JACC: CARDIOVASCULAR INTERVENTIONS VOL. 15, NO. 24, 2022

Differential Improvement in Angina and Health-Related Quality of Life After PCI in Focal and Diffuse Coronary Artery Disease

Carlos Collet, MD, PhD,[a,*] Damien Collison, MBBCh,[b,c,*] Takuya Mizukami, MD, PhD,[a,d,*] Peter McCartney, MBChB,[b,c] Jeroen Sonck, MD, PhD,[a] Thomas Ford, MD, PhD,[b,c] Daniel Munhoz, MD, PhD,[a] Colin Berry, MD, PhD,[b,c] Bernard De Bruyne, MD, PhD,[a,e] Keith Oldroyd, MBChB[b]

ABSTRACT

BACKGROUND An increase in fractional flow reserve (FFR) after percutaneous coronary intervention (PCI) is associated with improvement in angina. Coronary artery disease (CAD) patterns (focal vs diffuse) influence the FFR change after stenting and may predict angina relief.

OBJECTIVES The aim of this study was to investigate the differential improvement in patient-reported outcomes after PCI in focal and diffuse CAD as defined by the pullback pressure gradient (PPG).

METHODS This is a subanalysis of the TARGET-FFR (Trial of Angiography vs. pressure-Ratio-Guided Enhancement Techniques–Fractional Flow Reserve) randomized clinical trial. The 7-item Seattle Angina Questionnaire (SAQ-7) was administered at baseline and 3 months after PCI. The PPG index was calculated from manual pre-PCI FFR pullbacks. The median PPG value was used to define focal and diffuse CAD. Residual angina was defined as an SAQ-7 score <100.

RESULTS A total of 103 patients were analyzed. There were no differences in the baseline characteristics between patients with focal and diffuse CAD. Focal disease had larger increases in FFR after PCI than patients with diffuse disease (0.30 ± 0.14 vs 0.19 ± 0.12; $P < 0.001$). Patients with focal disease who underwent PCI for focal CAD had significantly higher SAQ-7 summary scores at follow-up than those with diffuse CAD (87.1 ± 20.3 vs 75.6 ± 24.4; mean difference = 11.5 [95% CI: 2.8-20.3]; $P = 0.01$). After PCI, residual angina was present in 39.8% but was significantly less in those with treated focal CAD (27.5% vs 51.9%; $P = 0.020$).

CONCLUSIONS Residual angina after PCI was almost twice as common in patients with a low PPG (diffuse disease), whereas patients with a high PPG (focal disease) reported greater improvement in angina and quality of life. The baseline pattern of CAD can predict the likelihood of angina relief. (Trial of Angiography vs. pressure-Ratio-Guided Enhancement Techniques–Fractional Flow Reserve [TARGET-FFR]; NCT03259815) (J Am Coll Cardiol Intv 2022;15:2506–2518) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Cardiovascular Center, OLV Hospital, Aalst, Belgium; [b]West of Scotland Regional Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, United Kingdom; [c]British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [d]Department of Clinical Pharmacology, Showa University, Tokyo, Japan; and the [e]Department of Cardiology, Lausanne University Center Hospital, Switzerland. *Drs Collet, Collison, and Mizukami contributed equally to this work.

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 June 23, 2022; revised manuscript received August 16, 2022, accepted September 27, 2022.

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2022.09.048

Ischemia relating to obstructive epicardial coronary artery disease (CAD) is a common cause of angina pectoris. The frequency and severity of anginal symptoms have been associated with cardiovascular mortality.[1] Revascularization, either through percutaneous coronary intervention (PCI) or coronary artery bypass grafting, can effectively reduce angina.[2] Nevertheless, approximately 1 in 4 patients remain symptomatic after PCI.[3] Residual angina impairs quality of life and portends a worse prognosis.[4]

The magnitude of change in fractional flow reserve (FFR) after PCI predicts improvements in angina.[5] Moreover, large gains in FFR after PCI are associated with freedom from angina.[6] The baseline CAD pattern influences the degree of FFR change achievable through stenting. PCI for focal CAD frequently yields high post-PCI FFR values, whereas more modest improvements can be expected when treating diffuse disease.[7] Therefore, the likelihood of successful angina relief from PCI can be anticipated by the baseline pattern of CAD. Nevertheless, the definition of diffuse CAD is not standardized and most often relies only on visual assessment, limiting its reliability and reproducibility.[8-11]

SEE PAGE 2519

We recently showed that a pressure pullback maneuver could quantify the longitudinal distribution of epicardial resistance. The pullback pressure gradient (PPG) is a novel metric that complements FFR and quantitatively defines CAD patterns (focality or diffuseness) on a scale from 0 to 1.[12,13] In the present study, we sought to investigate the differential effects of PCI in focal and diffuse CAD as defined by the preprocedural PPG on patient-reported outcomes.

METHODS

STUDY DESIGN. This study is a subanalysis of the TARGET-FFR (Trial of Angiography vs. pressure-Ratio-Guided Enhancement Techniques-Fractional Flow Reserve) randomized clinical trial. Briefly, TARGET-FFR was a prospective, single-center, randomized, controlled, parallel-group, blinded clinical trial conducted at the Golden Jubilee National Hospital and registered at ClinicalTrials.gov (NCT03259815).[5,14] All patients signed informed consent before their PCI. After angiographically successful PCI for either stable angina or medically stabilized non-ST-segment elevation myocardial infarction, eligible patients were randomized to an FFR pull back-guided PCI to a physiology-guided incremental optimization strategy (PIOS), using an FFR pullbacks, or a control group. Coronary physiology data were analyzed by a core laboratory (CoreAalst BV, Aalst, Belgium). There was no significant difference between groups in the primary endpoint of the proportion of patients with a final post-PCI FFR ≥0.90 (PIOS − control = 10%; 95% CI: −1.84 to 21.91; $P = 0.099$).

The objective of the present analysis was to compare the effectiveness of PCI in terms of angina relief and quality of life improvement in in patients with focal and diffuse CAD as defined by the PPG. For this purpose, patients with both pre-PCI FFR pullbacks (required for PPG calculation) and follow-up patient-reported outcome measure questionnaires were eligible for inclusion. A list of the inclusion and exclusion criteria is shown in Supplemental Table 1. The study received the proper ethical oversight.

