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ORIGINAL RESEARCH

Prognostic Implications of Prestent Pullback Pressure Gradient and Poststent Quantitative Flow Ratio in Patients Undergoing Percutaneous Coronary Intervention

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BACKGROUND: Coronary diffuse disease associates with poor outcomes, but little is known about its role after percutaneous coronary intervention (PCI). We aimed to investigate the prognostic implication of pre-PCI focal or diffuse disease patterns combined with post-PCI quantitative flow ratio (QFR).

METHODS AND RESULTS: Pre-PCI QFR derived pullback pressure gradient (PPG) (QFR-PPG) was measured to assess physiological disease patterns for 1685 included vessels; the vessels were classified according to dichotomous pre-PCI QFR-PPG and post-PCI QFR. Vessel-oriented composite outcome, a composite of vessel-related ischemia-driven revascularization, vessel-related myocardial infarction, or cardiac death at 2 years was compared among these groups. Vessels with low pre-PCI PPG (3.9% versus 2.0%, hazard ratio [HR], 1.93; 95% CI, 1.08–3.44; *P*=0.02) or low post-PCI QFR (9.8% versus 2.7%, HR, 3.78; 95% CI, 1.61–8.87; *P*=0.001) demonstrated higher vessel-oriented composite outcome risk after stent implantation. Of note, despite high post-PCI QFR achieved, vessels with low pre-PCI QFR-PPG presented higher risk of vessel-oriented composite outcome than those with high pre-PCI QFR-PPG (3.7% versus 1.8%, HR, 2.03; 95% CI, 1.09–3.76; *P*=0.03) and pre-PCI QFR-PPG demonstrated direct prognostic effect not mediated by post-PCI QFR. Integration of groups classified by pre-PCI QFR-PPG and post-PCI QFR showed significantly higher discriminant and reclassification abilities than clinical factors (C-index 0.77 versus 0.72, *P*=0.03; integrated discrimination improvement 0.93%, *P*=0.04; net reclassification index 0.33, *P*=0.02).

CONCLUSIONS: Prognostic value of pre-PCI focal or diffuse disease patterns assessed by QFR-PPG index was retained even after successful PCI, which is mostly explained by its direct effect that was not mediated by post-PCI QFR. Integration of both pre-PCI and post-PCI physiological information can provide better risk stratification in vessels with stent implantation.

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Key Words: percutaneous coronary intervention ■ prognosis ■ pullback pressure gradient ■ quantitative flow ratio

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CLINICAL PERSPECTIVE

What Is New?

- Pullback pressure gradient calculated from quantitative flow ratio estimates physiological coronary diffuse disease and retains its prognostic value even after successful percutaneous coronary intervention with high quantitative flow ratio achieved.

What Are the Clinical Implications?

- As both pre-percutaneous coronary intervention functional diffuseness and post-percutaneous coronary intervention residual disease are related to clinical outcomes, both should be considered in the paradigm for assessment and treatment in coronary artery disease patients.
- Randomized trials are required to confirm whether quantitative flow ratio-pullback pressure gradient guided treatment strategy provides better clinical outcome compared with current standard of care.

Nonstandard Abbreviations and Acronyms

FFR	fractional flow reserve
PPG	pullback pressure gradient
QFR	quantitative flow ratio
QFR-PPG	quantitative flow ratio derived pullback pressure gradient
SYNTAX	Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery
VOCO	vessel-oriented composite outcome

Although fractional flow reserve (FFR)-guided percutaneous coronary intervention (PCI) has been proven to improve clinical outcomes, a substantial proportion of patients continue to experience clinical events attributed to residual disease.[1,2] Accumulated evidence has supported that post-PCI physiological assessments such as FFR and quantitative flow ratio (QFR) could be deemed as functional markers of residual disease burden after stent implantation and are associated with clinical outcomes.[3–8]

However, it should be noted that PCI with stent implantation is basically a local treatment and its effect on final physiology is determined by the interaction of baseline physiological disease burden and plaque distribution (focal or diffuse), adequacy of PCI, and residual disease burden in a target vessel,[6] whereas post-PCI FFR or QFR just represents residual disease burden among these 3 factors. Therefore, evaluating pre-PCI atherosclerosis patterns might have an additional role beyond post-PCI physiology to predict the fate of a treated vessel.

FFR-derived pullback pressure gradient (PPG) index was recently developed to characterize coronary atherosclerosis patterns.[9] Nevertheless, the need of a motorized pressure wire pullback device during continuous hyperemia may pose a barrier to its clinical application. QFR can provide the virtual pullback curve by depicting pressure at each point along the interrogated vessel. A recent study has demonstrated that PPG derived from a virtual QFR pullback curve (QFR-PPG) is feasible to suggest the physiological plaque distribution and to discriminate focal from diffuse disease.[10,11] Absolute quantification of coronary disease patterns makes it possible to evaluate the prognostic value of baseline coronary diffuseness beyond the visual assessment, especially after stent implantation, which has been rarely investigated until now.

