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1-Year Outcomes of Blinded Physiological Assessment of Residual Ischemia After Successful PCI

DEFINE PCI Trial

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ABSTRACT

OBJECTIVES The aim of this study was to identify the post-percutaneous coronary intervention (PCI) target value of instantaneous wave-free ratio (iFR) that would best discriminate clinical events at 1 year in the DEFINE PCI (Physiologic Assessment of Coronary Stenosis Following PCI) study.

BACKGROUND The impact of residual ischemia detected by iFR post-PCI on clinical and symptom-related outcomes is unknown.

METHODS Blinded iFR pull back was performed after successful stent implantation in 500 patients. The primary endpoint was the rate of residual ischemia, defined as iFR ≤0.89, after operator-assessed angiographically successful PCI. Secondary endpoints included clinical events at 1 year and change in Seattle Angina Questionnaire angina frequency (SAQ-AF) score during follow-up.

RESULTS As reported, 24.0% of patients had residual ischemia (iFR ≤0.89) after successful PCI, with 81.6% of cases attributable to angiographically inapparent focal lesions. Post-PCI iFR ≥0.95 (present in 182 cases [39%]) was associated with a significant reduction in the composite of cardiac death, spontaneous myocardial infarction, or clinically driven target vessel revascularization compared with post-PCI iFR <0.95 (1.8% vs 5.7%; $P = 0.04$). Baseline SAQ-AF score was 73.3 ± 22.8. For highly symptomatic patients (baseline SAQ-AF score ≤60), SAQ-AF score increased by ≥10 points more frequently in patients with versus without post-PCI iFR ≥0.95 (100.0% vs 88.5%; $P = 0.01$).

CONCLUSIONS In DEFINE PCI, despite angiographically successful PCI, highly symptomatic patients at baseline without residual ischemia by post-PCI iFR had greater reductions in anginal symptoms at 1 year compared with patients with residual ischemia. Achieving post-PCI iFR ≥0.95 was also associated with improved 1-year event-free survival. (Physiologic Assessment of Coronary Stenosis Following PCI [DEFINE PCI]; NCT03084367) (J Am Coll Cardiol Intv 2022;15:52-61)

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The use of physiology to guide the decision to perform coronary revascularization, particularly percutaneous coronary intervention (PCI), has been demonstrated in several multicenter clinical trials (1-4). The most established index used to determine the hemodynamic significance of a coronary stenosis is fractional flow reserve (FFR), which is calculated directly from hyperemic pressure measurements (2,5). However, repeat FFR measurement after apparently successful angiographically guided PCI is rarely performed, even when FFR has been measured prior to PCI with the equipment already in use.

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Over the past decade, the instantaneous wave-free ratio (iFR), a physiological index that does not require the administration of a pharmacologic agent to induce hyperemia, was shown to be noninferior to FFR in 2 large randomized trials (6,7). In addition to a distal vessel spot iFR measurement, iFR pull back is capable of providing longitudinal vessel assessment and identifying the physiological significance of individual lesions that may be responsible for future clinical events, potentially simplifying repeated post-PCI physiology assessments. The DEFINE PCI (Physiologic Assessment of Coronary Stenosis Following PCI; NCT03084367) study prospectively evaluated the rate of abnormal postprocedural iFR and determined the pattern of residual ischemia as focal or diffuse in a blinded fashion after successful PCI on the basis of coronary angiography (8). As previously reported, 24.0% of patients had residual ischemia (iFR ≤0.89) after angiographically successful PCI, 81.6% of which was focal (defined as change in iFR of ≥0.03 units over a segment ≤15 mm in length). The long-term implications of either abnormal or suboptimal iFR after PCI have not been reported. Herein we present an analysis to identify the post-PCI iFR target value that would best discriminate clinical events and details of clinical events at 1 year, including change in the Seattle Angina Questionnaire angina frequency (SAQ-AF) score during follow-up from the DEFINE PCI study according to the post-PCI iFR.

METHODS

STUDY DESIGN AND PROCEDURES. The design and procedures of the DEFINE PCI study have been previously reported (8). Briefly, DEFINE PCI was a prospective, single-arm, blinded, multicenter study to assess the relationship between distal vessel iFR and iFR pull back and the distribution of physiologically significant coronary stenoses after successful PCI, as assessed by quantitative coronary angiography. DEFINE PCI was conducted at 28 sites in the United States and Europe. Institutional Review Boards or ethics committees at participating sites approved the study protocol, and all participants provided informed consent. The study was sponsored and funded by Philips/Volcano. The Cardiovascular Research Foundation was responsible for clinical event adjudication and core laboratory quantitative coronary angiographic and iFR analyses. An independent steering committee was responsible for the conduct, analysis, and reporting of the primary and 1-year findings of the study.

