre-PCI DS was 67.4 ± 11.1%. The mean number of stents implanted was 1.4 ± 0.8 per vessel, with a maximum device size of 3.3 ± 2.2 mm; 58.6% of vessels were post-dilated. Post-procedural QCA assessment showed a maximal (worst) in-vessel residual DS of 24.3 ± 15.0%, with 7.0% of lesions having residual stenoses of ≥50%.

PRE- AND POST-PROCEDURAL PHYSIOLOGY. iFR was available for core laboratory analysis in 494 of 500 patients pre-PCI (inadequate recording in 5 patients, unable to cross with wire in 1 patient) and in 480 of 500 patients post-PCI (no final iFR performed in 8 patients because of patient instability, inadequate recording in 9 patients, unable to cross with wire in 3 patients). A total of 548 and 535 vessels with pre-PCI and post-PCI iFR tracings were available, from which the core laboratory excluded 6 vessels pre-PCI for drift (n = 3) or waveform abnormalities (n = 3) and 15 vessels post-PCI for drift (n = 10) or waveform abnormalities (n = 5), leaving 542 and 520 analyzable pre-PCI and post-PCI iFR tracings for analysis. Mean pre-procedural iFR for all vessels was 0.69 ± 0.22, which improved to 0.93 ± 0.07 post-procedure (Figures 1A and 1B). In paired analysis in 508 vessels, the mean iFR improvement from pre- to post-PCI was 0.24 ± 0.23 (range −0.07 to 0.86). The distribution of iFR values before and after PCI is illustrated in Figure 2.

Residual ischemia (post-PCI iFR <0.90) after angiographically successful PCI was present in 114 of vessels (21.9%) (mean iFR 0.84 ± 0.06; range 0.60 to 0.89) and in 112 of patients (24.0%) (mean iFR 0.84 ± 0.06; range 0.60 to 0.89). Of the 114 vessels with abnormal post-PCI physiology, 93 (81.6%) had single or multiple residual focal lesions, and 21 (18.4%) had diffuse disease only (Central Illustration). Among the 93 vessels with focal disease, there were 146 segments (stent, proximal, or distal) that had significant residual pressure gradients; 56 (38.4%) were located within the stent segment, while 46 (31.5%) and 44 (30.1%) were proximal and distal to the stent, respectively. In 43 vessels (29.5%), there was mixed disease (focal and diffuse). Case examples are provided in Figure 3. Assuming all focal lesions with post-PCI iFR <0.90 were successfully treated with additional PCI, the mean iFR was modeled to improve from 0.84 ± 0.06 to 0.95 ± 0.05. Only 23 of all 520 (4.4%) vessels and 23 of the 467 patients (4.9%) with qualified post-PCI iFR pull backs would remain under the iFR ischemic threshold of <0.90.

CORRELATION BETWEEN POST-PCI ANGIOGRAPHY AND PHYSIOLOGY. The correlation between residual stenosis by QCA and post-procedural iFR was poor (R^2 = 0.03; p = 0.005). The incidence of an impaired post-PCI iFR was similar among patients with a residual QCA DS of ≥50% versus <50% (29.7% vs. 21.4%, respectively; p = 0.24). Mean post-PCI iFR and iFR distribution on the basis of angiographic lesion severity are displayed in Figure 4. Predictors of an impaired post-PCI iFR were pre-PCI reference vessel diameter (odds ratio: 0.32; 95% confidence interval: 0.18 to 0.58; p = 0.0002) and lesion location in the left anterior descending coronary artery (odds ratio: 5.65; 95% confidence interval: 3.07 to 10.40; p < 0.0001).

Post-PCI QCA DS was not a significant predictor of post-PCI impaired iFR ($p = 0.08$).

DISCUSSION

To the best of our knowledge, the present study is the first to assess post-PCI coronary physiology in a blinded fashion using the resting index iFR with core laboratory comparison between physiological and angiographic parameters. The principal findings are as follows: 1) despite angiographically successful PCI, residual ischemia with an iFR <0.90 was present in 24.0% of patients; 2) only a small number of vessels had significant residual DS by angiography underlying this finding, and the correlation between post-PCI QCA and iFR was poor; and 3) most patients (about four-fifths) with impaired post-PCI physiology had residual focal lesions related to or distant from the stented segment that potentially could be further optimized by additional PCI.