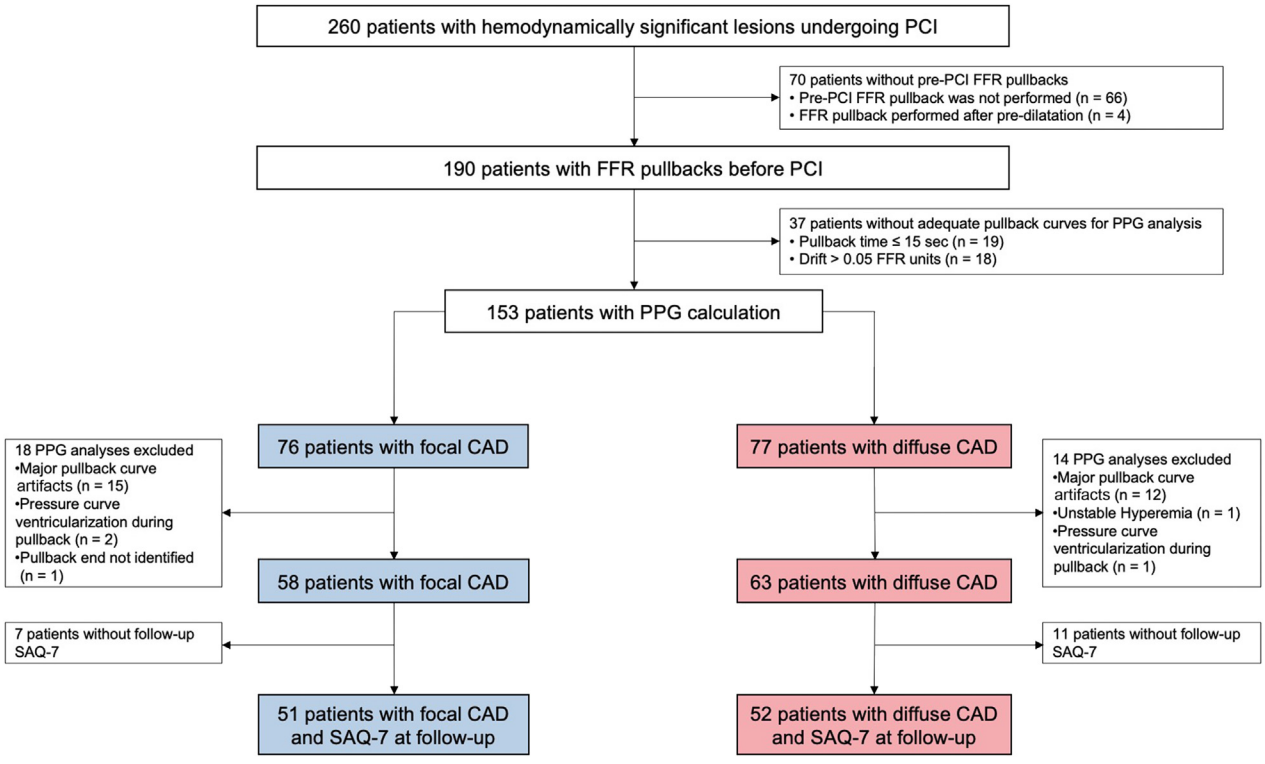
ANGINA AND QUALITY OF LIFE ASSESSMENTS. The 7-item Seattle Angina Questionnaire (SAQ-7) and the EuroQol 5-level 5-dimensional questionnaire (EQ-5D-5L) were administered at baseline and 3 months after PCI. The questionnaires were administered by telephone or mail by a research nurse blinded to the physiology results. The SAQ-7 addresses 3 domains (ie, angina frequency, physical limitation, and quality of life) that are combined in a summary score. Higher scores indicate better health status. A score of 100 in the angina frequency domain denotes freedom from angina.[15,16] The EQ-5D-5L consists of 5 dimensions (ie, mobility, self-care, usual activities, pain and discomfort, and anxiety and depression), each of which has 5 severity levels in each dimension; level 1 indicates no problem, and level 5 indicates extreme problems. The EQ-5D-5L is then summarized as a country-specific weighted health index (0-1), with higher values representing worse health status.

PROCEDURE. Details of the coronary physiology measurements and PCI procedures have been published previously.[5] FFR measurements were performed using the PressureWire X Guidewire (Abbott Laboratories). After the administration of a 200-μg bolus of intracoronary nitrate, the pressure wire sensor was positioned at the tip of the guide catheter and equalized with the aortic pressure. The pressure wire was then advanced to position the sensor in the distal third of the vessel. Hyperemia was induced by adenosine infusion into an antecubital vein at a rate of 140 μg/kg/min. Coronary flow reserve (CFR) was assessed using the bolus thermodilution technique. FFR pullback maneuvers were performed manually at a constant speed for 20 to 30 seconds. The specifics of the PCI procedure, including the use of intracoronary

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve
CAD = coronary artery disease
CFR = coronary flow reserve
EQ-5D-5L = EuroQol 5-level 5-dimensional questionnaire
FFR = fractional flow reserve
PCI = percutaneous coronary intervention
PIOS = physiological incremental optimization strategy
PPG = pullback pressure gradient
SAQ-7 = 7-item Seattle Angina Questionnaire

FIGURE 1 TARGET-FFR Pullback Pressure Gradient (PPG) Study Flowchart



The total number of patients included in the TARGET-FFR (Trial of Angiography vs. pressure-Ratio-Guided Enhancement Techniques-Fractional Flow Reserve) randomized clinical trial and in the present analysis. Focal coronary artery disease (CAD) was defined as a pullback pressure gradient (PPG) value ≥ 0.66 and diffuse CAD as PPG < 0.66. FU = follow-up; PCI = percutaneous coronary intervention; SAQ = Seattle Angina Questionnaire.

imaging, were at the operator's discretion. After angiographically successful PCI, a blinded coronary physiology assessment was repeated. Patients randomized to the PIOS group with post-PCI FFR <0.90 were eligible for additional intervention based on an assessment of the post-PCI FFR pullback. In the control group, post-PCI FFR and pullback information were acquired but concealed from the operator. The final coronary physiology results were not disclosed to patients.

PPG. The PPG index was calculated post hoc from the manual pre-PCI FFR pullback recordings using a commercially available console (Coroflow v3.5, Coroventis Research AB). The PPG combines 2 parameters extracted from FFR pullback curves (ie, the maximal pressure gradient over 20% of the pullback duration and the length of functional disease) to provide a value from 0 to 1. PPG values close to 1.0 represent focal disease, and values approaching 0 indicate diffuse CAD.[13] The following exclusion criteria were applied to the recordings: the absence of a dicrotic notch from the pressure waveforms, ventricularization, drift of more than 0.05 FFR units on the pullback to the guide catheter, unstable hyperemic conditions during the pullback maneuver, pullback duration <15 seconds, and pullback curves with major artifacts. To adjust for baseline disease severity, delta FFR was normalized by pre-PCI FFR (ie, post-PCI FFR − pre-PCI FFR divided by 1 − pre-PCI FFR). The median value of the PPG was used to differentiate focal from diffuse CAD.

STATISTICAL ANALYSIS. Data are expressed as mean ± SD and median (IQR) for normally and non-normally distributed data, respectively. Categoric variables are expressed as frequencies and percentages (%). Continuous variables were compared using the Student's *t*-test (or Mann-Whitney *U* tests as appropriate), and categorical variables were compared using the chi-square or Fisher exact test as appropriate. The SAQ-7 and EQ-5D-5L scores are reported stratified by CAD patterns. The SAQ-7 summary score was the primary outcome. The SAQ-7 summary score and scores from its component domains were used as continuous variables and

compared between patients with diffuse and focal CAD. In addition, SAQ-7 scores were categorized into daily or weekly, monthly, or none for the angina frequency domain and as poor or fair, good, or excellent health status for the physical limitation and quality of life domains. We also estimated the probability of being angina free as a function of baseline angina frequency. For this analysis, the model for the SAQ-7 angina frequency score was augmented by the inclusion of 2-way interaction terms (ie, CAD pattern and baseline SAQ-7 score) to estimate the probability of being angina free (ie, SAQ-7 angina frequency score equal to 100) at follow-up; restricted cubic splines were used to allow for nonlinear effects of baseline.[17] The predictors of residual angina were assessed using univariate and multivariate regression analyses. Variables included age, sex, hypertension, diabetes mellitus, renal function, SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) score, pre-PCI FFR, and PPG. A 2-sided *P* value of 0.05 or less was considered to indicate statistical significance. All statistical analyses were performed using R statistical software (R Foundation for Statistical Computing).

RESULTS

Between February 22, 2018, and November 22, 2019, 721 patients were screened, and 260 were randomized; among these, 190 patients had pre-PCI FFR pullback. After excluding pullback recordings of inadequate quality and patients without health status questionnaires at follow-up, 103 patients (51 with focal and 52 with diffuse disease) were included in the present analysis. The study flowchart is shown in **Figure 1**. The median PPG was 0.66 (IQR: 0.55-77). There were no differences in the baseline clinical characteristics between patients with focal and diffuse CAD (**Table 1**).