In this context, our study aimed to investigate the independent and additive prognostic implications of a novel risk stratification tool based on pre-PCI functional disease patterns assessed by QFR-PPG and post-PCI QFR in vessels with stent implantation.

METHODS

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

Study Population

The study population was derived from the PANDA III study[12] (Comparison of BuMA eG Based Biodegradable Polymer Stent With EXCEL Biodegradable Polymer Sirolimus-eluting Stent in "Real-World" Practice; NCT02017275).

Study flow is shown in Figure S1. In brief, vessels with measurable pre- and post-PCI QFR were included. After excluding vessels in which pre-PCI QFR-PPG index calculation failed, 1685 vessels from 1395 patients were included for final analysis. The enrolled patients were not taking part in conflicting studies and all provided written informed consent. The PANDA III trial and the present study protocol were approved by an institutional review committee and followed the principles of the Declaration of Helsinki and registered in clinicaltrials.gov (CHART-ORIGIN [Prognostic Implications of Pre-Stent Pullback Pressure Gradient and Post-stent Quantitative Flow Ratio in Patients Undergoing Percutaneous Coronary Intervention]; NCT05104580).

Study Procedure

Angiographic Analysis and Quantitative Coronary Angiography

Coronary angiography was performed according to standard techniques. Diagnostic angiograms were obtained after intracoronary nitrate (100 or 200 μg) administration.

All angiograms were analyzed at a core laboratory (CCRF, Beijing, China) in a blinded fashion. Quantitative coronary angiography was performed in optimal projections with validated software (QAngio software version 7.3, Medis Medical Imaging Systems, Leiden, the Netherlands). Minimum lumen diameter, reference vessel size, percent diameter stenosis, and lesion length were measured. Angiographic disease severity was also assessed by SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score.

Computational Analysis of QFR

Offline computational analysis of QFR was performed for all eligible patients in the PANDA III trial as described before[13] using commercial software (AngioPlus, Pulse Medical Imaging Technology, Shanghai, China). The pre- and post-PCI QFR analyses were performed in 2 independent core laboratories. Pre-PCI QFR was completed at core laboratory of CCRF, Beijing, China, and the post-PCI QFR analysis was calculated in Interventional Cardiovascular Imaging Core Laboratory, National Center for Cardiovascular Diseases, Beijing, China. Two core laboratories were blinded for any clinical data. QFR computation was performed following a standard operation procedure including 3-dimensional model reconstruction of the target vessel, reference vessel diameter confirmation, acquisition of fixed QFR with fixed hyperemic inflow velocity, and acquisition of contrast QFR with estimated contrast coronary flow using Thrombolysis in Myocardial Infarction frame-count adjustment as previously reported.[13] In the current study, the contrast QFR value was used.[14] Post-PCI QFR values were calculated using the angiography acquired at the end of the procedures. Conventional cutoff value of QFR ≤0.80 and a previous reported QFR cutoff value (<0.89)[7] were used in the analysis. As for patients with acute myocardial infarction, whose angiograms were generated during the index myocardial infarction procedure, most of the included vessels were nonculprit vessels because of the exclusion of total or subtotal occlusion.

Computational Analysis of PPG Index

Offline QFR virtual pullback curves analysis was conducted by an independent core laboratory at Zhongshan Hospital. With virtual QFR pullback curve, which depicts pressure at each point along the vessel(s), the functional pattern of coronary artery disease (CAD) was quantitatively characterized by hyperemic PPG index using the method described before.[9,10] QFR-PPG index was calculated by integrating the magnitude of maximum pressure drop over 20 mm and the extent of functional disease over the entire interrogated vessel. The QFR-PPG index is a continuous metric with higher values approaching 1.0 represent physiologically focal CAD, whereas lower values close to 0 represent physiologically diffuse CAD. For this analysis, cutoff value of QFR-PPG≤0.78 was used as described before.[15]

Data Collection and Follow-Up

Demographic data and cardiovascular risk factors were recorded at the time of the index procedure. In the original PANDA III trial, all adverse events were predefined and adjudicated by a blinded clinical events committee.[12]

As a post hoc analysis, the primary outcome of the present study was vessel-oriented composite outcome (VOCO) at 2 years, which was a composite of cardiac death, target-vessel related myocardial infarction, and ischemia-driven target-vessel revascularization. For the readjudication of VOCO, the original narratives, including initial coronary angiograms and source event documents, were independently reviewed and evaluated by 2 interventional cardiologists (R.Z. and Z.Q.). Cardiac death in patients with multivessel interrogation was assigned to each of the interrogated vessels. Myocardial infarction without clearly identifiable culprit vessel was attributed to all vessels initially treated. In case of disagreement, angiograms and the source documents were reviewed by a third cardiologist to reach the final decision.