Patients with stable or unstable coronary artery disease (CAD) who met clinical criteria for physiological lesion assessment on the basis of angiographic findings were eligible for inclusion. Patients with unstable angina, non-ST-segment elevation myocardial infarction (MI), or prior ST-segment elevation MI (>7 days) were included only if TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 was documented. Single-vessel CAD with at least 2 separate lesions (≥10 mm apart) of ≥40% stenosis by visual angiographic assessment, a single long lesion of ≥20 mm, or multivessel CAD was required for entry. Exclusion criteria included recent MI (within 7 days), chronically occluded vessels, and limited life expectancy.

iFR AND iFR PULL BACK PROCEDURES. Investigators were instructed to interrogate all vessels with 1 or more lesions with ≥40% diameter stenosis that were suitable for PCI with iFR (Verrata or Verrata PLUS Pressure Guide Wire, Philips/Volcano). Standard procedures, including instructions on pressure normalization in the aorta or the coronary ostia before pressure measurements, were recorded for core laboratory confirmation. After administration of intracoronary nitroglycerin, the wire was positioned in the distal third of the vessel. Patients with resting iFR measurements of ≤0.89 in at least 1 vessel were eligible for enrollment. In patients with multivessel CAD, all vessels with abnormal iFR were to be treated

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

FFR = fractional flow reserve

iFR = instantaneous wave-free ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

SAQ-AF = Seattle Angina Questionnaire angina frequency

TVR = target vessel revascularization

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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with PCI. PCI was performed on the basis of angiographic guidance and according to local practice; iFR pull back with interrogation of individual lesions was not allowed prior to PCI. Following successful PCI, with the operator ready to terminate the procedure, the pressure wire was reconnected or readvanced, and a blinded iFR distal spot measurement and pull back were performed. Monitors in the catheter laboratory procedure room were turned off to achieve blinding. Unblinded research staff members in the control room provided guidance around physiological measurements. However, blinded research staff members conducted all follow-up phone calls or visits and postprocedural patient contact.

CORE LABORATORY ANALYSIS. Blinded core laboratory analysis was performed on all pressure tracings at the physiology and angiography core laboratories for standardized and centralized review. Each iFR tracing was assessed for quality on the basis of prespecified criteria that included evaluation of the aortic and coronary pressure signal for waveform distortion or loss, aortic pressure ventricularization, and drift (defined as Pd/Pa <0.98 or >1.02 after pull back of the pressure wire to the aorta), as previously outlined (9). The blinded post-PCI iFR pull back was analyzed for trans-stenotic pressure gradients, which were categorized according to their location (distal vessel, stented segment that included 5 mm proximal and distal to the stent edges, or proximal vessel), and was classified as focal or diffuse. The physiology core laboratory was blinded to quantitative coronary angiographic data. The angiography core laboratory analyzed all angiograms before and after PCI using standard methods, blinded to physiological data. Post-PCI analysis consisted of quantification of all residual lesions of ≥30% severity as well as the stented segment.

STUDY ENDPOINTS. The DEFINE PCI study aimed to determine the rate of residual ischemia, defined as iFR ≤0.89 after operator-assessed angiographically successful PCI (residual diameter stenosis <50% in all treated lesions in the target vessel). The 1-year outcomes presented here focused on adverse clinical events and analysis of the SAQ-AF scale. Clinical endpoints included MI, defined as periprocedural or spontaneous; target vessel revascularization (TVR); clinically driven TVR; and cardiovascular death. Each of these endpoints was adjudicated by a central events committee whose members were blinded to the quantitative coronary angiographic and physiologic data. SAQ-AF score was assessed at 1, 6, and 12 months using standard questionnaires administered by trained personnel.

STATISTICAL ANALYSIS. In cases of multivessel disease, the lowest post-PCI iFR was used per patient. Normally distributed continuous variables are expressed as mean ± SD and were compared using Student's *t*-test. Skewed continuous variables are expressed as medians with IQRs and were compared using the Wilcoxon rank sum test. Categorical variables are summarized as counts and percentages and were compared using the chi-square test. The Fisher exact test was used when 1 cell had an expected frequency of ≤5. In a post hoc analysis, receiver-operating characteristic curve analysis was performed to determine the optimal post-PCI iFR cutoff value to predict cardiac death or spontaneous MI, derived using the Youden index. Analysis of covariance was used to compare the mean changes in SAQ-AF score from baseline to follow-up in the post-PCI iFR groups, adjusting for baseline SAQ-AF value. Analysis of covariance was fitted using the Bayesian method, which directly estimates the probability distribution of the optimal post-PCI iFR effect with posterior means and 95% posterior density intervals. The time-to-event rates are shown as Kaplan-Meier estimates and were compared using the log-rank test. 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).