TABLE 1 Clinical Characteristics Stratified by Coronary Artery Disease Patterns

	Overall (N = 103)	Focal (PPG ≥0.66) (n = 51)	Diffuse (PPG <0.66) (n = 52)	*P* Value
Female	14 (13.6)	5 (9.8)	9 (17.3)	0.410
Age, y	60.61 ± 8.11	60.24 ± 7.25	60.98 ± 8.93	0.643
BMI	29.39 ± 4.62	28.96 ± 4.57	29.81 ± 4.67	0.351
Family history of CAD	70 (68.0)	36 (70.6)	34 (65.4)	0.723
Smoking	70 (68.0)	37 (72.5)	33 (63.5)	0.437
Hypertension	45 (43.7)	22 (43.1)	23 (44.2)	1.000
Dyslipidemia	58 (56.3)	31 (60.8)	27 (51.9)	0.479
Diabetes	21 (20.4)	8 (15.7)	13 (25.0)	0.353
Insulin dependent	2 (9.5)	1 (12.5)	1 (7.7)	1.000
Renal insufficiency	2 (1.9)	1 (2.0)	1 (1.9)	1.000
Previous PCI	47 (45.6)	18 (35.3)	29 (55.8)	0.059
Angina	88 (85.4)	42 (82.4)	46 (88.5)	0.549
CCS class				0.148
CCS 1	23 (26.1)	15 (35.7)	8 (17.4)	
CCS 2	41 (46.6)	17 (40.5)	24 (52.2)	
CCS 3	24 (27.3)	10 (23.8)	14 (30.4)	
Medications				
Any antiplatelet	102 (99.0)	50 (98.0)	52 (100.0)	0.992
DAPT	79 (76.7)	41 (80.4)	38 (73.1)	0.519
Statins	99 (96.1)	49 (96.1)	50 (96.2)	1.000
Beta-blocker	96 (93.2)	48 (94.1)	48 (92.3)	1.000
ACE inhibitor	76 (73.8)	37 (72.5)	39 (75.0)	0.953
ARB	8 (7.8)	4 (7.8)	4 (7.7)	1.000
Calcium-channel blocker	20 (19.4)	8 (15.7)	12 (23.1)	0.485
Nitrates	29 (28.2)	10 (19.6)	19 (36.5)	0.091
GTN spray use	55 (53.4)	23 (45.1)	32 (61.5)	0.140
Frequency of GTN use				0.394
Daily	9 (16.4)	3 (13.0)	6 (18.8)	
Weekly	32 (58.2)	12 (52.2)	20 (62.5)	
Monthly	14 (25.5)	8 (34.8)	6 (18.8)	
Diuretics	10 (9.7)	4 (7.8)	6 (11.5)	0.764
Oral anticoagulation	7 (6.8)	3 (5.9)	4 (7.7)	1.000

Values are n (%) or mean ± SD unless otherwise indicated.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; DAPT = dual antiplatelet therapy; GTN = glyceryl trinitrate; PCI = percutaneous coronary intervention; PPG = pullback pressure gradient.

PROCEDURAL OUTCOMES. Patients with focal disease (PPG ≥0.66) had more angiographically severe lesions than diffuse disease (percentage diameter stenosis: 65.2% ± 16.4% vs 57.6% ± 14.2%; $P = 0.013$). However, the functional severity of the disease was similar between focal and diffuse disease (FFR: 0.59 ± 0.16 vs 0.64 ± 0.11; $P = 0.118$). Baseline CFR was negatively correlated with PPG (Supplemental Figure 1). Focal CAD was treated with shorter and fewer stents than diffuse disease (37.4 ± 19.2 mm vs 47.7 ± 22.6 mm; $P = 0.015$ and 1.3 ± 0.5 stents per vessel vs 1.6 ± 0.8 stents per vessel; $P = 0.022$; **Table 2**). The relationship between PPG and stent length is shown in Supplemental Figure 2.

Patients with focal disease attained higher post-PCI FFR compared with diffuse disease (0.89 ± 0.07 vs 0.83 ± 0.07; $P < 0.001$) and a greater change in FFR after PCI (0.30 ± 0.14 vs 0.19 ± 0.12 U; $P < 0.001$). As a continuous variable, the PPG showed significant correlations with post-PCI FFR and delta FFR (**Figure 2**). The improvement in CFR was also significantly higher in patients with focal CAD (delta CFR: 2.1 ± 1.5 vs 0.9 ± 1.7; $P = 0.001$).

PATIENT-REPORTED OUTCOMES. Baseline. At baseline, there were no differences in angina frequency, physical limitation, or quality of life between patients with focal or diffuse CAD. FFR was associated with baseline angina in symptomatic patients ($P = 0.037$) (Supplemental Figure 3). The clinical and procedural characteristics stratified by angina status at baseline

TABLE 2 Procedural Characteristics Stratified by Coronary Artery Disease Patterns

	Overall (N = 103)	Focal (PPG ≥0.66) (n = 51)	Diffuse (PPG <0.66) (n = 52)	*P* Value
Diameter stenosis, %	61.4 ± 15.7	65.2 ± 16.4	57.6 ± 14.3	0.013
Lesion length	11.6 ± 5.3	10.9 ± 4.9	12.3 ± 5.6	0.157
Reference vessel diameter, mm	2.8 ± 0.6	2.9 ± 0.6	2.8 ± 0.6	0.580
Vessel type				0.001
LAD	65	20 (39.2)	45 (86.5)	
LCX	14	11 (21.6)	3 (5.8)	
RCA	24	20 (39.2)	4 (7.7)	
AHA/ACC lesion type				0.195
A	18 (17.5)	8 (15.7)	10 (19.2)	
B	39 (37.9)	24 (47.1)	15 (28.8)	
B2	41 (39.8)	18 (35.3)	23 (44.2)	
C	5 (4.9)	1 (2.0)	4 (7.7)	
SYNTAX score	11.60 ± 8.20	9.21 ± 7.49	13.94 ± 8.26	0.003
Jeopardy score	5.18 ± 3.06	4.92 ± 3.08	5.44 ± 3.05	0.399
Pd/Pa	0.81 ± 0.14	0.80 ± 0.16	0.81 ± 0.12	0.665
FFR	0.61 ± 0.14	0.59 ± 0.16	0.64 ± 0.11	0.118
CFR	2.14 ± 0.95	1.83 ± 0.58	2.42 ± 1.13	0.002
PPG	0.65 ± 0.14	0.77 ± 0.06)	0.54 ± 0.09	<0.001
Predilatation	103 (100.0)	51 (100.0)	52 (100.0)	NA
Postdilatation	101 (98.1)	49 (96.1)	52 (100.0)	0.467
Intravascular imaging	20 (19.4)	4 (7.8)	16 (30.8)	0.007
PIOS[a]	53 (51.5)	26 (51.0)	27 (51.9)	1.000
Number of stents, per vessel	1.0 [1.0-2.0]	1.0 [1.0-2.0]	1.5 [1.0-2.0]	0.036
Stent diameter	3.20 ± 0.41	3.23 ± 0.44	3.17 ± 0.38	0.443
Total stent length, mm	42.61±21.51	37.43±19.20	47.69±22.61	0.015
Residual diameter stenosis	14.82 ± 9.13	14.78 ± 9.54	14.86 ± 8.80	0.962
Residual SYNTAX score	2.16 ± 4.02	2.76 ± 4.84	1.57 ± 2.92	0.146
Post-PCI Pd/Pa	0.93 ± 0.05	0.96 ± 0.05	0.91 ± 0.04	<0.001
Post-PCI FFR	0.86 ± 0.08	0.89 ± 0.07	0.83 ± 0.07	<0.001
Post-PCI CFR	3.60 ± 1.83	3.88 ± 1.66	3.30 ± 1.97	0.118
Delta FFR	0.25 ± 0.14	0.30 ± 0.14	0.19 ± 0.12	<0.001
Delta FFR normalized, %	61 ± 22	71 ± 19	50 ± 20	<0.001
Delta CFR	1.45 ± 1.70	2.06 ± 1.50	0.89 ± 1.71	0.001
Delta CFR normalized, %	88 ± 103	129 ± 109	50 ± 82	<0.001

Values are mean ± SD, n (%), or median [IQR] unless otherwise indicated. [a]Randomized to PIOS.

ACC = American College of Cardiology; AHA = American Heart Association; CFR = coronary flow reserve; FFR = fractional flow reserve; LAD = left anterior descending artery; LCX = left circumflex artery; NA = not applicable; Pa = aortic pressure; Pd = distal pressure; PIOS = physiological incremental optimization strategy; PPG = pullback pressure gradient; RCA = right coronary artery; SYNTAX = SYNergy between PCI with TAXUS and Cardiac Surgery.

are shown in Supplemental Table 2. The mean baseline SAQ-7 summary score was 66.1 ± 26.0 in focal CAD and 57.6 ± 25.6 in diffuse disease ($P = 0.099$). Overall, 44.7% of participants had daily or weekly angina, 26.2% had monthly angina, and 29.1% had no angina before PCI, and there were no differences between patients with focal and diffuse disease.