Statistical Analysis

All continuous variables are presented as mean and SD or median (interquartile range), according to their distributions (Gaussian distribution or not), which were checked by the Kolmogorov-Smirnov test. The categorical variables are described as number and relative frequency.

Correlation coefficients were calculated to assess relationship of pre-PCI QFR-PPG index and post-PCI QFR. In comparisons of clinical outcomes among groups classified by pre-PCI QFR-PPG index and post-PCI QFR, the cumulative incidence of VOCO was presented as Kaplan-Meier estimates. Cox proportional hazards model was used to estimate hazard ratios (HR) and 95% CI. Multivariable Cox proportional hazards regression analysis with incorporation of covariates was performed to identified independent predictor of 2-year VOCO with adjusted HR and 95% CI. The covariates with clinical relevance or a univariate association with outcome (P<0.10) were entered into multivariable Cox models. The included covariates were age, sex, hypertension, diabetes, hyperlipidemia, smoking, pre-PCI SYNTAX score,

post-PCI in-stent percent diameter stenosis by quantitative coronary angiography, and residual SYNTAX score. Subgroup analysis was performed according to the diagnosis of acute myocardial infarction (AMI) and the *P* value for interaction was calculated. Mediation analysis was used to explore the direct and indirect effect of pre-PCI QFR-PPG index on VOCO by setting post-PCI QFR as a mediator and the same covariates in multivariable Cox regression model as confounders.[16] Compared with the predictive model including clinical risk factors (age, hypertension, diabetes, creatinine clearance, family history of CAD, previous PCI, peripheral vascular disease, AMI, residual SYNTAX score), the additional prognostic value of new stratification by pre-PCI QFR-PPG and post-PCI QFR was evaluated by the receiver-operating characteristic curve analysis with area under the curve, category-free net reclassification index, and the integrated discrimination improvement.

All probability values were 2 sided, and *P* values <0.05 were considered statistically significant. The statistical package SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) and statistical package R, version 3.6.2 (R Foundation for Statistical Computing), were used for statistical analysis.

RESULTS

Patient and Lesion Characteristics

Among 2146 vessels from 1744 patients with analyzable paired pre- and post-PCI QFR, 430 vessels with total or subtotal occlusion were excluded, 31 vessels were excluded because of QFR pullback curve abstraction

Table 1. Baseline Characteristics According to Pre-PCI QFR-PPG and Post-PCI QFR

	Total (N_V=1685)	High post-PCI QFR (>0.80)		Low post-PCI QFR (≤0.80)
		Group 1 (N_V=881) High pre-PCI QFR-PPG	Group 2 (N_V=740) Low pre-PCI QFR-PPG	Group 3 (N_V=64)
Angiographic				
Vessel SYNTAX score	6.00 (3.00–9.00)	5.00 (2.00–7.00)	7.00 (5.00–12.00)	9.00 (5.00–15.75)
Vessel location				
Left anterior descending artery	857 (50.9)	397 (45.1)	426 (57.6)	34 (53.1)
Left circumflex artery	369 (21.9)	246 (27.9)	111 (15.0)	12 (18.8)
Right coronary artery	459 (27.2)	238 (27.0)	203 (27.4)	18 (28.1)
Bifurcation lesion	700 (41.5)	331 (37.6)	334 (45.1)	35 (54.7)
Severe tortuosity	81 (4.8)	20 (2.3)	53 (7.2)	8 (12.5)
Severe calcification	68 (4.0)	21 (2.4)	43 (5.8)	4 (6.3)
Tandem lesion*	417 (24.8)	57 (6.5)	303 (40.9)	57 (89.1)
Preprocedure QCA†				
Reference vessel diameter, mm	2.72 (2.44–3.08)	2.77 (2.47–3.15)	2.68 (2.41–3.02)	2.61 (2.32–3.00)
Minimal lumen diameter, mm	0.78 (0.50–1.06)	0.83 (0.54–1.09)	0.73 (0.48–1.01)	0.68 (0.46–1.07)
Diameter stenosis, %	69.05 (59.72–80.02)	69.04 (59.43–79.69)	69.08 (60.07–80.12)	68.66 (59.43–83.30)
Lesion length, mm	18.32 (11.99–28.28)	14.60 (11.03–21.13)	25.21 (15.73–36.75)	15.82 (9.25–21.51)
Procedural information				
Balloon predilation	1525 (91.3)	790 (90.6)	677 (92.1)	58 (92.1)
Stents per vessel	1.00 (1.00–2.00)	1.00 (1.00–1.00)	1.00 (1.00–2.00)	1.00 (1.00–1.00)
Total stent length per vessel, mm	28.00 (20.0–40.0)	24.00 (18.00–30.00)	36.00 (25.00–52.00)	24.00 (18.00–30.00)
Balloon post-dilation	933 (55.87)	457 (52.4)	438 (59.6)	38 (60.3)
Postprocedure QCA				
In-stent reference vessel diameter, mm	2.75 (2.47–3.09)	2.80 (2.51–3.18)	2.70 (2.43–2.99)	2.61 (2.40–2.97)
In-stent minimal lumen diameter, mm	2.51 (2.25–2.83)	2.58 (2.29–2.91)	2.43 (2.21–2.72)	2.45 (2.18–2.76)
In-stent diameter stenosis, %	7.64 (4.57–11.29)	7.34 (4.33–10.77)	7.92 (4.94–11.81)	8.03 (3.57–12.79)
Physiological index				
Pre-PCI QFR	0.68 (0.53–0.78)	0.74 (0.64–0.83)	0.60 (0.44–0.72)	0.45 (0.20–0.61)
Pre-PCI QFR-PPG	0.79 (0.67–0.87)	0.86 (0.82–0.90)	0.67 (0.58–0.73)	0.58 (0.49–0.64)
Post-PCI QFR	0.99 (0.96–1.00)	0.99 (0.98–1.00)	0.98 (0.94–0.99)	0.75 (0.66–0.78)