Although myocardial revascularization with PCI provides symptomatic benefit in patients with myocardial ischemia (18), numerous studies have demonstrated that up to 20% of patients experience recurrent angina in the year following PCI (18–20), necessitating costly noninvasive and invasive testing and repeat revascularization. Effective strategies to reduce the likelihood of post-PCI recurrent angina have not been identified. Among patients with stable angina, selection of angiographically indeterminate lesions for PCI by physiological assessment has been demonstrated to be a superior strategy compared with angiographic guidance alone, improving outcomes and reducing costs (2,21). Although routine assessment of intermediate coronary stenoses pre-PCI is common, post-PCI physiology is rarely performed in clinical practice due to limited data (12) and lack of any specific guideline recommendations. Previous studies using FFR after successful angiographically guided PCI have demonstrated impaired post-PCI physiology (FFR ≤0.80) in about 10% of cases (7). In a recent retrospective, single-center study of 574 patients (664 lesions), post-PCI FFR led to reclassification of about 20% of lesions requiring additional intervention, reducing the proportion of patients with significant post-PCI ischemia from 21% to 9% (9). The present study documented residual ischemia by iFR in 22.0% of vessels and 24.0% of patients despite angiographically successful stent implantation, a slightly higher rate of post-PCI ischemia than in prior FFR studies, possibly attributable to the present study's prospective design, strict enrollment criteria reducing selection bias, and blinded final iFR evaluation, which precluded further optimization on the basis of the physiological assessment. Whether patients presenting with recurrent anginal symptoms have significant residual ischemia post-PCI is unknown, although prior studies have demonstrated an association between lower post-PCI FFR values and increased rates of major adverse cardiac events (7,12).

In addition to determining the actual rate of significant post-PCI ischemia in a blinded and core laboratory-controlled fashion, we also attempted to identify the mechanism for the residual ischemia. The resting index iFR, which provides an instantaneous assessment of stenosis severity without the need for administration of vasodilators to induce hyperemia, has emerged as a tool to provide rapid lesion assessment (22,23) has been shown to be noninferior to FFR for PCI guidance in 2 large randomized clinical trials (14,15). Moreover, because of the stability of resting coronary flow in the absence of critical (>90%) coronary stenoses, isolating the hemodynamic significance of individual coronary segments can be reliably obtained by iFR pull back (24). In contrast, evaluating tandem lesions or diffuse disease with FFR is challenging because of the fluid dynamic interaction between lesions in the setting of maximal hyperemia (25), complicating the determination of each individual lesion's contribution to an impaired post-PCI FFR. The findings of the present study indicate that the vast majority of residual pressure gradients contributing to significant post-PCI ischemia are focal and thus could be potentially treated with additional PCI. Also of note, a substantial number (more than one-third) of residual focal pressure gradients were found within the stented segment (despite their angiographically benign appearance), while about two-thirds were present at the site of angiographically mild untreated lesions, indicating that further PCI (ideally with intravascular imaging) could lead to improved post-procedural physiology in the majority of patients. In this regard, a recent study evaluated the ability of pre-PCI iFR to predict post-PCI physiology with high reliability (24).

Of note, the relationship between post-PCI iFR and clinical outcomes is not yet established, and whether post-PCI iFR-based optimization is safe or effective is unknown. Thus, no further optimization of the PCI result was attempted in the present study. The association between post-PCI physiology and 1-year clinical outcomes will be evaluated in a second phase of this investigation. Ultimately, randomized trials will be required to determine whether a routine iFR pull

back strategy before and after PCI would lead to improved clinical outcomes compared with a conventional angiographically guided approach or pre-PCI iFR alone.

STUDY LIMITATIONS. Given the specific enrollment criteria, including patients with either multivessel or multilesion CAD, the actual proportion of "real-world" cases in which post-PCI physiology could be further optimized with additional PCI remains speculative. In addition, because intravascular imaging was not routinely performed, we are unable to describe the specific stent-related and untreated lesion-related characteristics that contributed to the decrement in pressure gradients. Whether FFR pull back would identify more or fewer lesions requiring optimization (and whether these lesions would be the same of different) compared with iFR pull back is unknown. Finally, for several reasons, our study may have underestimated the prevalence of post-PCI ischemia: 1) we did not interrogate angiographically "normal" appearing vessels in which PCI was not performed, some of which may have abnormal iFR and contribute to recurrent angina; and 2) we did not assess for the presence of nonepicardial coronary-related causes of ischemia, such as microvascular disease, using coronary flow reserve or other techniques (26).

CONCLUSIONS

Significant epicardial residual ischemia after angiographically successful PCI is not uncommon, occurring in nearly 25% of patients in the present study. Post-PCI angiography poorly correlated with physiological measures. In a large majority of cases, residual pressure gradients were focal and thus potentially amenable to treatment with additional PCI. The results of the present study suggest potential clinical utility for routine iFR pull back of stented vessels post-PCI to detect significant but angiographically inapparent pressure gradients and differentiate focal lesions from diffuse CAD.

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PERSPECTIVES

WHAT IS KNOWN? Residual ischemia as measured by FFR after apparent angiographically successful PCI occurs in 10% to 15% of cases.

WHAT IS NEW? Residual ischemia after PCI on the basis of the resting index iFR occurs in 24% of vessels. The vast majority of ischemic vessels are due to a missed focal lesion either proximal or distal to the stent or to a suboptimal stent result, potentially amenable to further optimization with additional PCI.

WHAT IS NEXT? Whether routine physiological assessment post-PCI will lead to further PCI optimization and improved long-term clinical outcomes is unknown and needs to be assessed in a randomized clinical trial.

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