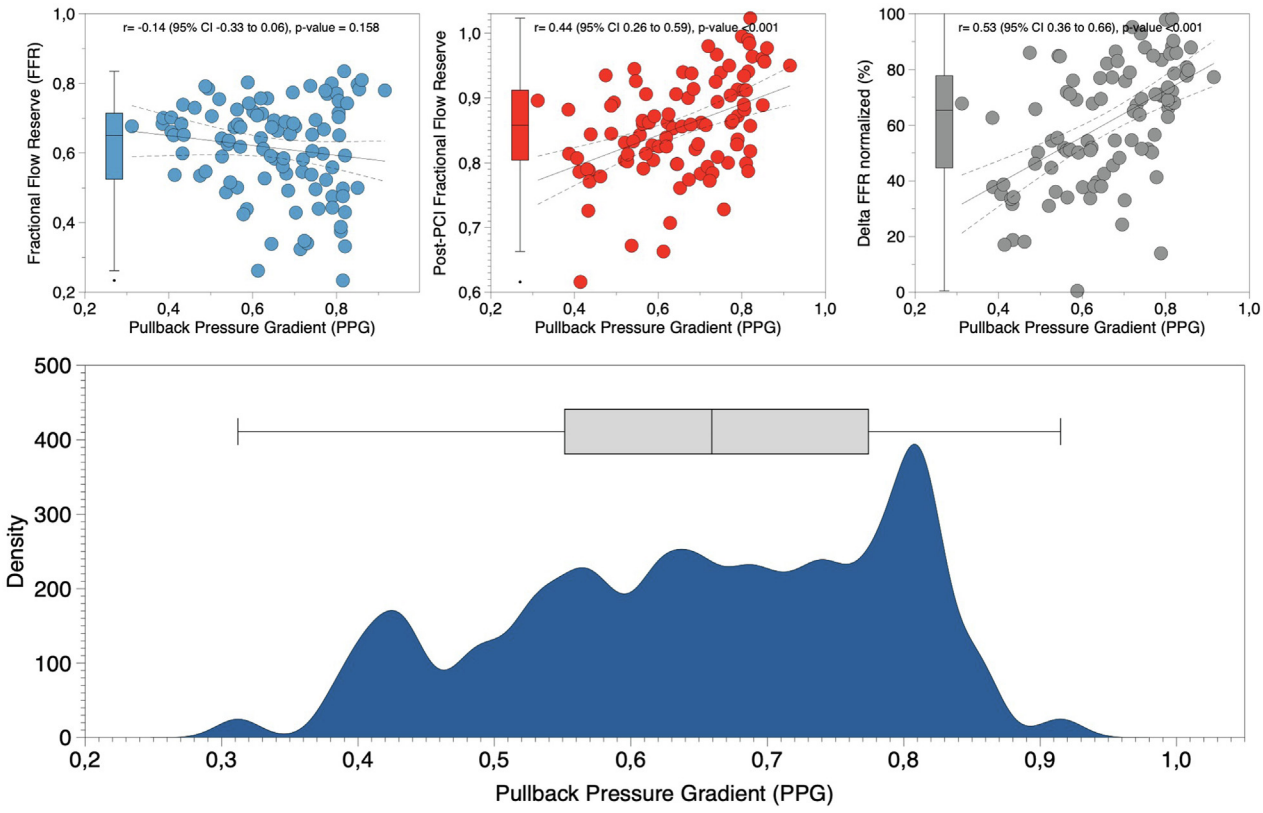
Follow-up after PCI. After PCI, residual angina was present in 39.8% of patients and was significantly lower in patients with focal CAD (27.5% focal vs 51.9% diffuse; $P = 0.020$). Two sensitivity analyses addressing the rate of residual angina after PCI in patients with single-vessel disease and with stable angina are shown in Supplemental Table 3. Patients with focal CAD reported less angina, less physical limitation, and better quality of life than patients with diffuse CAD (**Table 3, Figure 3**). The SAQ-7 summary score for patients with focal CAD was significantly higher than diffuse CAD (87.1 ± 20.3 vs 75.6 ± 24.4; mean difference = 11.5 SAQ-7 points [95% CI: 2.8-20.3]; $P = 0.010$). Similar magnitudes of benefit were observed in the individual SAQ-7 domains. Levels of daily or weekly and monthly angina were significantly lower in patients with focal CAD (**Figure 4**). Among patients with angina at baseline, PPG predicted a post-PCI angina-free status with an area under the curve (AUC) of 0.65 (95% CI: 0.52-0.78) and a best PPG cutoff of 0.68 (Supplemental Figure 1). The predictive capacity of the PPG for freedom from angina at follow-up adjusted by other clinical and procedural characteristics is shown in Supplemental Table 3. Diabetes mellitus, FFR at baseline, and PPG were independently associated with angina after PCI. Moreover, adding FFR and PPG to the baseline clinical characteristics significantly improved the predictive capacity for freedom from angina after PCI with an AUC of 0.81 ($P = 0.03$ vs clinical model; Supplemental Table 4, Supplemental Figure 4). There was a higher probability of being free from angina in patients with focal CAD compared with diffuse CAD. The difference was larger among patients who had angina at baseline but was minimal among those who were asymptomatic before PCI (**Figure 5**).

Health-related quality of life. At baseline, there were no differences in mobility, self-care, usual activities, pain, or discomfort between patients with focal and diffuse CAD (**Table 4**). At baseline, the EQ-5D-5L index was similar between focal and diffuse disease (0.80 ± 0.21 vs 0.75 ± 0.21; $P = 0.251$). After PCI, patients with focal disease reported increased mobility, self-care, and usual activities, and reduced pain and discomfort compared with patients with diffuse CAD. There were no differences in the level of anxiety and depression after PCI between patients with focal and diffuse CAD (Supplemental Figure 5). The EQ-5D-5L index was significantly higher in patients with focal CAD treated with PCI compared with patients with diffuse disease (0.9 ± 0.2 vs 0.8 ± 0.3; $P = 0.004$). The summary of the study findings is shown in the **Central Illustration**.

DISCUSSION

This study presents a novel approach for stratifying patients with hemodynamically significant CAD into focal and diffuse disease. These 2 phenotypes are

FIGURE 2 **Distribution of the PPG and its Correlation With Pre-PCI FFR, Post-PCI FFR, and Delta FFR**



The bottom part of the figure shows the distribution of pullback pressure gradient (PPG) values; the horizontal gray box plot shows the median value (0.66), range, and IQR. The top part of the figure shows the correlation between the PPG (x-axes) and, from left to right, pre-percutaneous coronary intervention (PCI) fractional flow reserve (FFR), post-PCI FFR, and delta FFR. The PPG was significantly correlated with post-PCI FFR and delta FFR.

differentially associated with the likelihood of symptom relief post-PCI. We found that patients with focal CAD (PPG closer to 1) treated with PCI had a more favorable prognosis in terms of angina relief and improvement in quality of life. In contrast, more than one-half of the patients with diffuse disease (PPG closer to 0) remained symptomatic after PCI. We also found that PPG was not associated with anginal symptoms at baseline, indicating that the severity of angina is associated with flow-limiting CAD rather than its distribution.

PCI reduces epicardial resistance, and the resultant increase in myocardial perfusion ameliorates anginal symptoms.[4] In the present study, PCI was more effective in cases with focal pressure gradients resulting in higher post-PCI FFR and a greater change in FFR than in cases with diffuse disease. The PPG determined 27% of the change in coronary flow with PCI. In other words, the improvement in myocardial perfusion achieved by PCI was partly determined by the baseline CAD pattern. Furthermore, adding FFR and PPG to clinical characteristics significantly improved the predictive capacity for freedom from angina, and both FFR and PPG remained independently associated with angina after PCI. This finding highlights the importance of integrating CAD patterns derived from coronary physiology to define the appropriateness of PCI. The quantitative and continuous nature of PPG allows the determination of cutoffs to predict improvements in angina, which may prove useful in clinical practice to predict the expected benefit of the intervention.