Values are median (interquartile range) or n (%). N_V indicates number of vessels; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; QFR, quantitative flow ratio; QFR-PPG, quantitative flow ratio derived pullback pressure gradient; and SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

*More or 2 lesions per vessel.

†Value derived from 3-dimensional angiography in QFR analysis.

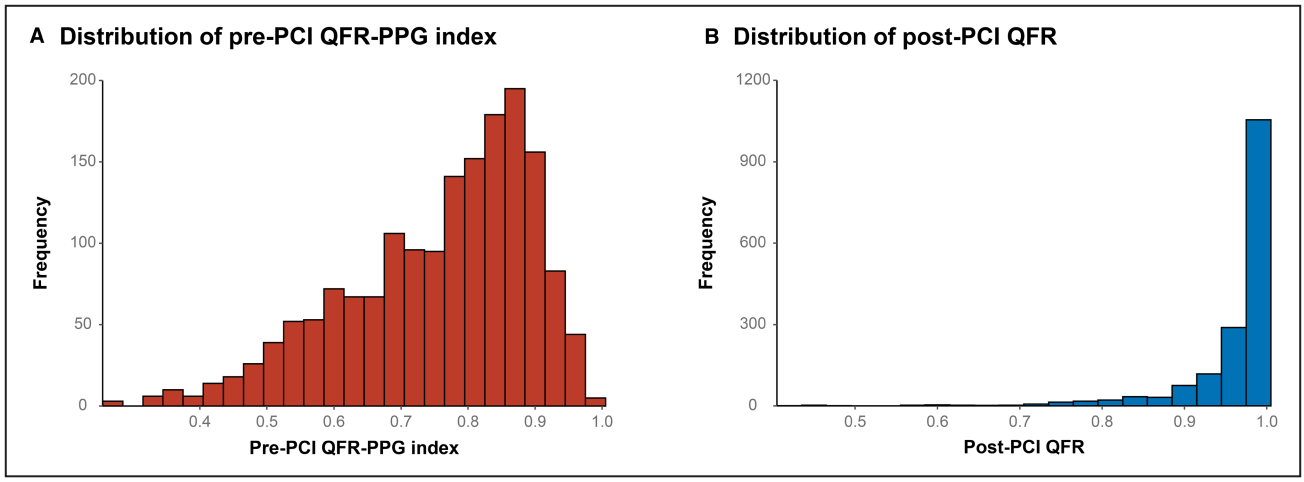


Figure 1. Distribution Pre-PCI QFR-PPG index and post-PCI QFR.
Distributions of (**A**) pre-PCI QFR-PPG index, and (**B**) post-PCI QFR are presented. PCI, percutaneous coronary intervention; QFR, quantitative flow reserve; QFR-PPG, quantitative flow reserve derived pullback pressure gradient.

failure, leaving 1395 patients with 1685 vessels included in our study. The mean age was 61.3±10.5 and 68.8% were men (Table S1). The patient-level comparison of characteristics between patients with high or low pre-PCI QFR-PPG (defined as at least 1 vessel QFR-PPG ≤0.78) is listed in Table S1. The characteristics for overall target vessels as well as when stratified according to binary pre-PCI QFR-PPG index and post-PCI QFR are presented in Table 1. Among the included vessels, 857 (50.9%) were left anterior descending arteries, 369 (21.9%) were left circumflex arteries, and 459 (27.2%) were right coronary arteries. The distribution of pre-PCI QFR-PPG index and post-PCI QFR is shown in Figure 1, with median values of 0.79 (0.67–0.87) and 0.99 (0.96–1.00), respectively.

