Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Influence of Pullback Pressure Gradient on Residual Angina at One Year

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BACKGROUND: The pullback pressure gradient (PPG) is a novel physiological metric that quantifies coronary artery disease patterns as focal or diffuse on a scale from 0 to 1. This study assessed the relationship between PPG and residual angina at 1 year.

METHODS: PPG Global is a prospective, investigator-initiated, single-arm, multicenter study that enrolled patients with at least 1 lesion with a fractional flow reserve ≤0.80 intended to be treated with PCI. After the PPG calculation, physicians could revise treatment assignment to medical therapy or coronary artery bypass graft surgery instead of PCI. Focal and diffuse disease were defined based on the median PPG value of 0.62. Patient-reported outcomes were assessed using the Seattle Angina Questionnaire at baseline and 1-year follow-up.

RESULTS: The study included 947 patients with PPG and the Seattle Angina Questionnaire at 1 year. The mean age was 67.6±10.2 years, 24% were female, and 29% had diabetes. At 1 year, patients with focal coronary artery disease reported less angina than those with diffuse coronary artery disease (Seattle Angina Questionnaire angina frequency score, 95.3±9.9 versus 92.5±15.0; *P*=0.006). PPG was independently associated with improvement in angina (*P*=0.017).

CONCLUSIONS: In patients with flow-limiting coronary artery disease, the presence of focal disease defined by high PPG was associated with greater symptomatic relief at 1 year compared with diffuse disease (low PPG). By reflecting the physiological pattern of disease and its relation to symptom relief after treatment, PPG may help inform revascularization strategies.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: coronary artery bypass ■ coronary artery disease ■ patient-centered care ■ percutaneous coronary intervention ■ physicians

Revascularization with percutaneous coronary intervention (PCI) predominantly aims to improve symptoms.[1] Nonetheless, ≈30% to 60% of patients remain symptomatic after an angiographically successful PCI.[2–4] Recent studies suggest that the effectiveness of PCI in restoring blood flow and, hence, angina relief is largely influenced by pathophysiological disease patterns.[5]

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This manuscript was sent to Morton J. Kern, Guest Editor, for review by expert referees, editorial decision, and final disposition.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCINTERVENTIONS.125.015851.
For Sources of Funding and Disclosures, see page XXX.

Circulation: Cardiovascular Interventions is available at www.ahajournals.org/journal/circinterventions

WHAT IS KNOWN

- Despite angiographically successful percutaneous coronary intervention, a significant proportion of patients continue to experience angina.
- One of the primary reasons for this residual angina may be suboptimal improvement in coronary flow following the intervention in patients with diffuse disease.

WHAT THE STUDY ADDS

- This study demonstrates that the pullback pressure gradient, a novel physiological index that characterizes the pattern of coronary artery disease as focal or diffuse, is associated with symptomatic relief after percutaneous coronary intervention.
- Patients with high pullback pressure gradient (focal disease) experienced greater improvement in angina at 1 year than those with low pullback pressure gradient (diffuse disease).
- Pullback pressure gradient may enable more personalized and symptom-guided revascularization strategies, supporting patient-centered decision-making.

Nonstandard Abbreviations and Acronyms

CABG	coronary artery bypass grafting
CAD	coronary artery disease
FFR	fractional flow reserve
PCI	percutaneous coronary intervention
PPG	pullback pressure gradient
SAQ	Seattle Angina Questionnaire
TVF	target vessel failure

Coronary physiology can characterize atherosclerotic patterns as focal or diffuse. The pullback pressure gradient (PPG) is a new metric that quantifies the distribution of pressure loss along the epicardial vessel on a scale from 0 to 1, with lower values indicating diffuse disease.[6] PPG has been shown to have an excellent predictive capacity for blood flow improvement after PCI.[5]

Previous studies in patients undergoing PCI have shown that PPG is associated with improvement in angina and quality of life.[7] Given the growing emphasis on patient-centered care, understanding how PPG associates with angina relief is of paramount importance.[8–10] This study aims to evaluate the impact of PPG on patient-reported outcomes in patients with hemodynamically significant coronary artery disease (CAD).

METHODS

Study Design and Population

This is the 1-year clinical outcome report of PPG Global—a prospective, investigator-initiated, single-arm, multicenter study designed to assess the capacity of PPG to predict optimal functional revascularization based on fractional flow reserve (FFR) after PCI. Its design and main results have been published.[5,11] The current study represents a predefined secondary analysis focusing on patient-reported outcomes—specifically, the presence of residual angina after PCI. The study enrolled patients from 25 centers with at least 1 coronary lesion and an FFR ≤0.80 intended to undergo PCI. A complete list of inclusion and exclusion criteria is provided in Table S1. For this analysis, we included patient-reported and clinical outcomes at 1 year. PPG was calculated from FFR pullbacks, and after PPG calculation, operators could revise treatment strategy and opt for medical therapy or coronary artery bypass grafting (CABG) surgery instead of PCI. The change in revascularization mode after PPG was left to the operator's discretion; no prespecified PPG cutoff was provided to guide clinical decision-making. The Seattle Angina Questionnaire of 7 items was administered at baseline and 1-year follow-up. The results are presented in the overall population and those reporting angina at baseline (Seattle Angina Questionnaire [SAQ] angina frequency <100). An external core laboratory analyzed all angiographic and physiological data. Every participant gave written informed consent, and every site received approval from its local institutional review board.

The data that support the findings of this study are available from the corresponding author on reasonable request.

Invasive Physiological Procedure

Patients underwent a standardized invasive physiological assessment using a coronary pressure wire (PressureWire X, Abbott Vascular, Santa Clara, CA). The pressure wire was positioned in the distal coronary artery in a segment ≥2 mm in diameter and at least 15 mm beyond the most distal stenosis by visual estimation.[12] A pullback maneuver was performed manually at a constant speed for 20 to 30 seconds. When the pressure sensor reached the catheter tip, the pullback recording was stopped, and PPG was calculated onsite using CoroFlow software v3.5.1 (Coroventis Research AB, Uppsala, Sweden). Operators were trained during the site initiation visit to standardize pullback maneuvers. The calculation of the PPG involves the integration of 2 parameters derived from the pressure pullback curve, specifically the maximal pressure gradient over a 20% window of the pullback duration and the extent of functional disease over the complete pullback curve.[6] PCI was performed according to local practice. Similarly, medical therapy was left to the judgment of the treating physicians.

Imaging and Intracoronary Pressure Analysis

All angiographic and physiological data underwent centralized, independent review at the CoreAalst core laboratory. A 2- or 3-dimensional quantitative coronary angiography was performed with CAAS 8.2 software (Pie Medical Imaging, Maastricht, the Netherlands). The physiology core laboratory assessed each recording for quality following predefined criteria, including an examination of the aortic and coronary pressure tracings for any signs of waveform distortion or loss and aortic pressure ventricularization.

Patient-Reported and Clinical Outcomes

The SAQ was administered at baseline and 1-year follow-up. We applied the 7-item SAQ that evaluates health status in

3 domains: angina frequency, physical limitation, and quality of life. The SAQ scale ranges from 0 to 100, with higher scores indicating better health status. The presence of angina was defined as an SAQ angina frequency score of <100. Mild, moderate, and severe angina were defined as SAQ scores >80, 80 to 60, and <60 points, respectively.[13] SAQ were administered in local languages during a visit or postal contact.