RESULTS

PATIENT FOLLOW-UP AND POST HOC IDENTIFICATION OF OPTIMAL iFR OF 0.95. DEFINE PCI enrolled 500 patients, 20 of whom did not have analyzable iFR values, because of patient instability, inadequate recording, or inability to cross the lesion. Of the remaining 480 patients and 535 vessels with post-PCI iFR values, 15 vessels from 13 patients were rejected after core laboratory analysis because of pressure drift or waveform abnormalities. Therefore, post-PCI iFR was available in 520 vessels from 467 patients (**Figure 1**). Median follow-up duration was 375 days (IQR: 368-389 days). An iFR of <0.95 was identified as the best cutoff value to discriminate cardiac death or spontaneous MI during 1-year follow-up (area under the curve: 0.74; 95% CI: 0.61-0.88) (Supplemental Figure 1).

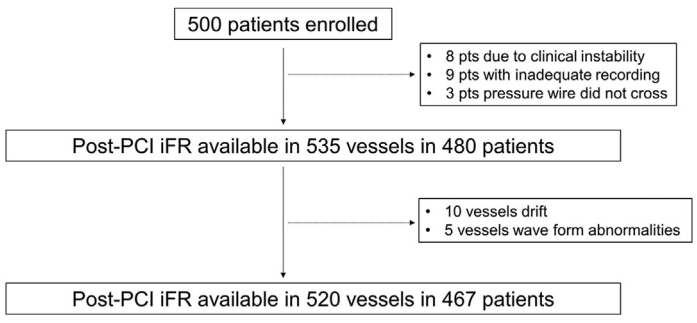
PATIENT DEMOGRAPHICS. Patient demographics and medical history are presented in **Table 1** by overall

cohort and according to a post-PCI iFR cutoff of 0.95. Post-PCI iFR values of ≥0.95 and <0.95 were present in 182 (39%) and 285 (61%) patients, respectively. In general, baseline demographics and medical history did not significantly vary according to post-PCI iFR, although body mass index was slightly lower in patients with higher post-PCI iFR values (Table 1).

SAQ-AF SCORE AT FOLLOW-UP. The results of baseline, 6-month, and 12-month SAQ-AF findings are presented in Table 2. Trends toward improvement in SAQ-AF scores were seen in patients with post-PCI iFR ≥0.95. In those patients with the most angina at baseline, identified by SAQ-AF scores ≤60, an absolute change of ≥10 points at 1-year follow-up was more likely with post-PCI iFR ≥0.95 compared with <0.95 (100.0% vs 88.5%; $P = 0.01$). Distributions of the difference in angina at 1 and 12 months post-PCI compared with baseline by Bayesian analysis in all patients and by frequency of angina are presented in Figure 2.

CLINICAL EVENTS. Clinical events at 1 year are presented in Table 3. The Kaplan-Meier estimated 1-year composite of cardiac death, spontaneous MI, or clinically driven TVR occurred in 1.8% of patients with post-PCI iFR ≥0.95 compared with 5.7% of patients with post-PCI iFR <0.95 ($P = 0.04$) (Central Illustration B). Cardiac death or spontaneous MI within 1 year occurred in 0% and 3.2% of patients with post-PCI iFR ≥0.95 compared with <0.95, respectively ($P = 0.02$) (Central Illustration C). There were fewer other clinical events in those with post-PCI iFR ≥0.95 versus <0.95, including all-cause death (2 vs 4), all MIs (2 vs 11), and revascularizations (13 vs 21). Of note, among 285

FIGURE 1 DEFINE PCI Study Flow Diagram



DEFINE PCI = Physiologic Assessment of Coronary Stenosis Following PCI; iFR = instantaneous wave-free ratio; PCI = percutaneous coronary intervention.