Structural and functional alterations of coronary circulation have been proposed as causes of persistent angina after PCI.[18] In the present study, we investigated the impact of diffuse CAD on patient-reported outcomes. After PCI, we found that diffuse CAD was associated with significantly more residual angina. In the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial, patients randomized to

TABLE 3 The SAQ-7 at Baseline and Follow-Up Stratified by Coronary Artery Disease Patterns

	Overall (N = 103)	Focal (PPG ≥0.66) (n = 51)	Diffuse (PPG <0.66) (n = 52)	*P* Value
Baseline SAQ-7				
Physical limitation score	67.8 ± 27.6	73.3 ± 27.9	62.8 ± 26.6	0.061
Angina frequency	69.5 ± 27.6	73.5 ± 26.9	65.6 ± 28.0	0.145
Quality of life	48.2 ± 31.5	52.2 ± 31.8	44.2 ± 31.0	0.200
Summary score	61.8 ± 26.0	66.1 ± 26.0	57.6 ± 25.6	0.099
Physical limitation				0.127
Poor or fair	24 (25.3)	10 (22.2)	14 (28.0)	
Good	24 (25.3)	8 (17.8)	16 (32.0)	
Excellent	47 (49.5)	27 (60.0)	20 (40.0)	
Angina frequency				0.511
Daily or weekly	46 (44.7)	20 (39.2)	26 (50.0)	
Monthly	27 (26.2)	14 (27.5)	13 (25.0)	
None	30 (29.1)	17 (33.3)	13 (25.0)	
Quality of life				0.232
Poor or fair	53 (51.5)	22 (43.1)	31 (59.6)	
Good	20 (19.4)	11 (21.6)	9 (17.3)	
Excellent	30 (29.1)	18 (35.3)	12 (23.1)	
Follow-up SAQ-7				
Physical limitation score	79.9 ± 26.8	85.0± 24.4	74.0 ± 28.4	0.049
Angina frequency	85.5 ± 22.6	91.8±17.1	79.4 ± 25.7	0.005
Quality of life	78.3 ± 28.3	84.3 ± 24.5	72.4 ± 30.8	0.032
Summary score	81.3 ± 23.1	87.1 ± 20.3	75.6 ± 24.4	0.010
Physical limitation				0.242
Poor or fair	12 (13.0)	4 (8.2)	8 (18.6)	
Good	13 (14.1)	6 (12.2)	7 (16.3)	
Excellent	67 (72.8)	39 (79.6)	28 (65.1)	
Angina frequency				0.008
Daily or weekly	20 (19.4)	4 (7.8)	16 (30.8)	
Monthly	21 (20.4)	10 (19.6)	11 (21.2)	
None	62 (60.2)	37 (72.5)	25 (48.1)	
Quality of life				0.211
Poor or fair	14 (13.6)	4 (7.8)	10 (19.2)	
Good	15 (14.6)	7 (13.7)	8 (15.4)	
Excellent	74 (71.8)	40 (78.4)	34 (65.4)	
Residual angina	41 (39.8)	14 (27.5)	27 (51.9)	0.020

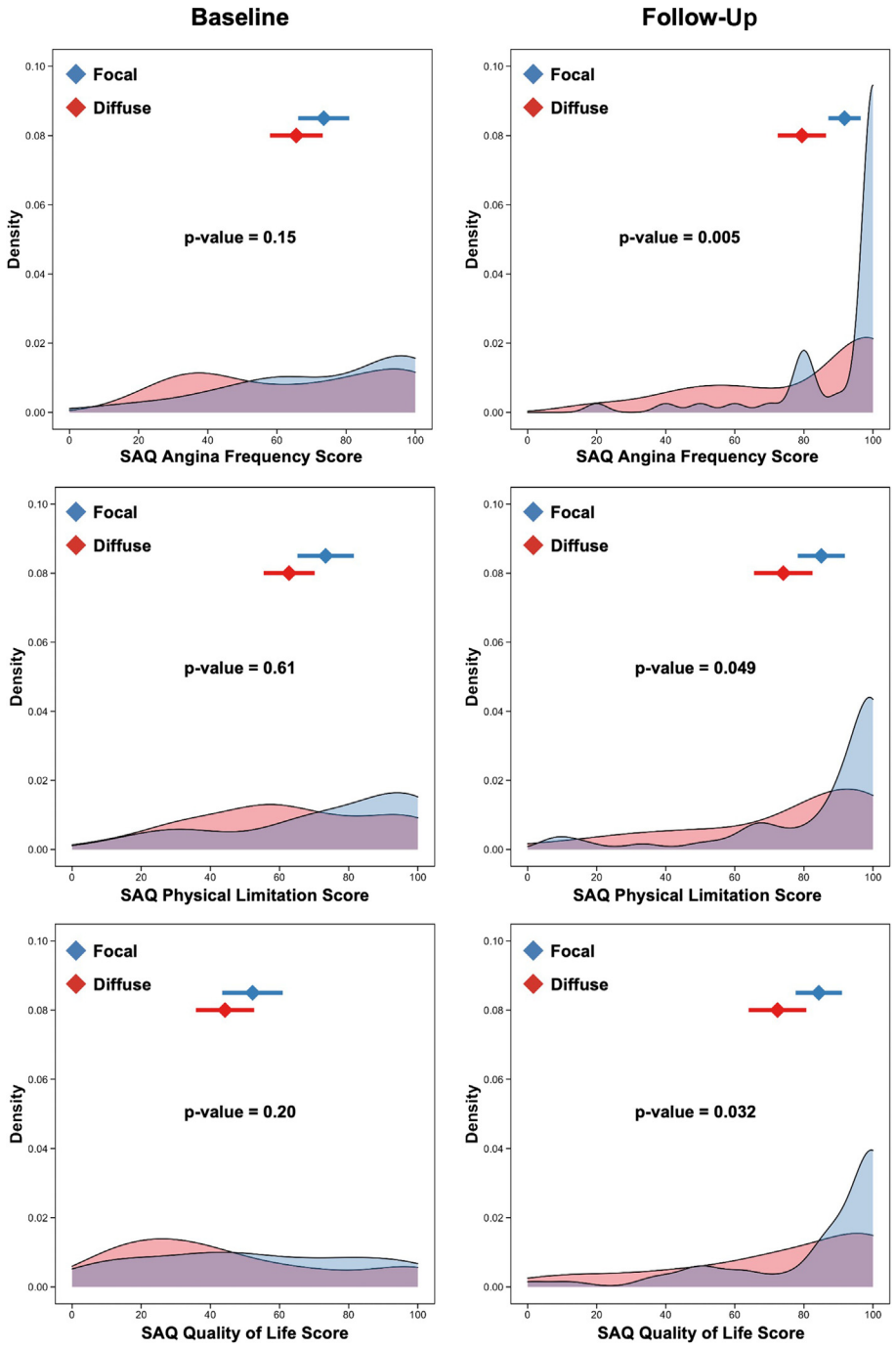
Values are mean ± SD or n (%) unless otherwise indicated.
PPG = pullback pressure gradient; SAQ-7 = 7-item Seattle Angina Questionnaire.

the invasive strategy had greater improvement in angina than those assigned to the conservative strategy. The benefit of the invasive strategy was captured by a difference in SAQ-7 summary scores of 2.9 points (84.7 ± 16 invasive arm vs 81.8 ± 17 conservative arm at 3 months).[2] In the present study, the difference in the SAQ-7 summary score between patients with focal and diffuse CAD was 11.5 points during the same follow-up period. The benefit of revascularization was 3 times higher in patients with focal CAD than in patients with diffuse disease. Moreover, the proportion of symptomatic patients was comparable between the ISCHEMIA trial (65%) and the present study (71%). In symptomatic participants, the observed difference in the probability of being free from angina between focal and diffuse CAD was greater, similar to the larger effect on patient-reported outcomes observed between the invasive strategy versus the conservative strategy in the ISCHEMIA trial.[2]

The ORBITA (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) trial investigated the impact of CAD patterns derived from visual assessment of focal disease on the resting instantaneous wave-free ratio pullback curve. This approach identified patients with focal CAD who benefited from PCI in terms of ischemia reduction assessed by stress echocardiography; however, there was no relationship between CAD patterns and patient-reported outcomes.[19] Several reasons may explain the discrepancy with the present report. First, assessing CAD patterns in hyperemic conditions magnifies focal pressure losses, allowing the assessment of focal pressure gradients with less signal-to-noise ratio. Several reports have suggested that resting coronary flow conditions might be insufficient to elicit pressure gradients, particularly in focal stenoses. A second element relates to the definition of focal CAD in the instantaneous wave-free ratio pullback curve. Focal disease was based on the presence of a focal pressure gradient only. This approach disregards pressure losses proximal and distal to the focal gradient, which are equally important for evaluating the absolute improvement in myocardial perfusion after PCI contributing to the resolution of angina. The PPG formula assesses both the magnitude of focal pressure drops and the diffuseness of the disease, providing a comprehensive approach that correlates with symptom improvement.