Clinical outcomes were collected at 1 year. Target vessel failure (TVF) was defined as cardiac death, target-vessel (peri-procedural and spontaneous) myocardial infarction, and ischemia-driven target vessel revascularization. Periprocedural myocardial infarction was defined according to the Fourth Universal Definition of Myocardial Infarction.[14] Clinical outcomes were adjudicated by an independent committee blinded to the PPG value.

Statistical Analysis

Statistical analyses were conducted to compare baseline characteristics, treatment strategies, and patient-reported outcomes between focal and diffuse disease. The median PPG of 0.62 was used to categorize patients into those with predominantly focal disease (PPG >0.62) versus diffuse CAD (PPG ≤0.62). We also report the results using an alternative cutoff of PPG 0.50, which was associated with a negative likelihood ratio of

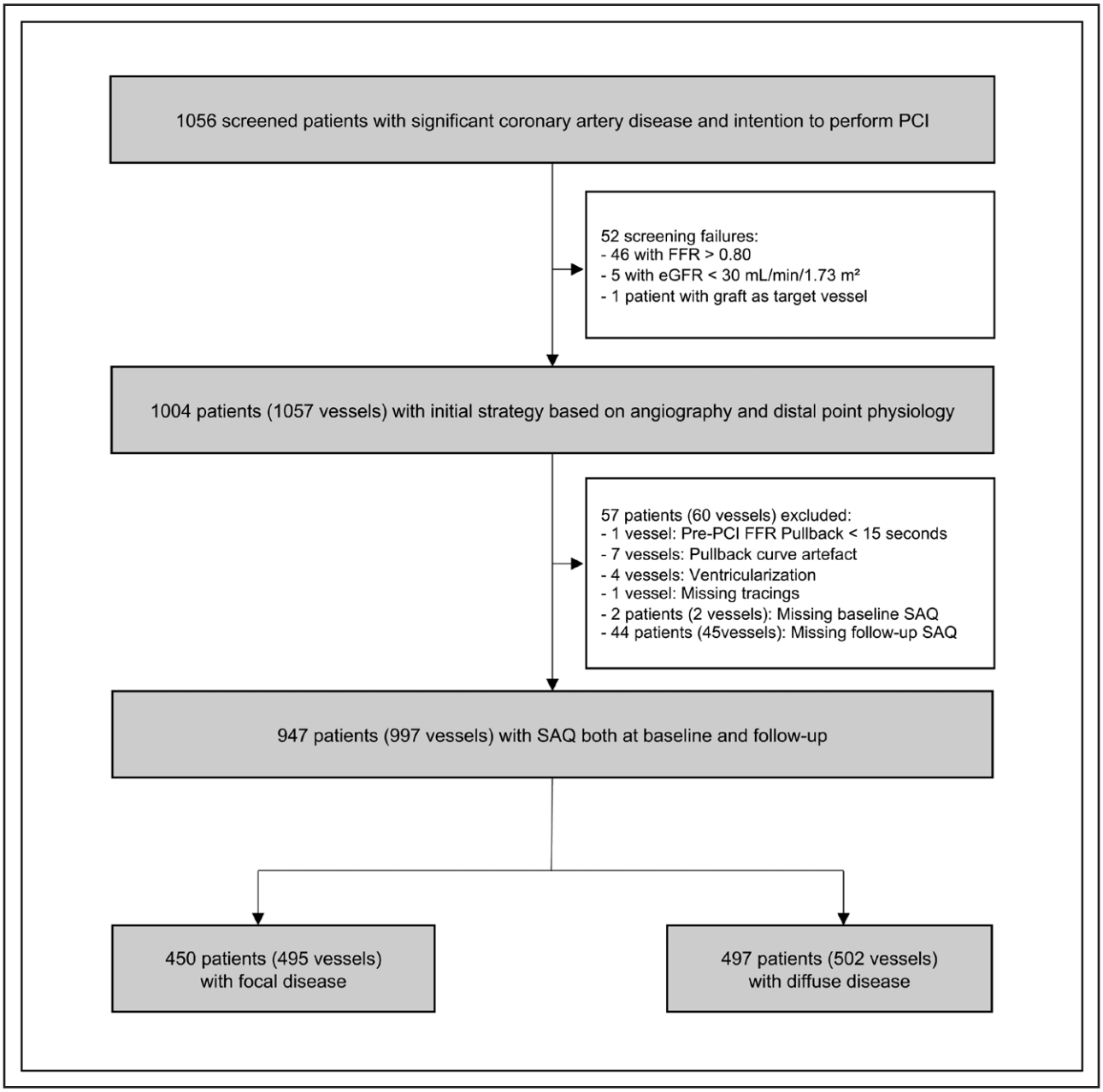

Figure 1. Study flowchart.
eGFR indicates estimated glomerular filtration rate; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; and SAQ, Seattle Angina Questionnaire.

0.40 for achieving optimal revascularization.[5] Descriptive statistics (mean±SD, median [interquartile range], and frequency [%]) were used to summarize variables. Continuous variables were compared using the Student *t* test, and categorical variables were compared using either the χ^2 test or the Fisher exact test, as appropriate. Univariate and multivariable linear regression analysis assessed the association between PPG, as a continuous variable, with improvement in angina at 1 year (ie, delta SAQ in the angina frequency domain). Clinical and patient-reported outcomes were compared between treatment strategies (PCI, CABG, and medical therapy). The log-rank test was used to compare TVF rates between groups; patients with focal disease who did not receive PCI (3.1% of the population) were excluded from these analyses due to their small size. TVF rates at 1 year were also assessed after excluding periprocedural myocardial infarction. For cases with multivessel evaluation, the lowest PPG value was used to categorize the patient for the outcomes analyses. Univariate and multivariate

Table 1. Baseline and Procedural Characteristics Stratified by Disease Patterns

Variable	Overall	Focal	Diffuse	*P* value
Number of patients	947	450	497	
Age, y, mean±SD	67.6±10.2	67.7±10.3	67.5±10.2	0.728
Gender (male), n (%)	717 (75.7)	331 (73.6)	386 (77.7)	0.162
BMI, kg/m² (%), mean±SD	26.7±4.5	26.3±4.5	27.0±4.6	0.016
Dyslipidemia, n (%)	700 (73.9)	328 (72.9)	372 (74.8)	0.541
Hypertension, n (%)	662 (69.9)	308 (68.4)	354 (71.2)	0.389
Diabetes, n (%)	272 (28.7)	127 (28.2)	145 (29.2)	0.801
Current smoking, n (%)	154 (16.3)	83 (18.4)	71 (14.3)	0.100
Prior PCI for nontarget vessel, n (%)	261 (27.6)	114 (25.3)	147 (29.6)	0.160
Prior PCI for target vessel, n (%)	108 (11.4)	43 (9.6)	65 (13.1)	0.107
Prior MI, n (%)	185 (19.5)	76 (16.9)	109 (21.9)	0.061
Peripheral artery disease, n (%)	58 (6.1)	24 (5.3)	34 (6.8)	0.406
Clinical presentation, n (%)				0.203
NSTEMI	55 (5.8)	20 (4.4)	35 (7.1)	
Unstable angina	51 (5.4)	23 (5.1)	28 (5.7)	
Stable angina	839 (88.8)	407 (90.4)	432 (87.3)	
Symptom (Stable angina), n (%)*				0.003
Asymptomatic	108 (12.9)	41 (10.1)	67 (15.5)	
Silent ischemia†	133 (15.9)	49 (12.0)	84 (19.4)	
CCS I	298 (35.5)	159 (39.1)	139 (32.2)	
CCS II	215 (25.6)	109 (26.8)	106 (24.5)	
CCS III	67 (8.0)	39 (9.6)	28 (6.5)	
CCS IV	18 (2.1)	10 (2.5)	8 (1.9)	
LVEF (%), mean±SD	58.4±9.5	59.3±9.5	57.5±9.5	0.005
PPG, mean±SD	0.62±0.16	0.76±0.09	0.49±0.08	<0.001
Pre-PCI FFR, mean±SD	0.67±0.12	0.63±0.14	0.72±0.08	<0.001
Post-PCI FFR, mean±SD	0.87±0.07	0.89±0.07	0.84±0.06	<0.001
Post-PCI FFR >0.80, n (%)	734 (83.6)	442 (90.6)	292 (74.9)	<0.001
Post-PCI FFR >0.88, n (%)	409 (46.4)	307 (62.9)	102 (26.0)	<0.001
Residual SYNTAX score	2.37±4.60	2.28±4.96	2.47±4.16	0.555
Treatment strategy, n (%)				<0.001
PCI	814 (86.0)	436 (96.9)	378 (76.1)	
CABG	48 (5.1)	10 (2.2)	38 (7.6)	
OMT	85 (9.0)	4 (0.9)	81 (16.3)	