TABLE 1 Baseline Demographics and Medical History According to Post-PCI iFR

	iFR <0.95 (n = 285)	iFR ≥0.95 (n = 182)	Total (N = 467)	*P* Value
Demographics				
Sex				
Female	22.8 (65/285)	25.8 (47/182)	24.0 (112/467)	0.46
Male	77.2 (220/285)	74.2 (135/182)	76.0 (355/467)	0.46
Age, y	67.0 (60.0-74.0)	67.0 (59.0-72.0)	67.0 (60.0-73.0)	0.30
Medical history				
Current smoking	13.3 (38/285)	20.3 (37/182)	16.1 (75/467)	0.04
Diabetes	34.4 (98/285)	30.8 (56/182)	33.0 (154/467)	0.42
Insulin-treated diabetes	30.6 (30/98)	23.2 (13/56)	27.9 (43/154)	0.32
Hypertension	76.1 (217/285)	76.4 (139/182)	76.2 (356/467)	0.95
Hyperlipidemia	70.2 (200/285)	68.1 (124/182)	69.4 (324/467)	0.64
Renal disease	8.1 (23/285)	6.6 (12/182)	7.5 (35/467)	0.55
Prior PCI	47.7 (136/285)	39.6 (72/182)	44.5 (208/467)	0.08
Prior MI	28.1 (80/285)	25.8 (47/182)	27.2 (127/467)	0.59
BMI, kg/m^2	30.1 (26.2-34.6)	29.1 (25.4-32.9)	29.7 (25.9-33.7)	0.0453
Ejection fraction	(n = 194)	(n = 124)	(n = 318)	0.98
Median (IQR), %	57.0 (50.0-60.0)	55.0 (50.0-64.1)	56.5 (50.0-61.0)	
Ejection fraction <40%	3.1 (6/194)	4.8 (6/124)	3.8 (12/318)	0.55
Clinical presentation				
Stable angina	44.2 (126/285)	39.0 (71/182)	42.2 (197/467)	0.27
Silent ischemia	4.6 (13/285)	7.1 (13/182)	5.6 (26/467)	0.24
Unstable angina	31.2 (89/285)	30.2 (55/182)	30.8 (144/467)	0.82
NSTEMI	15.1 (43/285)	19.8 (36/182)	16.9 (79/467)	0.19
Recent MI (including STEMI >7 d)	4.9 (14/285)	3.8 (7/182)	4.5 (21/467)	0.59

Values are as % (n/N) or median (IQR).

BMI = body mass index; iFR = instantaneous wave-free ratio; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

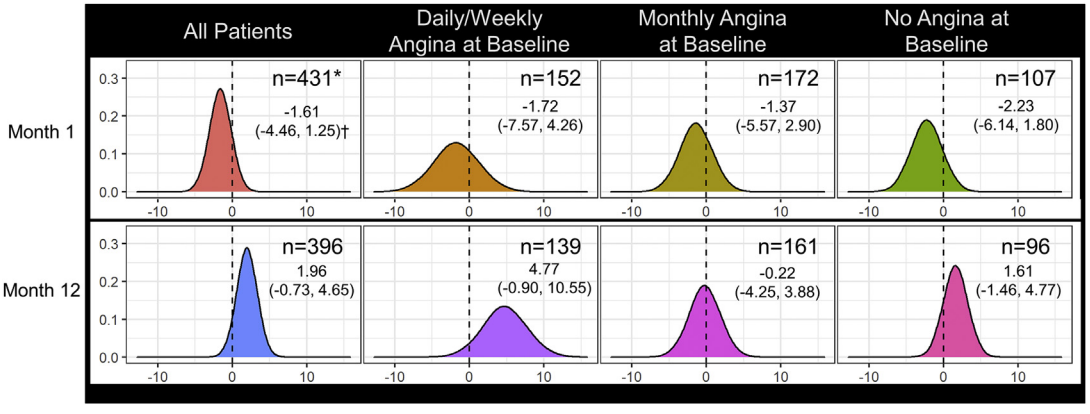
TABLE 2 SAQ-AF Scores According to Post-Percutaneous Coronary Intervention iFR

	iFR <0.95 (n = 285)	iFR ≥0.95 (n = 182)	Total (N = 467)	*P* Value
Baseline				
n	284	180	464	
Mean ± SD	71.69 ± 23.51	75.72 ± 21.43	73.25 ± 22.79	
Median (IQR)	70.00 (60.00-90.00)	80.00 (60.00-100.00)	80.00 (60.00-90.00)	
Anginal classification				0.29
Daily angina (SAQ-AF score 0-30)	7.7 (22/284)	3.9 (7/180)	6.3 (29/464)	
Weekly angina (SAQ-AF score 31-60)	28.2 (80/284)	30.0 (54/180)	28.9 (134/464)	
Monthly angina (SAQ-AF score 61-99)	41.2 (117/284)	38.9 (70/180)	40.3 (187/464)	
No angina (SAQ-AF score 100)	22.9 (65/284)	27.2 (49/180)	24.6 (114/464)	
12 mo				
n	247	151	398	
Mean ± SD	93.48 ± 14.76	95.83 ± 10.48	94.37 ± 13.33	
Median (IQR)	100.00 (100.00-100.00)	100.00 (100.00-100.00)	100.00 (100.00-100.00)	
Anginal classification				0.20[a]
Daily angina (SAQ-AF score 0-30)	0.8 (2/247)	0.0 (0/151)	0.5 (2/398)	
Weekly angina (SAQ AF score 31-60)	7.7 (19/247)	3.3 (5/151)	6.0 (24/398)	
Monthly angina (SAQ AF score 61-99)	13.0 (32/247)	15.9 (24/151)	14.1 (56/398)	
No angina (SAQ-AF score 100)	78.5 (194/247)	80.8 (122/151)	79.4 (316/398)	
Absolute change from baseline				
n	246	150	396	
Mean ± SD	21.42 ± 24.99	20.73 ± 21.83	21.16 ± 23.82	
Median (IQR)	20.00 (0.00-40.00)	20.00 (0.00-40.00)	20.00 (0.00-40.00)	
Absolute change from baseline ≥10	67.1 (165/246)	68.7 (103/150)	67.7 (268/396)	0.74
Absolute change from baseline ≥10 in patients with SAQ-AF score 0-60 at baseline	88.5 (77/87)	100.0 (52/52)	92.8 (129/139)	0.01[a]
Relative change from baseline				
n	245	150	395	
Mean ± SD	59.53 ± 138.98	45.62 ± 90.48	54.25 ± 122.90	
Median (IQR)	25.00 (0.00-66.67)	25.00 (0.00-66.67)	25.00 (0.00-66.67)	