Clinical Outcomes According to Pre-PCI QFR-PPG Index or Post-PCI QFR

Figure 2 presents the cumulative incidence of VOCO during 2 years of follow-up. There were 800 vessels with low pre-PCI QFR-PPG and 885 vessels with high pre-PCI QFR-PPG, respectively. Vessels with low pre-PCI QFR-PPG index had a higher risk of VOCO than those with high pre-PCI QFR-PPG index (3.9% versus

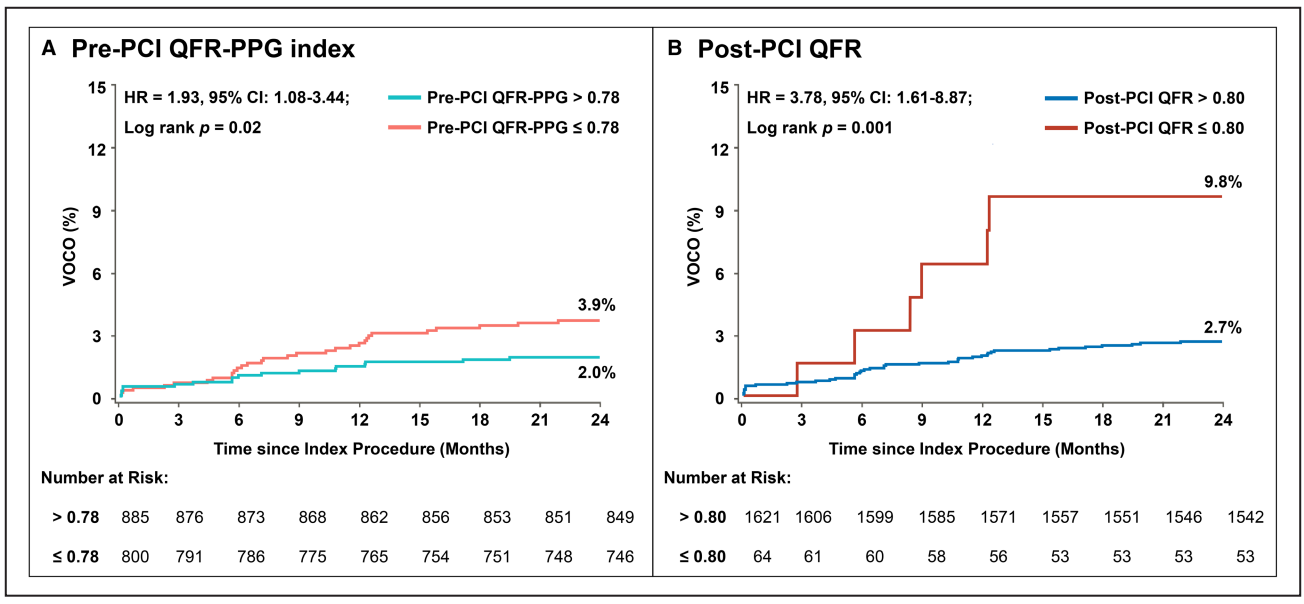


Figure 2. Cumulative incidence of VOCO at 2 years from index procedure according to pre-PCI QFR-PPG index or post-PCI QFR levels.
Kaplan-Meier curves of VOCO at 2-year follow-up are presented according to high and low (**A**) pre-PCI QFR-PPG index or (**B**) post-PCI QFR. HR indicates hazard ratio; PCI, percutaneous coronary intervention; QFR, quantitative flow reserve; QFR-PPG, quantitative flow reserve derived pullback pressure gradient; and VOCO, vessel-oriented composite outcome.

2.0%; HR, 1.93; 95% CI, 1.08–3.44; *P*=0.02). Similarly, vessels with low post-PCI QFR had a higher risk of VOCO than those with high post-PCI QFR (9.8% versus 2.7%; HR, 3.78; 95% CI, 1.61–8.87; *P*=0.001).

Both pre-PCI QFR-PPG index (per 0.1 decrease of QFR-PPG, HR, 1.28; 95% CI, 1.07–1.54; *P*=0.007) and post-PCI QFR (per 0.1 decrease of QFR, HR, 1.66; 95% CI, 1.34–2.06; *P*<0.001) showed significant association with the cumulative incidence of VOCO. After multivariate adjustment for potential confounding factors, both of these indices remained independently associated with increase in the risk for VOCO (per 0.1 decrease of PPG, adjusted HR, 1.23; 95% CI, 1.01–1.51; *P*=0.04; per 0.1 decrease of QFR, adjusted HR, 1.60; 95% CI, 1.26–2.02; *P*<0.001) (Tables S2 and S3).