For patients with multivessel interrogation, the lowest PPG was used for the patient-level analysis. Focal disease was defined as a PPG >0.62, and diffuse disease was defined as a PPG ≤0.62. BMI indicates body mass index; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society Angina Score; FFR, fractional flow reserve; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PPG, pullback pressure gradient; RCA, right coronary artery; and SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

*As assessed by the treating physician.

†Defined as a positive functional noninvasive test in an asymptomatic patient.

Cox regression analysis were performed to assess the association between the physiological CAD pattern and TVF. The multivariate linear and Cox regression models were adjusted by age, gender (male), body mass index, dyslipidemia, hypertension, diabetes, smoking, prior PCI in the target vessel, clinical presentation (stable angina versus ACS), PPG, pre-PCI FFR, vessel type (left anterior descending artery), and antianginal medication use at follow-up. A *P* value of <0.05 was considered statistically significant. Analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

Nine hundred 47 patients were included. The study flowchart is shown in Figure 1. Baseline characteristics in patients with focal and diffuse disease are shown in Table 1. Patients with focal disease had lower FFR compared with those with diffuse CAD. PCI was performed in 96.9% (436/450) of patients with focal CAD and 76.1% (378/497) of patients with diffuse disease. Patients with diffuse disease were managed medically in 16.3% of cases, and 7.6% underwent CABG. Procedural and angiographic characteristics are shown in Table S2. Figure 2 shows the distribution of PPG stratified by treatment groups. Patients' characteristics stratified by treatment strategy are shown in Table S3.

Patients Reported Outcomes Stratified by CAD Patterns

At baseline, patients with focal CAD (high PPG) had more angina, more physical limitation, and lower quality of life than those with diffuse CAD (Table 2). At 1 year, patients with focal disease (high PPG) reported a greater improvement in angina, physical limitation, and quality of life compared with those with diffuse disease (low PPG). PPG was independently associated with angina relief (delta SAQ angina frequency) after adjustment for clinical characteristics and FFR (Table 3). Furthermore, after accounting for medication use at the 12-month follow-up and the achievement of physiological revascularization, defined as FFR >0.88, PPG remained an independent factor associated with angina improvement (Table S4). Six hundred and 12 patients (65%) reported SAQ angina at baseline (SAQ <100). A comparison between symptomatic and asymptomatic patients is shown in Table S5. In symptomatic patients at baseline, patients with focal CAD reported significantly

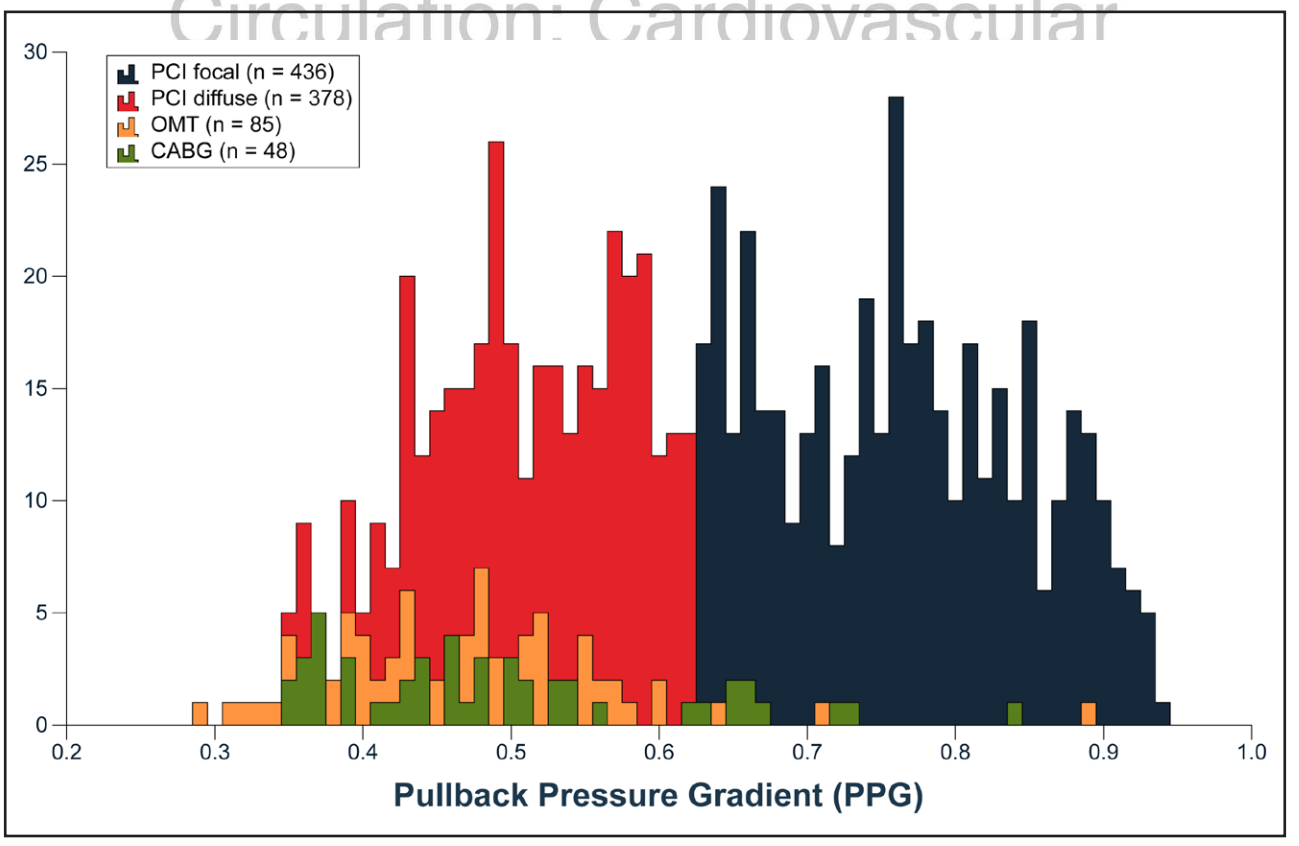

Figure 2. Distribution of pullback pressure gradient (PPG) stratified by treatment.
Patients treated with percutaneous coronary intervention (PCI) for focal disease (blue, PPG >0.62) had significantly higher mean PPG values (0.76±0.09) compared with those undergoing PCI for diffuse disease (red, PPG ≤0.62; 0.50±0.07), coronary artery bypass grafting (green; 0.49±0.12), or medical therapy (yellow; 0.46±0.09; *P*<0.001). CABG indicates coronary artery bypass grafting; and OMT, optimal medical therapy.