Categorical variables were compared between treatment groups using the chi-square test. [a]Fisher exact *P* values for risk difference are provided when at least one cell has an expected frequency of 5 or less. Continuous variables were compared between treatment groups using the two-sample Student's *t*-test. If normality fails ($P < 0.05$), the distributions are compared using the Wilcoxon rank sum test.

iFR = instantaneous wave-free ratio; SAQ-AF = Seattle Angina Questionnaire angina frequency.

FIGURE 2 Bayesian Distributions of Differences in SAQ-AF Scores at 1 and 12 Months in Patients With Post-PCI iFR <0.95 Versus ≥0.95 in All Patients and According to Baseline Frequency of Angina



The x-axis represents change in Seattle Angina Questionnaire angina frequency (SAQ-AF) score from baseline to follow-up, with a positive value signifying less angina in patients with post-PCI IFR ≥0.95 compared with <0.95. At 12 months, angina tended to be less in patients with baseline daily or weekly angina (SAQ-AF score ≤60) who achieved post-PCI iFR ≥0.95. In contrast, angina frequency at 12-month follow-up was unrelated to post-PCI iFR in patients with baseline monthly or no angina. *Number of patients. †Posterior estimate (95% confidence interval). Abbreviations as in Figure 1.

TABLE 3 1-Year Clinical Events According to Post-PCI iFR

	iFR <0.95 (n = 285)	iFR ≥0.95 (n = 182)	Total (N = 467)	*P* Value
MACE[a]	5.7 (16)	1.8 (3)	4.2 (19)	0.04
Cardiac death or spontaneous MI	3.2 (9)	0 (0)	2.0 (9)	0.02
Death (ARC defined)	1.4 (4)	1.1 (2)	1.3 (6)	0.81
Cardiac	0.4 (1)	0.0 (0)	0.2 (1)	0.44
Vascular	0.0 (0)	0.0 (0)	0.0 (0)	NA
Noncardiovascular	1.1 (3)	1.1 (2)	1.1 (5)	0.93
MI, all	3.9 (11)	1.1 (2)	2.8 (13)	0.08
Spontaneous MI	2.8 (8)[b]	0.0 (0)	1.8 (8)	0.02
Periprocedural MI	1.1 (3)	1.1 (2)	1.1 (5)	0.96
Target vessel MI	2.1 (6)	1.1 (2)	1.7 (8)	0.42
Acute ECG pattern				
STEMI	0.4 (1)	0.0 (0)	0.2 (1)	0.43
NSTEMI	1.8 (5)	1.1 (2)	1.5 (7)	0.58
Chronic ECG pattern				
Q-wave MI	0.4 (1)	0.0 (0)	0.2 (1)	0.43
Non-Q-wave MI	1.8 (5)	1.1 (2)	1.5 (7)	0.58
Non-target vessel MI	0.7 (2)	0.0 (0)	0.4 (2)	0.27
Acute ECG pattern				
STEMI	0.0 (0)	0.0 (0)	0.0 (0)	NA
NSTEMI	0.7 (2)	0.0 (0)	0.4 (2)	0.27
Chronic ECG pattern				
Q-wave MI	0.0 (0)	0.0 (0)	0.0 (0)	NA
Non-Q-wave MI	0.7 (2)	0.0 (0)	0.4 (2)	0.27
Unknown vessel MI	1.1 (3)	0.0 (0)	0.7 (3)	0.17
Unknown or target vessel MI	3.2 (9)	1.1 (2)	2.4 (11)	0.16
Clinically driven revascularization	7.4 (21)	7.4 (13)	7.4 (34)	0.98
Target vessel revascularization	3.6 (10)	1.8 (3)	2.9 (13)	0.25
Target lesion revascularization	3.2 (9)	1.8 (3)	2.7 (12)	0.34
Non-target lesion revascularization	1.8 (5)	0.6 (1)	1.3 (6)	0.28
Non-target vessel revascularization	5.0 (14)	6.3 (11)	5.5 (25)	0.56
PCI revascularization	6.7 (19)	6.8 (12)	6.8 (31)	0.98
CABG revascularization	1.1 (3)	0.6 (1)	0.9 (4)	0.59