However, the prognostic value of post-PCI QFR was attenuated among vessels with low pre-PCI QFR-PPG index (Figure S2).

Clinical Outcomes Classified by High and Low Pre-PCI QFR-PPG Index and Post-PCI QFR

Scatter plots between pre-PCI QFR-PPG index and post-PCI QFR are illustrated in Figure S3, and a modest correlation (*R*=0.37, *P*<0.001) was observed. Based on pre-PCI QFR-PPG index and post-PCI QFR, included vessels were classified into 3 groups: Group 1, high pre-PCI QFR-PPG index and high post-PCI QFR; Group 2, low pre-PCI QFR-PPG index and high post-PCI QFR; and Group 3, low post-PCI QFR regardless of pre-PCI QFR-PPG index.

Table 2 describes the details of clinical events. VOCO event curves for the 3 groups classified according to pre-PCI QFR-PPG index and post-PCI QFR are shown in Figure 3. The cumulative incidence of VOCO at 2 years was 1.8%, 3.7%, and 9.8% for Group 1 to Group 3, respectively, among which vessels with low post-PCI QFR showed the highest risk compared with other groups regardless of pre-PCI QFR-PPG index (all *P* values for comparisons <0.05). Among vessels with high post-PCI QFR, those with low pre-PCI QFR-PPG index presented higher VOCO risk (3.7% versus 1.8%, HR, 2.03; 95% CI, 1.09–3.76; *P*=0.03) compared with those with high pre-PCI QFR-PPG index. An analysis with a previous reported post-PCI QFR cutoff value (0.89) had consistent results (Figure S4). The groups classified by pre-PCI QFR-PPG and post-PCI QFR were independently associated with the occurrence of VOCO (Table S4). The subgroup group analysis revealed similar results in AMI and no-AMI groups with no significant interaction between AMI and the 3 groups stratified by post-PCI QFR and pre-PCI QFR-PPG (Table S5).

Mediation analysis with post-PCI QFR as a mediator revealed that pre-PCI QFR-PPG index exerted a significant direct effect (80.0%) on the risk of VOCO, which was not mediated by post-PCI QFR (Figure 4). Predictability of clinical factors was compared with combination of groups classified by pre-PCI QFR-PPG index and post-PCI QFR, the latter showed a higher C-index than clinical factors alone (C-index 0.77 versus 0.72; integrated discrimination improvement 0.93%, P=0.04; category-free net reclassification index 0.33, P=0.02) (Figure 5).

DISCUSSION

The current study investigated the clinical relevance of baseline physiological disease patterns assessed by

Table 2. Two-Year Clinical Outcomes According to Pre-PCI QFR-PPG and Post-PCI QFR

	Stratifications	No. of events/total vessels (%)*	Crude HR (95% CI)	Crude *P* value	Adjusted HR† (95% CI)	Adjusted *P* value
Vessel-oriented composite outcome	Group 1	16/881 (1.8)	Reference	…	Reference	…
	Group 2	27/740 (3.7)	2.03 (1.09–3.76)	0.03	1.95 (1.02–3.71)	0.04
	Group 3	6/64 (9.8)	5.54 (2.17–14.2)	<0.001	5.28 (1.89–14.8)	0.002
Cardiac death	Group 1	6/881 (0.7)	Reference	…	Reference	…
	Group 2	7/740 (1.0)	1.39 (0.47–4.14)	0.55	1.48 (0.47–4.65)	0.50
	Group 3	1/64 (1.6)	2.36 (0.28–19.6)	0.43	3.31 (0.35–31.7)	0.30
Nonprocedural vessel-related myocardial infarction	Group 1	5/881 (0.6)	Reference	…	Reference	…
	Group 2	7/740 (1.0)	1.67 (0.53–5.26)	0.38	1.15 (0.33–3.99)	0.82
	Group 3	2/64 (3.3)	5.76 (1.12–29.7)	0.04	3.74 (0.52–26.7)	0.19
Ischemia-driven target vessel revascularization	Group 1	8/881 (0.9)	Reference	…	Reference	…
	Group 2	17/740 (2.3)	2.56 (1.10–5.92)	0.03	2.69 (1.13–6.44)	0.03
	Group 3	4/64 (6.7)	7.43 (2.24–24.7)	0.001	7.57 (2.05–27.9)	0.002

HR indicates hazard ratio; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; QFR-PPG, quantitative flow ratio derived pullback pressure gradient; and SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

*Values are Kaplan-Meier estimated rates.

†The included covariates in the multivariable-adjusted model were age, sex, hypertension, diabetes, hyperlipidemia, smoking, pre-PCI SYNTAX score, residual SYNTAX score, post-PCI percent diameter stenosis.