Table 2. Patients Reported Outcomes Stratified by Disease Patterns

Variable	Overall	Focal	Diffuse	*P* value
All patients				
Number of patients	947	450	497	
Baseline SAQ				
SAQ PL score	77.9±27.1	75.0±28.4	80.5±25.7	0.002
SAQ AF score	80.5±20.8	78.6±20.2	82.1±21.2	0.011
SAQ QOL score	56.3±29.4	52.3±29.4	59.9±29.0	<0.001
SAQ summary score	71.6±21.8	68.6±22.2	74.3±21.1	<0.001
One-year SAQ				
SAQ PL score	90.5±19.7	90.6±19.9	90.4±19.5	0.882
SAQ AF score	95.4±11.1	96.0±9.1	94.8±12.6	0.077
SAQ QOL	87.4±20.0	87.7±19.3	87.1±20.5	0.631
SAQ summary score	91.2±13.8	91.5±13.0	91.0±14.5	0.542
Change from baseline				
SAQ PL score	11.8±29.7	15.3±30.2	8.4±28.8	0.001
SAQ AF score	14.9±20.4	17.4±20.4	12.7±20.2	<0.001
SAQ QOL score	31.1±32.6	35.4±31.7	27.3±32.9	<0.001
SAQ summary score	19.7±22.8	22.9±22.1	16.7±23.0	<0.001
Absolute SAQ summary score change ≥5 points	648 (68.4)	337 (74.9)	311 (62.6)	<0.001
Absolute SAQ summary score change ≥10 points	587 (62.0)	308 (68.4)	279 (56.1)	<0.001
Symptomatic patients*				
Number of patients†	612	320	292	
Baseline SAQ				
SAQ PL score	70.6±28.7	68.2±29.4	73.1±27.7	0.040
SAQ AF score	69.8±18.5	70.0±17.7	69.5±19.4	0.765
SAQ QOL score	42.6±23.4	40.9±23.3	44.5±23.3	0.054
SAQ summary score	60.9±18.8	59.6±18.9	62.4±18.6	0.066
One-year SAQ				
SAQ PL score	88.9±20.5	89.1±20.8	88.6±20.3	0.786
SAQ AF score	94.0±12.7	95.3±9.90	92.5±15.0	0.006
SAQ QOL score	84.9±22.0	85.6±20.9	84.2±23.1	0.450
SAQ summary score	89.4±15.3	90.0±14.1	88.7±16.4	0.276
Change from baseline				
SAQ PL score	17.4±31.7	20.6±31.1	13.7±32.0	0.011
SAQ AF score	24.3±19.3	25.4±18.6	23.0±20.1	0.132
SAQ QOL score	42.4±30.9	44.7±29.7	39.8±31.9	0.049
SAQ summary score	28.5±22.2	30.4±20.7	26.3±23.5	0.021
Absolute SAQ summary score change ≥5 points	530 (86.6)	289 (90.3)	241 (82.5)	0.007
Absolute SAQ summary score change ≥10 points	501 (81.9)	274 (85.6)	227 (77.7)	0.015

Focal disease was defined as a PPG >0.62, and diffuse disease was defined as a PPG ≤0.62. AF indicates angina frequency; PL, physical limitation; QOL, quality of life; and SAQ, Seattle Angina Questionnaire.

*SAQ data available in the angina frequency domain.

†SAQ data at 1 year are available for 612 patients.

less angina frequency at 1 year than those with diffuse CAD (SAQ angina frequency, 95.3±9.90 versus 92.5±15.0; *P*=0.006; Table 2). In addition, the presence and severity of residual angina were lower in patients with focal versus diffuse CAD (Figure 3). The improvement in the SAQ summary score was also greater in patients with focal CAD (Table 2).

Residual Angina After PCI in Focal and Diffuse Disease

In symptomatic patients undergoing PCI (n=523), those with focal disease reported significantly less angina at 1-year follow-up than those with diffuse CAD (SAQ angina frequency, 95.5±9.7 versus 93.1±14.1; *P*=0.023).

Table 3. Univariate and Multivariable Regression Analysis for Angina Improvement

Variables	Univariate		Multivariable	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Age	0.1 (−0.03 to 0.23)	0.132	0.09 (−0.04 to 0.23)	0.19
Gender (male)	−2.57 (−5.6 to 0.45)	0.096	−1.75 (−4.78 to 1.28)	0.258
BMI	0.05 (−0.24 to 0.33)	0.754	0.08 (−0.22 to 0.38)	0.606
Dyslipidemia	−1.45 (−4.41 to 1.51)	0.338	−1.61 (−4.56 to 1.35)	0.286
Hypertension	1.32 (−1.52 to 4.15)	0.363	0.89 (−2.01 to 3.8)	0.546
Diabetes	0.94 (−1.94 to 3.81)	0.523	0.58 (−2.27 to 3.42)	0.692
Smoking	0.95 (−2.58 to 4.47)	0.598	1.31 (−2.23 to 4.85)	0.468
Prior PCI in the target vessel	2.18 (−1.88 to 6.23)	0.293	2.76 (−1.3 to 6.82)	0.183
Clinical presentation (stable)	−8.77 (−12.86 to −4.68)	<0.001	−7.94 (−12.02 to −3.85)	<0.001
PPG	15.4 (7.06 to 23.7)	<0.001	12.77 (2.61 to 22.93)	0.014
Pre–PCI FFR	−14.3 (−25.2 to −3.38)	0.01	−8.23 (−20 to 3.54)	0.171
Vessel type (LAD)	4.28 (1.25 to 7.31)	0.006	1.47 (−1.93 to 4.88)	0.396
Nitrate use at 1-year follow-up	2.84 (−0.91 to 6.59)	0.138	2.7 (−1.01 to 6.41)	0.154

Angina improvement was defined as SAQ angina frequency baseline minus SAQ angina frequency 12 months. PPG and pre-PCI FFR were used as continuous variables. Clinical presentation indicated stable or acute coronary syndrome. BMI indicates body mass index; FFR, fractional flow reserve; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; PPG, pullback pressure gradient; and SAQ, Seattle Angina Questionnaire.

There were no significant differences between the groups in physical limitation (SAQ-PL, 89.0±21.1 versus 87.8±21.7; *P*=0.519) or quality of life (SAQ-QOL, 85.6±21.0 versus 84.0±23.6; *P*=0.405) at 1 year.

When comparing all treatment strategies, that is, PCI versus CABG versus optimal medical therapy, there were no differences in SAQ AF scores at baseline. At 1 year, patients with focal disease treated with PCI reported a greater improvement in angina and quality of life compared with those with diffuse disease treated with PCI, those treated with CABG, and patients managed medically (Figure 4; Table S6). Patients who received optimal medical therapy reported a higher usage of antianginal medications (Table S7).

Clinical Outcomes

TVF was associated with the physiological CAD pattern, as defined by PPG, after adjustment for clinically relevant factors in whole population (adjusted hazard ratio, 1.75 [95% CI, 1.01–3.04], *P*=0.045; Figure 5) and in patients who underwent PCI (adjusted hazard ratio, 1.87 [95% CI, 1.08–3.23], *P*=0.025; Figure S1). Details of TVF components and clinical outcomes, stratified by focal versus diffuse CAD, are presented in Table S8. When stratified by treatment strategies, patients with diffuse disease treated with PCI had a significantly higher TVF rate driven by a higher incidence of peri-procedural myocardial infarction (Figure 6). After excluding peri-procedural MI, there were no differences in the 1-year TVF between treatment strategies.