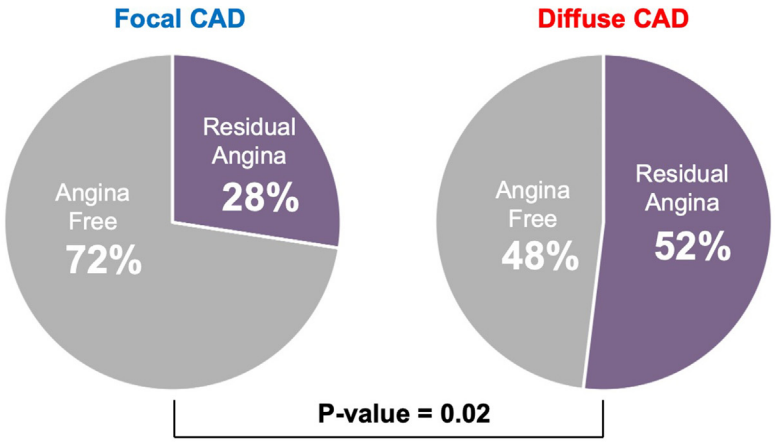
Using pressure pullbacks to assess CAD patterns is an example of personalized medicine to determine the appropriateness of PCI. The PPG quantifies CAD patterns, enhancing clinical decision making and reducing the uncertainty associated with a visual interpretation of the pullback curve. In clinical practice, this technique adds 30 to 40 seconds to the classical FFR measurement and can be performed in a reproducible manner with standard pressure wires.[20] Based on the results of this study, patients with high PPG are ideal candidates for PCI and are expected to achieve near-complete resolution of their symptoms with improved quality of life. Conversely, the best treatment strategy for patients with diffuse disease requires further study. An additional consideration when deciding between treatment options for patients with diffuse disease is the higher rate of device-related adverse events observed after PCI.[10,21] In this study, patients with low PPG required longer and more stents during PCI. Consequently, decision making in diffuse CAD must be individualized,

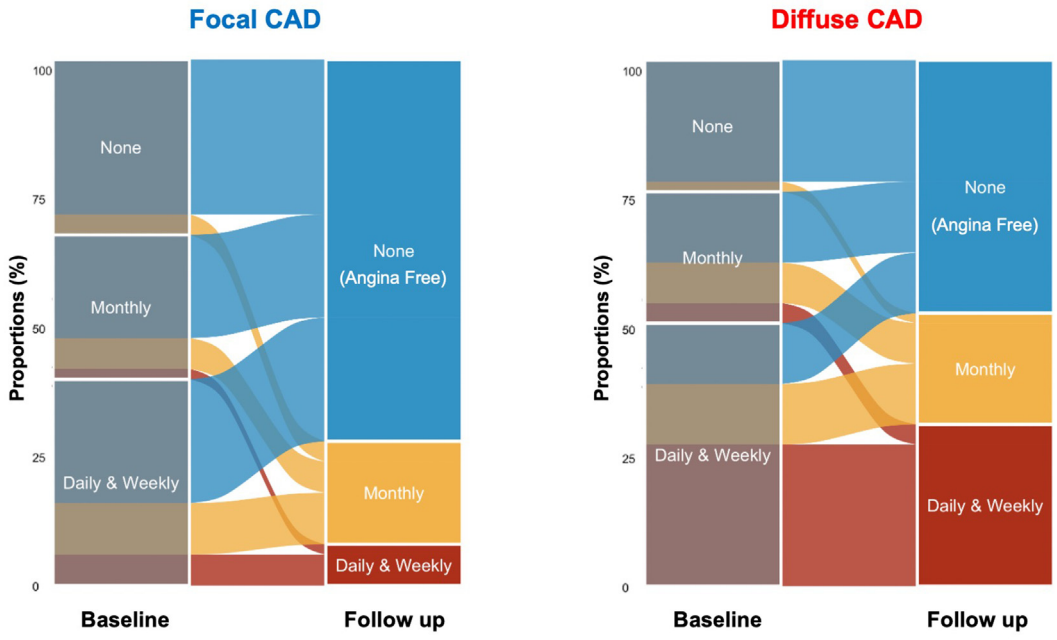
FIGURE 3 **Distribution of SAQ Scores at Baseline and Follow-Up Stratified by CAD Patterns**



The **top panels** show the Seattle Angina Questionnaire (SAQ) angina frequency score at **(left)** baseline and **(right)** follow-up. The **middle panels** show the SAQ physical limitation score at **(left)** baseline and **(right)** follow-up. The **bottom panels** show the SAQ quality of life score at **(left)** baseline and **(right)** follow-up. Patients with focal disease (PPG ≥ 0.66) are represented in blue and diffuse disease in red. The area of each color depicts the frequency of the score's interval, and the height of the bar represents the score's density. The **blue and red lines** with diamonds represent the mean ± SD of each score stratified by the coronary artery disease (CAD) pattern. At baseline, there were no differences in the angina frequency, physical limitation, or quality of life domains between focal and diffuse disease. At follow-up, patients with focal disease reported significantly higher scores in the angina frequency, physical limitation, and quality of life domains; $P < 0.05$ for all.

FIGURE 4 Rate of Freedom From Angina After Percutaneous Coronary Intervention Stratified by CAD Patterns





		Follow up		
		Daily or weekly	Monthly	None
Baseline	Daily or weekly	3	5	12
	Monthly	1	3	10
	None	0	2	15

		Follow up		
		Daily or weekly	Monthly	None
Baseline	Daily or weekly	14	6	6
	Monthly	2	4	7
	None	0	1	12

The pie charts show the proportions of angina-free (SAQ Angina Frequency score = 100) and residual angina (SAQ Angina Frequency score <100) patients with **(left)** diffuse and **(right)** focal CAD. There were significantly more patients free from angina after percutaneous coronary intervention if the baseline CAD pattern was focal (pullback pressure gradient ≥0.66). The bottom panel shows a Sankey diagram depicting the changes in angina frequency (daily or weekly, monthly, or none) from baseline to follow-up stratified by **(left)** diffuse and **(right)** focal CAD. Abbreviations as in Figure 3.

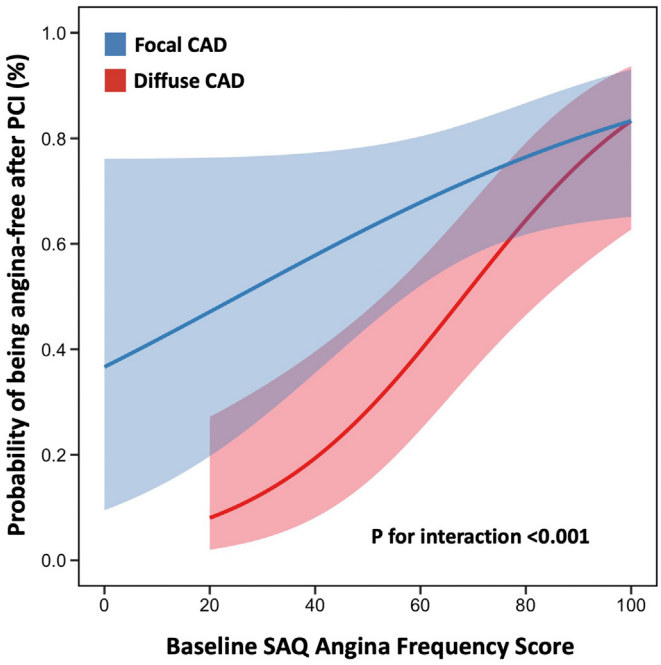
accounting for the patient's symptom burden, the anatomical scenario, lesion severity, and the baseline pattern of CAD, along with other clinical information. In our view, most patients with low PPG can be treated with optimal medical therapy.[11] A randomized clinical trial evaluating treatment options for patients with diffuse disease is warranted; the availability of PPG may serve as a method to standardize selection criteria.