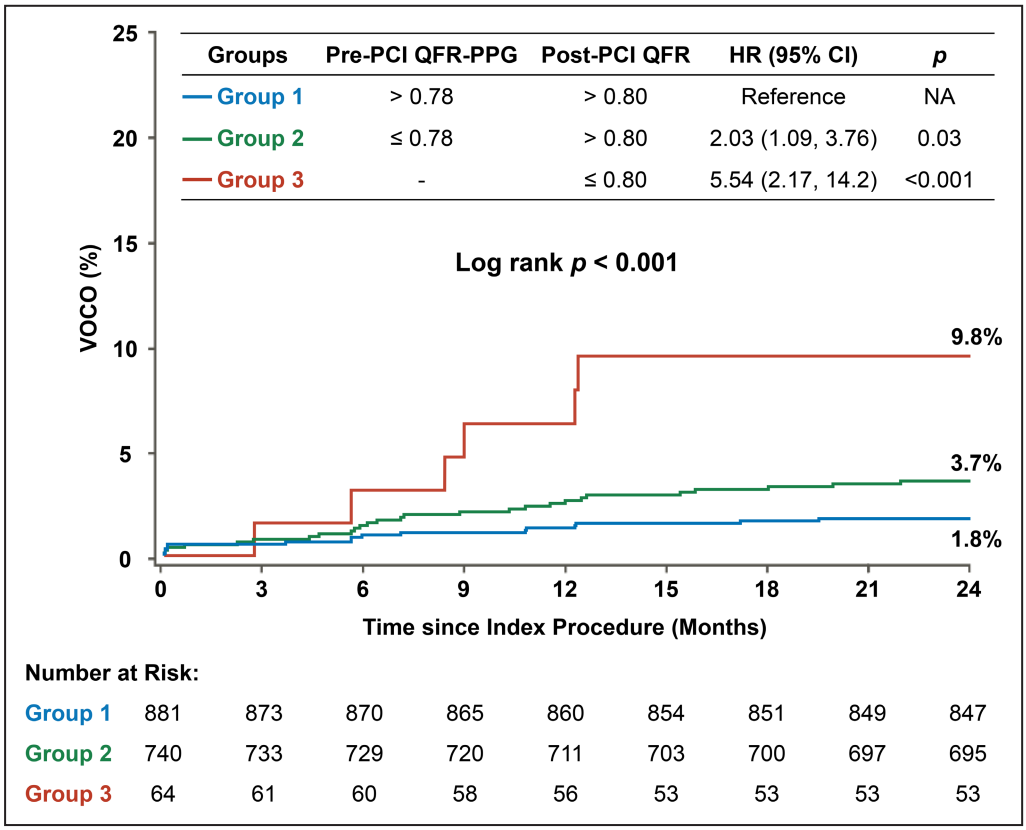
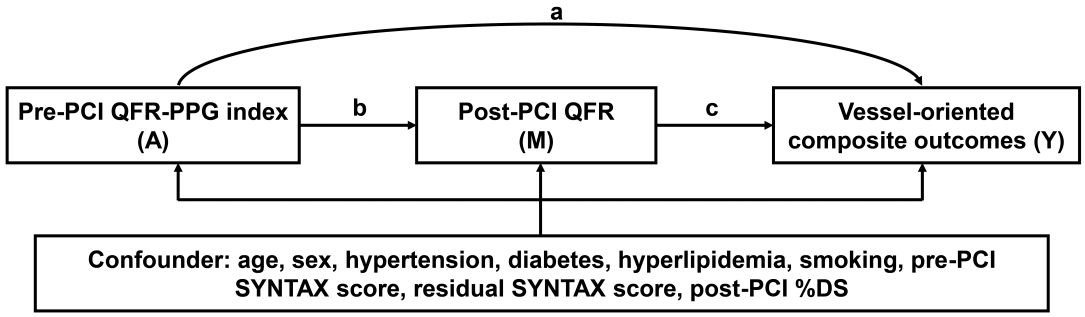


Figure 3. Cumulative incidence of VOCO at 2 years from index procedure according to pre-PCI QFR-PPG index and post-PCI QFR levels.
The vessels were classified according to pre-PCI QFR-PPG index and post-PCI QFR. Kaplan-Meir estimates of 3 groups (Group 1, high pre-PCI QFR-PPG index and high post-PCI QFR; Group 2, low pre-PCI QFR-PPG index and high post-PCI QFR; and Group 3, low post-PCI QFR regardless of pre-PCI QFR-PPG index) are presented. HR indicates hazard ratio; PCI, percutaneous coronary intervention; QFR, quantitative flow reserve; QFR-PPG, quantitative flow reserve derived pullback pressure gradient; and VOCO, vessel-oriented composite outcome.

QFR-PPG index and the prognostic impact of its combination with post-PCI QFR among vessels receiving stent implantation.