DISCUSSION

The findings of this study highlight the importance of pathophysiological disease patterns in predicting symptom improvement in patients with obstructive CAD. Focal obstructive disease, identified by a high PPG, resulted in a greater symptomatic improvement compared with those with diffuse disease at 1-year follow-up after PCI. Moreover, PPG was independently associated with angina improvement.

Approximately 50% of the improvement in blood flow after PCI is determined by the underlying pathophysiological CAD pattern, which can be quantified by PPG. In the present study, PPG was shown to be directly correlated with the change in FFR following PCI.[5] Moreover, patients with focal CAD achieve a higher degree of revascularization measured through post-PCI FFR, which translates into improved patient-reported outcomes. Importantly, 25% of the patients with diffuse disease remained with an FFR below the threshold associated with ischemia (FFR ≤0.80; Table 1). Mechanistically, a successful PCI procedure should be associated with the disappearance or marked decrease of translesional pressure gradients. In vessels with diffuse disease, pressure loss is distributed over a long coronary segment (ie, low PPG); in these cases, PCI fails in normalizing coronary hemodynamics. In line with previous studies, patients with focal disease (high PPG) have lower baseline FFR values compared with those with diffuse disease.[15] Previous studies have linked the changes in FFR after PCI with angina relief. In the FAME trials, the larger the improvement in FFR after PCI, the greater the symptomatic relief.[16] These findings were confirmed in the TARGET-FFR (Trial of Angiography Versus Pressure-Ratio-Guided Enhancement Techniques—Fractional Flow Reserve) randomized clinical trial, where the change in FFR after PCI was significantly associated with the improvement in angina, with better SAQ scores observed in patients with the largest FFR

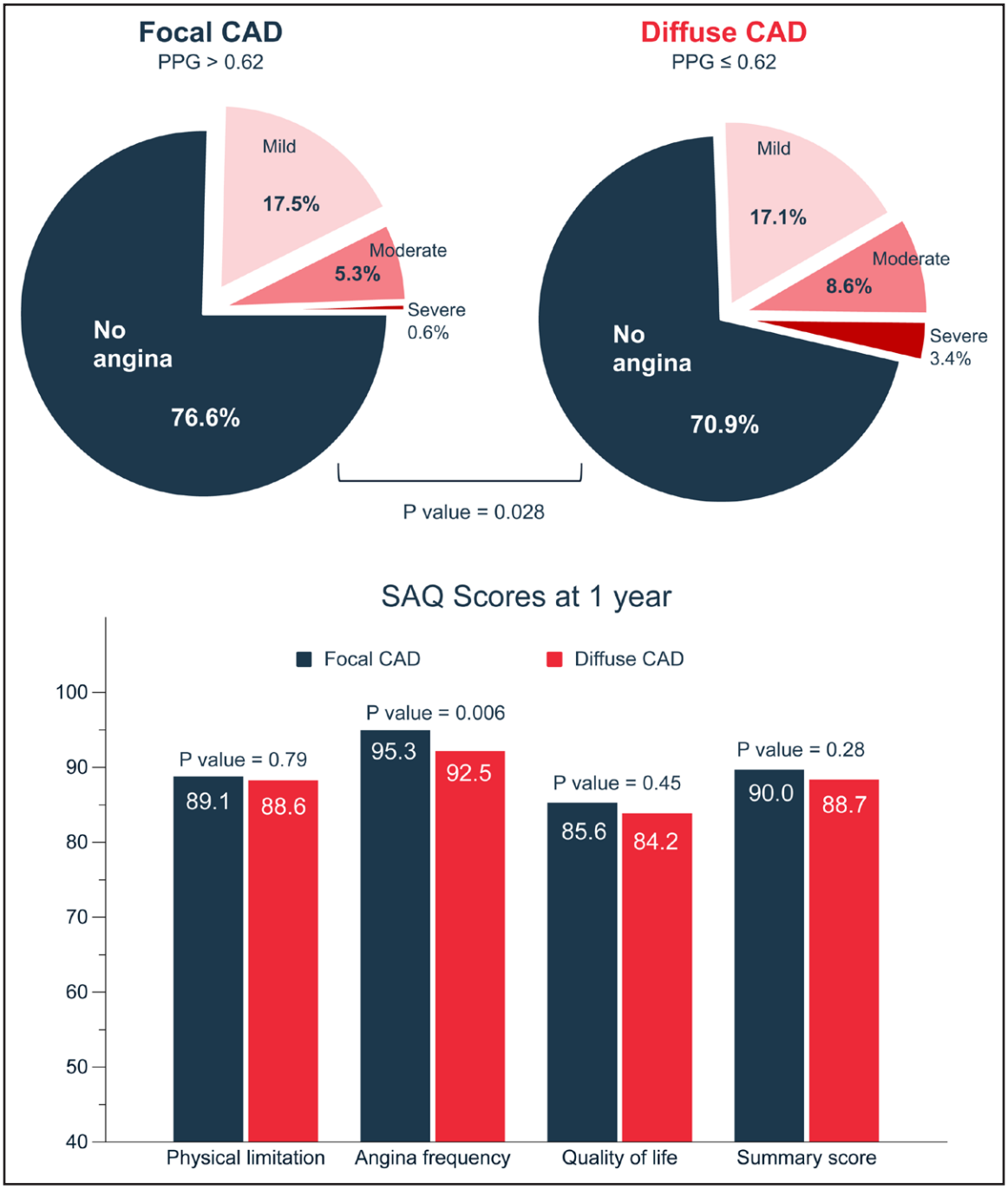

Figure 3. Seattle Angina Questionnaire (SAQ) outcomes in symptomatic patients stratified by coronary artery disease (CAD) patterns at 1 year.

The top panel shows the SAQ scores at 1 year between patients with symptoms at baseline stratified by focal (pullback pressure gradient [PPG] >0.62) or diffuse disease (PPG ≤0.62). Patients with focal disease had higher SAQ angina frequency score compared with patients with diffuse disease. The bottom panel shows the presence and severity of angina stratified by PPG.

improvements.[7,17] Therefore, by forecasting the change in FFR after PCI, PPG extends the use of coronary physiology to predict symptom relief before interventions.

This study confirms previous findings that patients with high PPG experience less angina after PCI. We used the SAQ to assess patients' symptoms. Among patients undergoing PCI, the 1-year difference in SAQ scores between those with focal versus diffuse disease was 2.4 points—a magnitude comparable to the 2.8-point difference observed in the ISCHEMIA trial between patients treated with revascularization versus medical therapy for ischemic CAD.[1] This degree of SAQ change is also aligned with the ORBITA trial, where the SAQ score difference between PCI and placebo was 3.5 points.[4]