Values are Kaplan-Meier estimate % (n). [a]Cardiac death, spontaneous MI, or clinically driven target vessel revascularization. [b]Of the 8 spontaneous MIs, 3 were attributed to the target vessel, 2 were attributed to a nontarget vessel, and in 3 cases the vessel location from which the MI originated was indeterminate.

ARC = Academic Research Consortium; CABG = coronary artery bypass grafting; ECG = electrocardiographic; MACE = major adverse cardiovascular event(s); NA = not applicable; other abbreviations as in Table 1.

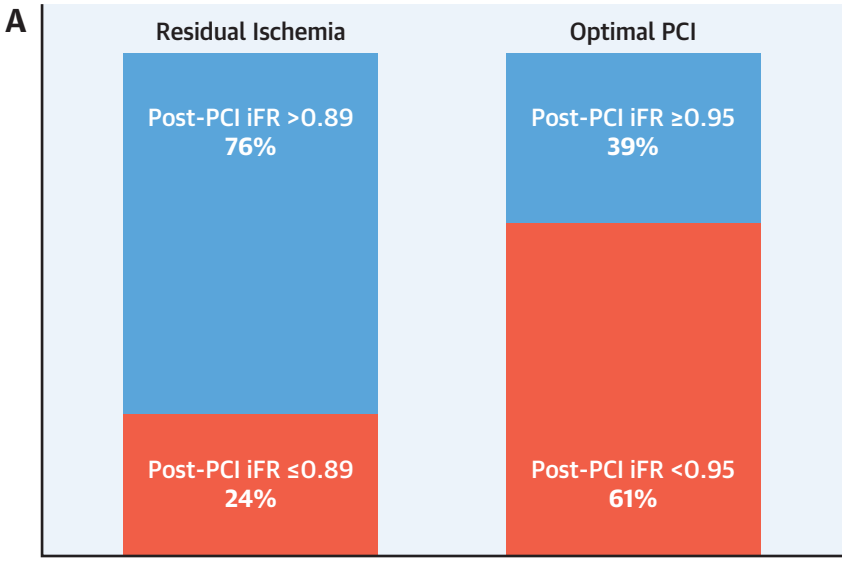
patients with iFR <0.95, the 1-year rate of major adverse cardiovascular events was 9 of 103 (8.7%) among patients with diffuse disease and 7 of 182 (3.8%) among patients with focal disease ($P = 0.09$).

DISCUSSION

In the DEFINE PCI study, despite angiographically successful PCI, residual post-PCI ischemia as assessed by iFR was common, occurring in 24% of patients. Post-PCI angiography poorly correlated with physiological measures, and residual pressure gradients were focal in >80% of cases. At 1-year follow-up in DEFINE PCI, post-PCI iFR ≥0.95 compared with <0.95 was associated with diminished anginal symptoms at 12 months, particularly in patients with significant angina (SAQ-AF score ≤60; ie, daily or weekly angina) at baseline. Furthermore, achieving post-PCI iFR ≥0.95 was associated with a lower composite rate of cardiac death, spontaneous MI, or clinically driven TVR during 1 year of follow-up. These findings should be considered hypothesis generating but suggest that the use of intracoronary physiology during PCI may improve clinical outcomes not only by assisting in the selection of appropriate lesions for intervention but also by potentially guiding the achievement of an optimal postprocedural result.

To date, the majority of research in coronary revascularization has focused on when to revascularize, with several physiological studies and data demonstrating improved clinical outcomes with physiologically guided revascularization reserved for lesions with FFR ≤0.80 or iFR ≤0.89 (6,7,10). Using physiology in this manner has been shown to reclassify coronary stenoses with substantial changes in treatment plans and improved clinical outcomes after PCI (11).