STUDY LIMITATIONS. The first limitation of the present study is that it is a single-center randomized clinical trial of moderate size. Attrition from the original sample size resulted from the lack of pre-PCI FFR pullback evaluation in 27% of the patients. The main reason for this was that the pre-PCI pullback maneuvers were performed at the operator's discretion. Second, this is a post hoc analysis of a randomized clinical trial; therefore, prospective validation is required to confirm these findings. Third, patient-reported outcomes were collected at a 3-month follow-up interval. Although the effect of PCI is certainly discernible within this time frame, a longer-term follow-up would be required to better understand the durability of the findings. Fourth, the PPG calculation was performed off-line; thus, the clinical outcomes after a PPG-guided PCI strategy require further investigation. Fifth, we used the median PPG to distinguish focal from diffuse CAD for this analysis. Despite the AUC analysis suggesting a PPG threshold for symptom improvement, we believe that PPG should be interpreted as a continuous variable with lower values associated with lower PCI clinical success rates and higher values related to nearly complete resolution of angina. The ongoing PPG Global Registry (NCT04789317) will include approximately 1,000 stable patients with the collection of clinical and patient-reported outcomes to confirm the present findings and further inform about PPG cutoffs for clinical decision making.

CONCLUSIONS

Residual angina after PCI was frequent and predominantly observed in patients with diffuse CAD as defined by the pre-PCI PPG. Patients with focal disease reported greater improvement in angina and quality of life with PCI. The PPG identified patients most likely to benefit from PCI in terms of angina relief. Therefore, the distribution of the epicardial resistance should be factored into the clinical decision-making process about the appropriateness and the modality of revascularization. A randomized clinical trial assessing the clinical and economic impact of a PPG-guided PCI strategy is warranted.

FIGURE 5 Effect of Coronary Artery Disease Pattern and Results of PCI as a Function of Patients' Baseline SAQ Angina Frequency Score



The probability of being angina-free (Seattle Angina Questionnaire [SAQ] Angina Frequency score = 100) at 3 months after percutaneous coronary intervention (PCI) if the baseline coronary artery disease pattern was focal **(blue)** or diffuse **(red)** as a function of patients' baseline SAQ Angina Frequency score. **Shading** represents 95% CIs.

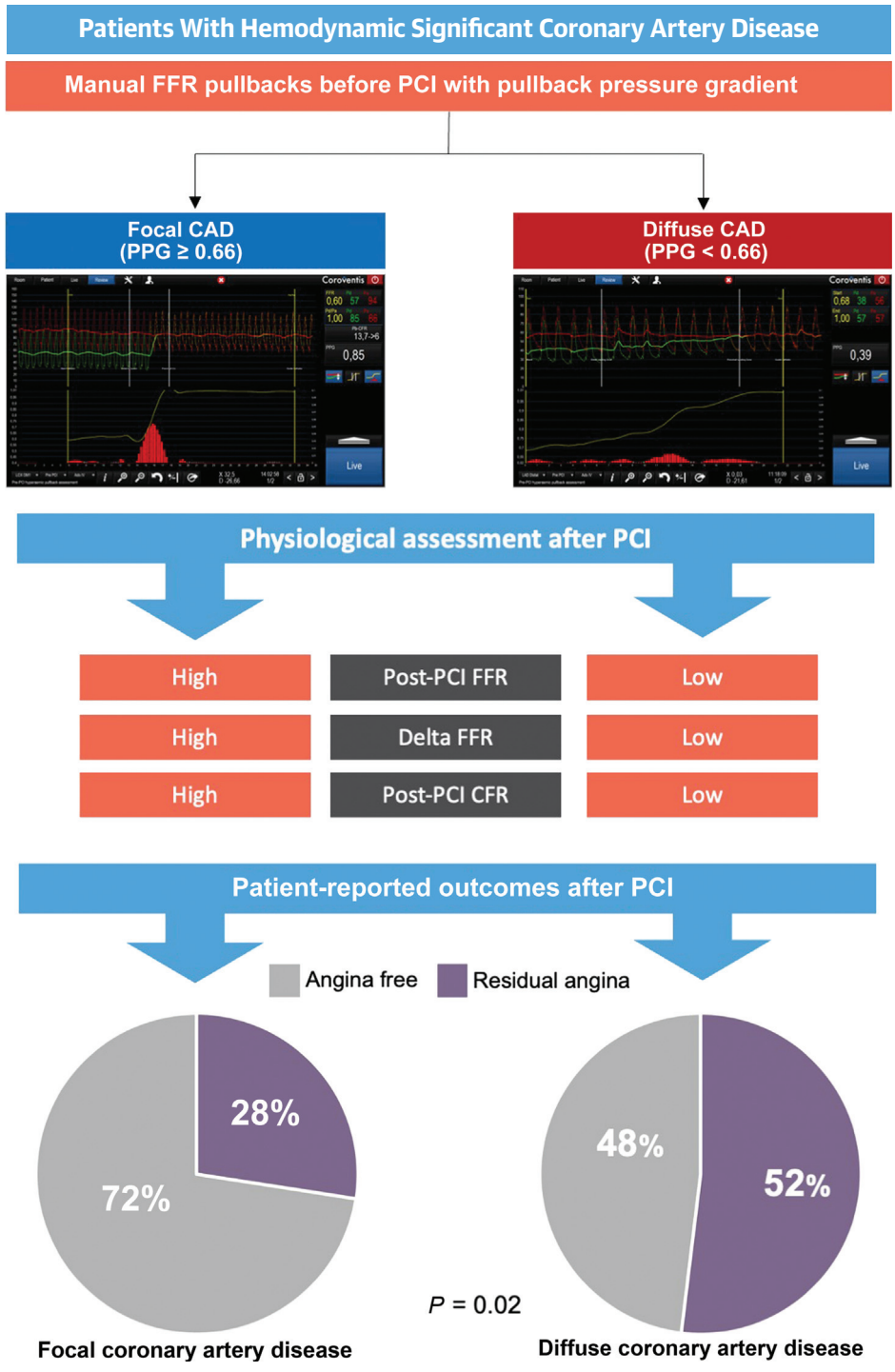
TABLE 4 EQ-5D-5L Questionnaire at Baseline and Follow-Up Stratified by Coronary Artery Disease Patterns

	Overall	Focal (PPG ≥0.66)	Diffuse (PPG <0.66)	*P* Value
Baseline EQ-5D-5L				
Mobility score	1.8 ± 1.1	1.6 ± 1.1	1.9 ± 1.0	0.175
Self-care score	1.3 ± 0.6	1.2 ±0.5	1.4 ± 0.6	0.177
Usual activities score	2.2 ± 1.1	2.2 ± 1.2	2.3 ± 1.1	0.699
Pain score	2.1 ± 1.0	1.9 ± 0.9	2.2 ± 1.03	0.125
Anxiety and depression score	1.8 ±1.0)	1.7 ± 0.9	2.0 ± 1.00	0.169
Visual analog scale	69.0 ± 19.5	69.0 ± 20.2	68.9 ± 18.9	0.984
EQ-5D-5L index	0.78 ± 0.21	0.80 ± 0.21	0.75 ± 0.21	0.251
Follow-up EQ-5D-5L				
Mobility score	1.62 ± 1.0	1.4 ± 0.8	1.9 ± 1.2	0.014
Self-care score	1.4 ± 0.7	1.2 ± 0.6	1.5 ± 0.8	0.015
Usual activities score	1.8 ± 1.0	1.5 ± 0.9	2.0 ± 1.1	0.027
Pain score	1.7 ± 1.0	1.4 ± 0.7	2.1 ± 1.1	<0.001
Anxiety and depression score	1.7 ± 1.0	1.5 ± 0.8	1.9 ± 1.2	0.076
Visual analog scale	75.7 ± 20.9	79.8 ±19.1	71.7 ± 21.9	0.048
EQ-5D-5L index	0.8 ± 0.2	0.9 ± 0.2	0.8 ± 0.3	0.004

Values are mean ± SD.
EQ-5D-5L = EuroQol 5-level 5-dimensional questionnaire; PPG = pullback pressure gradient.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 15, NO. 24, 2022
DECEMBER 26, 2022:2506–2518

CENTRAL ILLUSTRATION **Procedural and Patient-Reported Outcomes After PCI in Focal and Diffuse Coronary Artery Disease**



Collet C, et al. J Am Coll Cardiol Intv. 2022;15(24):2506–2518.