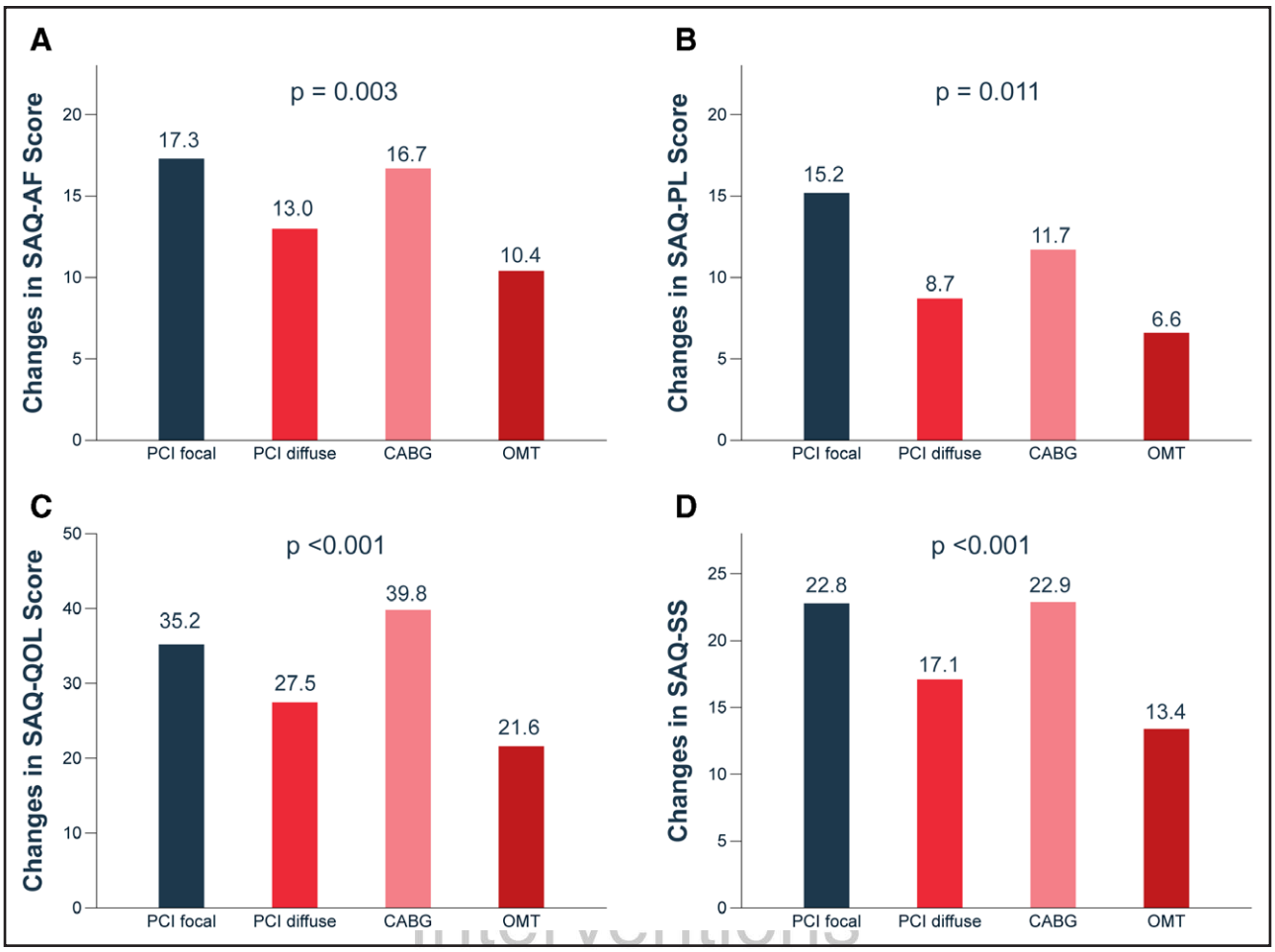

Figure 4. Improvement in patient-reported outcomes (Seattle Angina Questionnaire [SAQ]) stratified by treatment at 1 year. **A** through **D**, Changes in patient-reported outcomes at 1 year across the 4 domains of the SAQ. **A**, Angina frequency (AF), (**B**) physical limitation (PL), (**C**) quality of life (QOL), and (**D**) the overall summary score. PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass grafting; and OMT, optimal medical therapy.

Despite its extensive clinical validation, the SAQ has limitations in fully capturing the complex nature of patients' symptoms. Additionally, the SAQ may be less sensitive to detecting changes, particularly in patients with milder baseline symptoms. Novel strategies with symptom-recording apps might be preferable for future studies because of a more patient-specific symptoms assessment and the possibility of obtaining a daily symptoms assessment.[4] Nevertheless, the findings of this study confirm the greater effectiveness of PCI in patients with high PPG indicative of functional focal CAD. Besides the pathophysiological CAD pattern, other procedural factors have been linked with symptomatic improvement. For example, the ORBITA-STAR study (Systematic Trial of Angina Assessment Before Revascularization) showed that the similarity of the symptoms during balloon inflation predicted symptom improvement after PCI.[18] Furthermore, the presence of microvascular dysfunction has been postulated as a potential cause of angina after PCI. The CorMicA-PCI study (Angina After PCI: A Systems Medicine Study, NCT06854302) is currently investigating the role of diffuse coronary atherosclerosis and microvascular dysfunction on angina post-PCI.

One of the main advantages of PPG is the standardization of the diagnosis of diffuse disease. Until now, there has been no consensus on how to treat diffuse CAD. Van Beek,[19], in a single-center study, found no difference between CABG and optimal medical therapy in terms of symptom reduction or clinical outcomes after 2 years of follow-up in patients with hemodynamically significant diffuse disease based on FFR pullbacks. The present study shows a differential symptom improvement among patients treated with PCI, CABG, or medical therapy. Patients with focal disease treated with PCI reported the greatest improvement across all SAQ domains compared with those with diffuse disease treated with PCI, CABG, or medical therapy. The findings of this study also suggest that CABG may provide a greater symptomatic benefit compared with optimal medical therapy. However, a randomized clinical trial is warranted to determine the optimal treatment strategy for patients with diffuse disease. The emergence of the PPG provides a valuable