CENTRAL ILLUSTRATION **Rate of Residual Ischemia Post-PCI and Clinical Outcomes**



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(A) Residual ischemia and post-percutaneous coronary intervention (PCI) optimal PCI. **(B)** Cardiac death, spontaneous myocardial infarction (MI), or clinically driven target vessel revascularization at 1 year by post-instantaneous wave-free ratio (iFR). **(C)** Cardiac death or spontaneous MI at 1 year by post-iFR.

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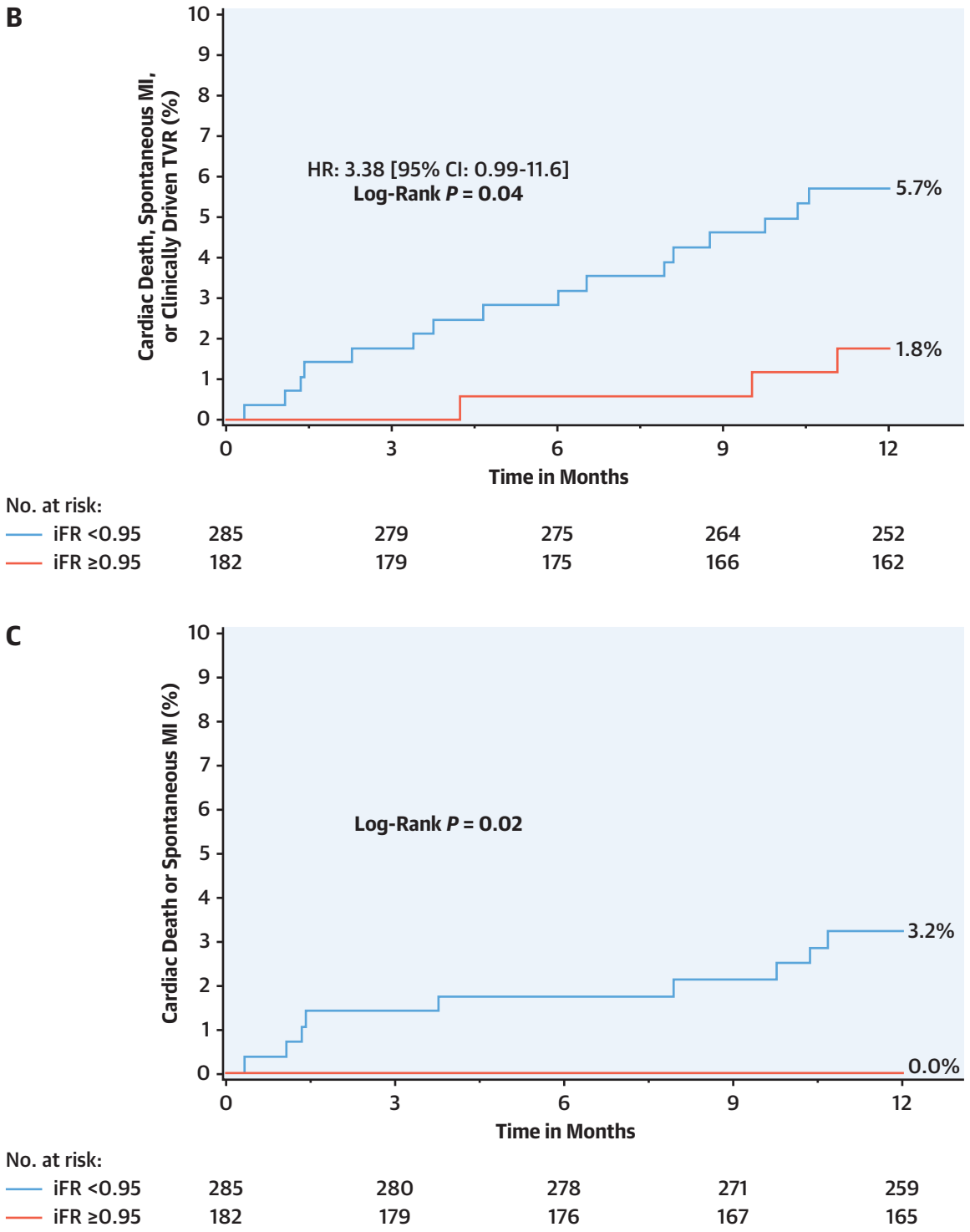
Conversely, despite positive emerging data, the use of coronary physiology to direct and potentially optimize acute PCI results is not widespread. Post-PCI FFR measures have been associated with clinical outcomes (12-14). A large meta-regression analysis of 59 studies with clinical outcomes demonstrated that higher post-PCI FFR was associated with reduced rates of repeat intervention and major adverse cardiovascular events (15). However, no large-scale randomized trials have been performed to evaluate the use of FFR to direct care post-PCI, and the clinical adoption of post-PCI physiology assessment remains limited. This may be due to the operational complexity of repeated administration of adenosine and difficulty with physiological interpretation of tandem lesions. iFR is a nonhyperemic, pressure wire-based method that simplifies repeated measurements, and iFR pull back assessment has been shown to discriminate tandem lesion physiology (16). In DEFINE PCI, using the standard cutoff of ≤0.89, post-PCI iFR detected residual ischemia in a substantial proportion (24%) of cases (8). In the present study, post-PCI iFR <0.95, present in 61% of cases, was the best discriminator of future adverse cardiovascular events and angina after contemporary drug-eluting stent implantation. These findings, identifying a post-PCI iFR target of ≥0.95 as the goal for an optimal PCI result, provide a new therapeutic target to further improve outcomes after PCI.