Patients with hemodynamically significant coronary stenoses underwent manual fractional flow reserve (FFR) pullbacks with pullback pressure gradient (PPG) calculation. Percutaneous coronary intervention (PCI) in patients with focal disease depicted by a high PPG (outcomes **shown on the left side**) resulted in higher post-PCI FFR, higher delta FFR, and higher post-PCI FFR compared to patients with diffuse disease **(shown on the right side)**. The improved procedural outcomes in patients with focal disease translated into a higher proportion of angina-free patients after PCI **(lower panel)**.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Collet has received research grants from Biosensor, Coroventis Research, Medis Medical Imaging, Pie Medical Imaging, CathWorks, Boston Scientific, Siemens, HeartFlow, and Abbott Vascular; and has received consultancy fees from HeartFlow, OpSens, Abbott Vascular, and Philips Volcano. Dr Collison has received consultancy and speaker fees from Abbott. Dr Munhoz has received research grants provided by the Cardiopath PhD program. Dr Berry is employed by the University of Glasgow, which holds consultancy and research agreements for his work with Abbott Vascular, AstraZeneca, Auxilius Pharma, Boehringer Ingelheim, Causeway Therapeutics, Coroventis, Genentech, GlaxoSmithKline, HeartFlow, Menarini, Neovasc, Siemens Healthcare, and Valo Health; and has received research funding from the British Heart Foundation grant (RE/18/6134217) and EPSRC (EP/R511705/1, EP/S030875/1). Dr De Bruyne has received consultancy fees from Boston Scientific and Abbott Vascular; has received research grants from Coroventis Research, Pie Medical Imaging, CathWorks, Boston Scientific, Siemens, HeartFlow, and Abbott Vascular; and owns equity in Siemens, GE, Philips, HeartFlow, Edwards Life Sciences, Bayer, Sanofi, and Celyad. Dr Oldroyd is an employee of Biosensors International. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Carlos Collet, Cardiovascular Center Aalst, OLV Hospital, Moorselbaan 164, Aalst 9300, Belgium. E-mail: carloscollet@gmail.com.

PERSPECTIVES

WHAT IS KNOWN? Residual angina after PCI is well recognized and may affect 20% to 40% of patients. Diffuse CAD is one of the mechanisms underlying residual angina after PCI. PPG is a novel metric standardizing the diagnosis of CAD patterns and distinguishing focal versus diffuse disease based on coronary physiology. The effectiveness of PCI in terms of angina relief in focal and diffuse disease was evaluated in this study.

WHAT IS NEW? Patients with focal CAD (PPG closer to 1) treated with PCI had a more favorable prognosis regarding angina, physical limitations, and quality of life than patients with diffuse disease. More than one-half of the patients with diffuse disease (PPG closer to 0) remained symptomatic after PCI. The assessment of CAD patterns using FFR pullback provides information on the likelihood of symptom relief post-PCI.

WHAT IS NEXT? Although patients with focal CAD have a good prognosis after PCI, the best treatment strategy for patients with diffuse disease remains to be determined. Leveraging the PPG for the evaluation of CAD patterns, future clinical trials should focus on defining how to approach patients with diffuse CAD.

REFERENCES

1. Mozaffarian D, Bryson CL, Spertus JA, McDonell MB, Fihn SD. Anginal symptoms consistently predict total mortality among outpatients with coronary artery disease. *Am Heart J*. 2003;146:1015–1022.

2. Spertus JA, Jones PG, Maron DJ, et al. Health-status outcomes with invasive or conservative care in coronary disease. *N Engl J Med*. 2020;382:1408–1419.

3. Venkitachalam L, Kip KE, Mulukutla SR, et al. Temporal trends in patient-reported angina at 1 year after percutaneous coronary revascularization in the stent era: a report from the National Heart, Lung, and Blood Institute-sponsored 1997-2006 dynamic registry. *Circ Cardiovasc Qual Outcomes*. 2009;2:607–615.

4. Shaw LJ, Berman DS, Maron DJ, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283–1291.

5. Collison D, Didagelos M, Aetesam-Ur-Rahman M, et al. Post-stenting fractional flow reserve vs coronary angiography for optimisation of percutaneous coronary intervention: TARGET-FFR trial. *Eur Heart J*. 2021;42(45):4656–4668.

6. Fournier S, Ciccarelli G, Toth GG, et al. Association of improvement in fractional flow reserve with outcomes, including symptomatic relief, after percutaneous coronary intervention. *JAMA Cardiol*. 2019;4:370–374.

7. Ando H, Takashima H, Suzuki A, et al. Impact of lesion characteristics on the prediction of optimal poststent fractional flow reserve. *Am Heart J*. 2016;182:119–124.

8. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease. *EuroIntervention*. 2005;1:219–227.

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

10. Di Sciascio G, Patti G, Nasso G, Manzoli A, D'Ambrosio A, Abbate A. Early and long-term results of stenting of diffuse coronary artery disease. *Am J Cardiol*. 2000;86:1166–1170.

11. van Beek KAJ, van Steenbergen GJ, Vervaat FE, et al. Single center experience in the treatment of hemodynamically significant diffuse coronary artery disease of the left anterior descending. *Int J Cardiol*. 2022;352:40–44.

12. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med*. 1979;301:61–68.

13. Collet C, Sonck J, Vandeloo B, et al. Measurement of hyperemic pullback pressure gradients to characterize patterns of coronary atherosclerosis. *J Am Coll Cardiol*. 2019;74:1772–1784.

14. Collison D, McClure JD, Berry C, Oldroyd KG. A randomized controlled trial of a physiology-guided percutaneous coronary intervention optimization strategy: rationale and design of the TARGET FFR study. *Clin Cardiol*. 2020;43:414–422.

15. Spertus JA, Winder JA, Dewhurst TA, et al. Development and evaluation of the Seattle Angina Questionnaire: a new functional status measure for coronary artery disease. *J Am Coll Cardiol*. 1995;25:333–341.

16. Chan PS, Jones PG, Arnold SA, Spertus JA. Development and validation of a short version of the Seattle angina questionnaire. *Circ Cardiovasc Qual Outcomes*. 2014;7:640–647.

17. Thomas M, Jones PG, Arnold SV, Spertus JA. Interpretation of the Seattle Angina Questionnaire as an outcome measure in clinical trials and clinical care: a review. *JAMA Cardiol*. 2021;6:593–599.

18. Crea F, Bairey Merz CN, Beltrame JF, et al. Mechanisms and diagnostic evaluation of persistent or recurrent angina following percutaneous coronary revascularization. *Eur Heart J*. 2019;40(29):2455–2462.

19. Rajkumar CA, Shun-Shin M, Seligman H, et al. Placebo-controlled efficacy of percutaneous coronary intervention for focal and diffuse patterns of stable coronary artery disease. *Circ Cardiovasc Interv*. 2021;14(8):e009891.

20. Sonck J, Mizukami T, Johnson NP, et al. Development, validation, and reproducibility of the pullback pressure gradient (PPG) derived from manual fractional flow reserve pullbacks. *Catheter Cardiovasc Interv*. 2022;99:1518–1525.

21. Quadri G, D'Ascenzo F, Bollati M, et al. Diffuse coronary disease: short- and long-term outcome after percutaneous coronary intervention. *Acta Cardiol*. 2013;68:151–160.

KEY WORDS angina, coronary physiology, diffuse disease, percutaneous coronary intervention, revascularization

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