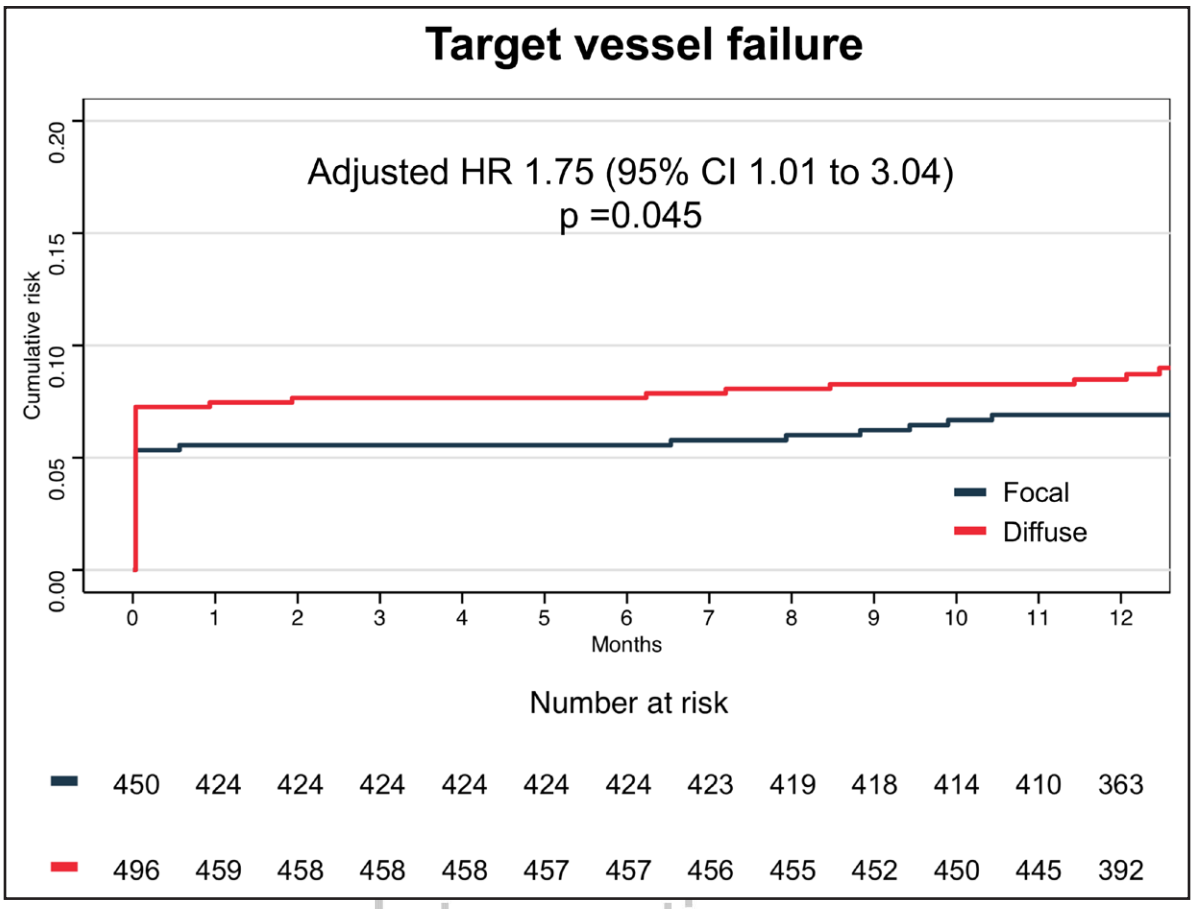

Figure 5. Kaplan-Meier of target vessel failure stratified by focal and diffuse coronary artery disease.
The red line corresponds to patients with diffuse disease (pullback pressure gradient [PPG] <0.62), while the blue line represents patients with focal disease. Hazard ratio (HR) adjusted by age, gender (male), body mass index (BMI), dyslipidemia, hypertension, diabetes, smoking, prior percutaneous coronary intervention (PCI) in the target vessel, clinical presentation (stable angina vs ACS), pullback pressure gradient (PPG), pre-PCI fractional flow reserve (FFR), vessel type (left anterior descending [LAD]), and antianginal medication use at follow-up.

tool to characterize this population and support future trials targeting diffuse CAD.

The 1-year TVF rate was higher in patients with diffuse CAD treated with PCI compared with those with focal CAD treated with PCI, as well as those treated with CABG or medical therapy. This difference was primarily driven by a higher incidence of periprocedural myocardial infarction in the diffuse PCI group. After excluding procedural complications, overall event rates were low and comparable across all treatment strategies. Notably, the low event rate in patients with hemodynamically significant diffuse disease managed with medical therapy is reassuring. These findings support the idea that an initial conservative approach with medical therapy may be appropriate for patients with diffuse disease.

The study's results have significant implications for the management of CAD. Patients with high PPG undergoing PCI are expected to be free from symptoms at follow-up. This may influence the medical management after the procedure and the interpretation of new or residual symptoms at follow-up. In contrast, in patients with low PPG treated with PCI, residual angina can be expected, and this may help to individualize antianginal medication after the procedure. Moreover, understanding the association between CAD patterns assessed by PPG and residual symptoms may also be helpful in the shared clinical decision-making process during patient consent for PCI. Furthermore, because of the predictive capacity of PPG for post-PCI FFR and the association between low post-PCI FFR and adverse clinical outcomes, patients with low PPG indicative of diffuse coronary atherosclerosis may be at higher risk of events after PCI. In this study, patients with diffuse disease received more, longer, and smaller stents; procedural factors associated with target vessel failure at follow-up.[5] Larger studies with longer follow-ups should address the impact of PPG on clinical outcomes.

Limitations

While the study provides unique insights using a novel characterization of CAD based on coronary physiology with PPG, it has limitations. The single-arm design and the lack of a control group limit the ability to draw definitive

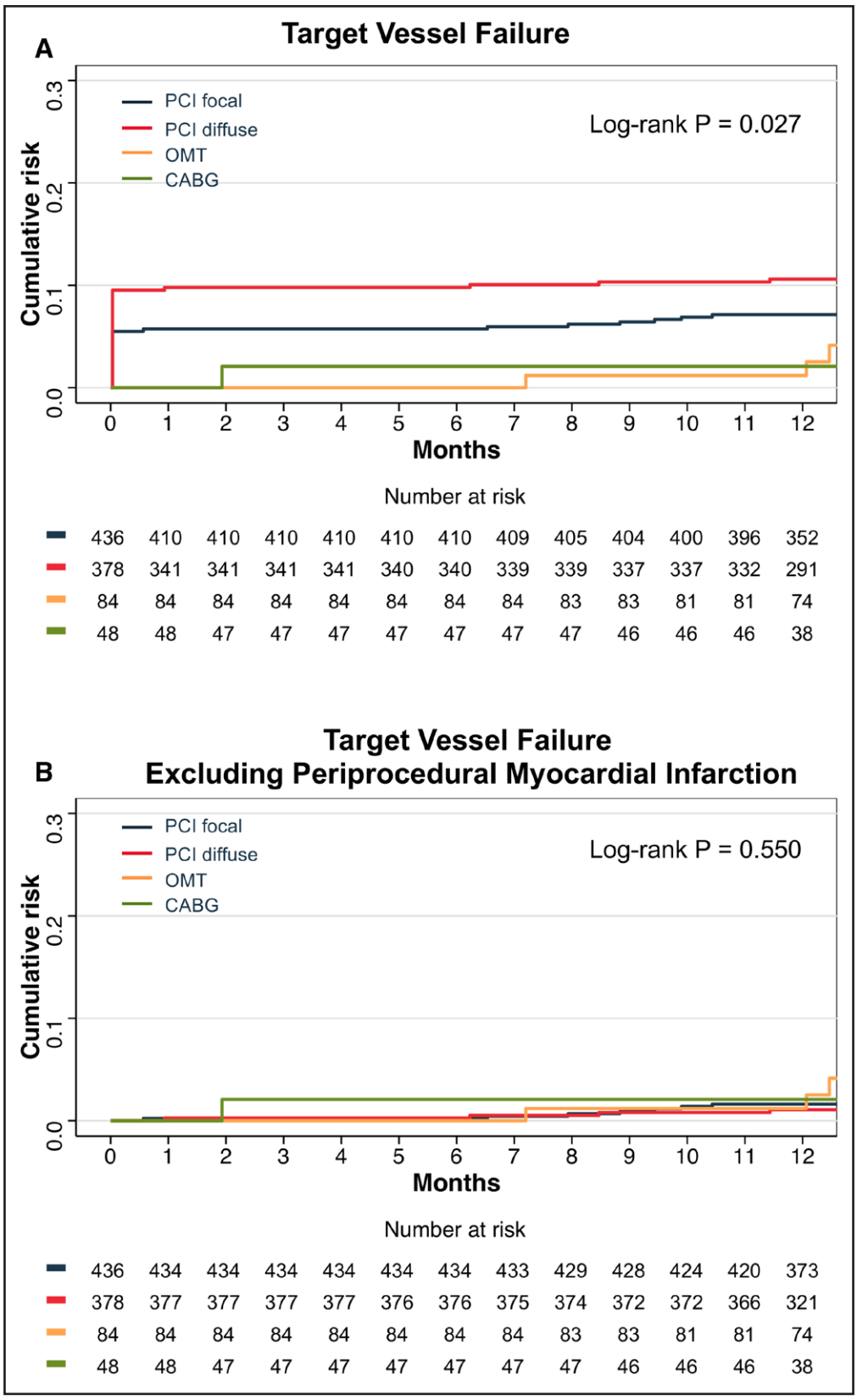

Figure 6. Target vessel failure (TVF) rate stratified by treatment at 1 year.
A, Survival curves with the TVF rate were highest in patients with diffuse disease treated with percutaneous coronary intervention (PCI), followed by those with focal disease treated with PCI, and lower in patients treated with coronary artery bypass grafting (CABG) and optimal medical therapy (OMT). **B**, After excluding periprocedural myocardial infarction (MI), TVF rates were similar across all treatment groups.