In addition to measuring post-PCI physiology, anatomical identification of the location of the reduction in pressure (eg, focal vs diffuse) will be critical to direct care to improve outcomes. In this regard, DEFINE PCI identified that 81.6% of patients with residual physiological ischemia (iFR ≤0.89) had one or multiple focal lesions. Additionally, a significant proportion of these focal lesions were within or adjacent to the stent. These findings highlight the integrated use of intracoronary imaging with stent optimization as key steps in converting the diagnostic information into therapeutic benefit for patients. However, caution is needed before targeting a post-PCI iFR value of 0.95 can be routinely recommended in patients. Specifically, adequately powered randomized trials are needed to evaluate the outcomes of post-PCI ischemia-driven interventions with prespecified treatment algorithms in patients with noncomplex and complex coronary anatomy. Specifically, the small but appreciable risk with optimization, including implantation of more stents in the vessel, must be warranted by reduced symptoms and improved clinical outcomes to change clinical practice.

CENTRAL ILLUSTRATION Continued



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STUDY LIMITATIONS. The optimal post-PCI iFR target value of 0.95 was identified post hoc and requires prospective validation with clinical outcomes before being adopted into clinical practice. The number of clinical events and follow-up SAQ-AF data in this 500-patient pilot study add some imprecision. DEFINE PCI excluded many high-risk patients and those with complex lesions in whom the rate of residual ischemia (iFR ≤0.89) may be >24% and in whom suboptimal results (iFR <0.95) may be as frequent as 61%, as seen in the present study. Of note, 2.8% of pull backs post-PCI were not analyzable or were poorly performed, a rate that will need to be accounted for in future studies. Finally, how frequently a target iFR ≥0.95 post-PCI may be achieved without complications is unknown and can be assessed only in an adequately powered randomized trial in which consecutive patients are enrolled. To that end, the ongoing DEFINE GPS (Distal Evaluation of Functional Performance With Intravascular Sensors to Assess the Narrowing Effect: Guided Physiologic Stenting; NCT04451044) trial is randomizing up to 3,212 patients with stable or unstable ischemic heart disease undergoing non-emergent PCI at up to 125 international sites to standard coronary intervention or standard intervention using iFR coregistration to prospectively guide stent placement, including post-PCI physiologic assessment, with the goal of optimizing target vessel iFR. Intravascular imaging will be allowed in both arms as per standard of care. The primary outcome measure is a composite of cardiac death, MI, ischemia-driven revascularization, or hospitalization for progressive or unstable angina at 2 years.

CONCLUSIONS

In the DEFINE PCI study, despite angiographically successful PCI, highly symptomatic patients at baseline with post-PCI iFR ≥0.95 had greater reductions in anginal symptoms and improvements in event-free survival at 1 year compared with patients with post-PCI iFR <0.95. On the basis of these findings, the safety and effectiveness of iFR guidance to detect post-PCI ischemia, normalize postintervention physiology, and reduce clinical events will be prospectively evaluated in the large-scale, multicenter DEFINE GPS trial.

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PERSPECTIVES

WHAT IS KNOWN? Coronary physiology is used to help determine when to perform revascularization. To date, postrevascularization physiological testing to determine the completeness of revascularization is not widely used, because of uncertainty regarding whether attempting to achieve optimal physiological revascularization in all cases safely improves long-term clinical outcomes.

WHAT IS NEW? Current angina relief postrevascularization is suboptimal, and strategies based on postrevascularization physiology and completeness may help determine how to optimize revascularization in individual patients.

WHAT IS NEXT? As this was a relatively short-term study pilot study (1-year follow-up), longer term prospectively driven studies are needed to demonstrate the value of postrevascularization physiology.

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KEY WORDS instantaneous wave-free ratio, percutaneous coronary intervention, physiological measurements, residual ischemia, Seattle Angina Questionnaire Angina Frequency

APPENDIX For supplemental figure, please see the online version of this paper.