conclusions about the benefit of a PPG-guided treatment strategy. Moreover, the study design does not provide an answer to the question of the optimal treatment approach for diffuse disease. The open-label nature also introduced treatment bias (confounding by indication), as patients with the most extensive diffuse disease or fewer symptoms were more likely to be deferred from PCI; this fact limits the comparison between treatment options for diffuse disease. In addition, PPG Global was not powered to assess differences in clinical outcomes; hence, the study's results should be interpreted as hypothesis-generating. The study also relied on physician discretion for treatment selection, and the study protocol did not guide how to manage the patient according to the PPG value. Although we presented the results using a PPG cutoff, future research should focus on defining a PPG threshold to inform clinical decision-making. Importantly, inclusion criteria relied on the presence of significant stenosis amenable to PCI; therefore, these results do not apply to patients with extensive multivessel CAD considered for CABG. Further research, with a randomized controlled trial, is necessary to validate these findings and establish the benefits of a PPG-guided PCI strategy.

Conclusions

PPG was significantly associated with symptom improvement in patients with obstructive CAD. Patients with high PPG experienced greater angina relief at 1 year compared with those with low PPG. Importantly, this association was independent of FFR, highlighting PPG's added value in predicting symptomatic benefit from PCI. By reflecting the physiological pattern of disease and its relation to symptom relief after treatment, PPG may help inform revascularization strategies. The health and economic benefits merit prospective evaluation in a randomized trial.

ARTICLE INFORMATION

Received July 23, 2025; accepted January 7, 2026.

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Acknowledgments

The authors would like to thank the team of OPTIMA Education for their assistance in designing the figures.

Sources of Funding

Pullback Pressure Gradient Global was sponsored by the Cardiovascular Research Institute Aalst with a Research Grant from Abbott Vascular.

Disclosures

Dr Mizukami reports receiving research grants from Boston Scientific and speaker fees from Abbott Vascular, CathWorks, and Boston Scientific. Dr Munhoz reports speaker fees from Abbott Vascular. Dr Matsuo has received consulting fees from Kaneka and Zeon, and speaker's fees from Abbott Medical Japan, Boston Scientific, Philips, and Amgen. Dr Amano reports receiving lecture fees from Astellas Pharma, AstraZeneca, Bayer, Daiichi Sankyo, and Bristol-Myers Squibb. Dr Ko has received consulting fees from Canon Medical, Abbott, Medtronic, and has equity in Artrya. Dr Biscaglia received research grants provided by Sahajanand Medical Technologies (SMT), Medis Medical Imaging, Eukon S.r.l., Siemens Healthineers, Abbott Vascular, General Electric (GE) Healthcare, and Insight Lifetech and a speaker's fee from SMT, Medis Medical Imaging, Eukon S.r.l., Abbott Vascular, and Siemens Healthineers. reports speaker and advisory board fees from Abbott, Boston Scientific, and Novo Nordisk. Dr Leone reports receiving consultancy fees from Abbott and honoraria for sponsored symposiums from Abbott, Medtronic, and Abiomed. Dr Fearon receives institutional research support from Abbott, CathWorks, and Medtronic and has consulting relationships with ShockWave and Edwards LifeScience and stock options from HeartFlow. Dr Christiansen has received consulting fees from Abbott Medical Denmark A/s. Dr Yong has received minor honoraria from Abbott Vascular and research grants from Abbott Vascular and Philips. Dr Escaned is supported by the Intensification of Research Activity project INT22/00088 from the Spanish Instituto de Salud Carlos III, and received speaker and advisory board member fees from Abbott and Philips. Dr Storozhenko reports a grant provided by the EAPCI Fellowship program. Dr Collison has received consulting fees from Abbott. Dr Berry is used by the University of Glasgow, which holds consultancy and research agreements for his work with Abbott Vascular, AskBio, AstraZeneca, Boehringer Ingelheim, CorFlow, Edwards Lifesciences, Merck, Servier, Novartis, Roche, Siemens Healthcare, and Zoll Medical. Dr Berry receives research funding from the British Heart Foundation (RG/F/23/110104, FS/MBPhD/22/28011, PG/19/28/34310, PG/18/52/33892) and Medical Research Council (MR/S018905/1). TWJ has received consultancy/speaker fees from Abbott Vascular, Boston Scientific, Medtronic, Shockwave, and Terumo, and research grants from Abbott Vascular. Dr Perera has received research grant support from Abbott Vascular, HeartFlow, and Philips. Dr Jeremias has received consulting fees from Canon Medical, Artrya Medical, and Boston Scientific. NHJP has received research grants from Abbott and Hexacath, and consultancy fees from Abbott, GE, Philips, and HeartFlow, and has equity in General Electric (GE), Philips, and HeartFlow. Dr Ali reports institutional grant support from Abbott, Abiomed, Acist, Amgen, Boston Scientific, CathWorks, Canon Medical, Conavi, Heartflow, Inari, Medtronic, the US National Institutes of Health, Nipro, OpSens Medical, Medis, Philips, Shockwave, Siemens, SpectraWAVE, Teleflex. Consulting fees from Abiomed, AstraZeneca, Boston

Scientific, CathWorks, OpSens Medical, Philips, Shockwave, and equity in Elucid, Lifelink, SpectraWAVE, and VitalConnect. Dr Korngold is an employee of Abbott Vascular. Dr Wilgenhof reports a research grant provided by the CardioPaTh PhD program and speaker fees from Abbott Vascular. Dr Pijls reports receiving research grants from Abbott and Hexacath, has equity in ASML, Heartflow, Philips, and General Electrics Receives fees from Coroventis and Hexacath, and has patents pending in the field of the Coronary Microcirculation and Aortic valve stenosis. Dr De Bruyne reports receiving consultancy fees from Boston Scientific and Abbott and research grants from Coroventis Research, Pie Medical Imaging, CathWorks, Boston Scientific, Siemens, HeartFlow, and Abbott Vascular. Dr Johnson received internal funding from the Weatherhead PET Center for Preventing and Reversing Atherosclerosis; has received significant institutional research support from St. Jude Medical (CONTRAST, NCT02184117) and Philips Volcano (DEFINE-FLOW, NCT02328820) for other studies using intracoronary pressure and flow sensors; has an institutional licensing agreement with Boston Scientific for the smart-minimum FFR algorithm (now commercialized under 510(k) K191008); and has patents pending on diagnostic methods for quantifying aortic stenosis and TAVI physiology, and on methods to correct pressure tracings from fluid-filled catheters. Dr Collet reports receiving research grants from Biosensors, Coroventis Research, Medis Medical Imaging, Pie Medical Imaging, CathWorks, Boston Scientific, Siemens, HeartFlow, and Abbott Vascular; and consultancy fees from HeartFlow, OpSens Medical, Abbott Vascular, and Philips Volcano, and has patents pending on diagnostic methods for coronary artery disease. The other authors report no conflicts.

Supplemental Material

Figure S1
Tables S1–S8

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