Our main findings were as follows. First, both pre-PCI QFR-PPG index and post-PCI QFR were associated with the risk of VOCO after PCI. Second, among vessels receiving stent implantation, those with low post-PCI QFR demonstrated poor prognosis; nevertheless, even among vessels achieving high post-PCI QFR, those with baseline diffused disease, represented as low QFR-PPG, had higher VOCO risk than those with focal disease. Third, the association of pre-PCI QFR-PPG with VOCO was mostly mediated by its direct effect and only partly mediated by post-PCI QFR. Fourth, integration of pre-PCI QFR-PPG index and post-PCI QFR into clinical factors showed significantly improved discrimination and reclassification ability for 2-year VOCO in vessels receiving PCI.

As a 3-dimensional quantitative coronary angiography-based FFR, QFR has been validated against pressure wire-based FFR to assess the functional significance of coronary stenosis.[13,17] Of note, the recently published FAVOR III China study (Comparison of Quantitative Flow Ratio Guided and Angiography Guided Percutaneous Intervention in Patients With Coronary Artery Disease) demonstrated that QFR guided PCI improved clinical outcomes compared with standard angiography-guided PCI at 1-year follow-up.[18] However, 5.8% patients suffered from adverse events in the QFR-guided group. It is of great clinical importance to explore the potential reasons. First, studies have indicated that a considerable number of patients presenting with anatomically successful PCI results still suffered from functionally unresolved ischemia.[19,20] Moreover, recent studies have demonstrated the post-PCI QFR as a sensitive tool to discriminate patients with residual risk after procedure, and a QFR-based suboptimal functional PCI result was significantly associated with worse outcomes.[7,8] Our results are consistent with these findings, further confirming that lower values of QFR after PCI predict subsequent adverse events. Second, physiological CAD



Association	Estimate	Standard Error	OR (95% CI)	Z	*Pr* > |Z|	Proportion Mediated
Exposure: pre-PCI QFR-PPG ≤0.78; mediator: post-PCI QFR ≤0.80						
Natural direct effect	0.730	0.235	2.08 (1.31-3.29)	3.100	0.002	80.0%
Natural indirect effect	0.124	0.053	1.13 (1.02-1.25)	2.355	0.02	20.0%
Total effect	0.854	0.225	2.35 (1.51-3.65)	3.794	<0.001	100.0%

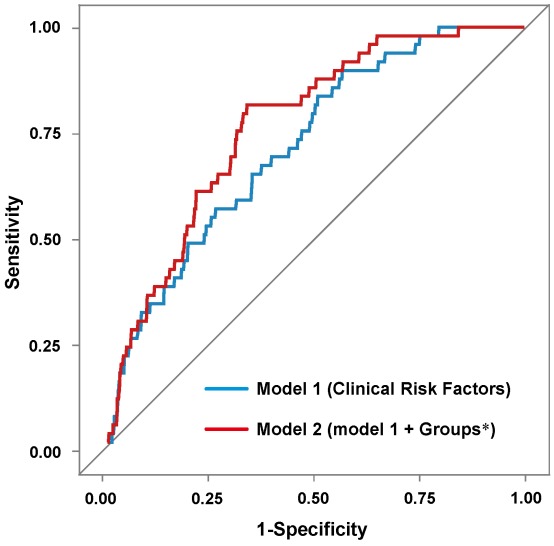
Figure 4. Prognostic value of pre-PCI QFR-PPG index mediated by post-PCI QFR.
The descriptive figure of adjusted mediation analysis by clinical risk factors is presented. Arrows indicate the flow of association. A (exposure) is pre-PCI QFR-PPG index, M (mediator), post-PCI QFR, is a variable that may modify the exposure-outcome association. Y (outcome) is VOCO, a primary end point of this study. L represents a set of confounders. Pathways a, and b-c indicate the direct and indirect pathway from the exposure to the outcome, respectively. DS indicates diameter stenosis; OR, odds ratio; PCI, percutaneous coronary intervention; QFR, quantitative flow reserve; QFR-PPG, quantitative flow reserve derived pullback pressure gradient; and SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

pattern (eg, physiological diffuse disease or focal disease) has also been introduced to explain the unsatisfactory prognosis after anatomically successful PCI.[9] In line with this, we have indicated that not all vessels with physiological ischemia (QFR ≤0.80) can benefit from PCI by showing a higher risk of VOCO among vessels with physiological diffuse disease.[11]

Because stent implantation is a local treatment, vessels with diffuse or focal disease patterns may have different functional results after PCI. Previous studies have demonstrated that post-PCI physiological results depend on pre-PCI pressure drop patterns.[15,21] Vessels with focal disease patterns are more likely to achieve ischemia resolution by implanting stents, whereas those with diffuse disease would require more and longer stents, which is related with decreased procedural success and increased periprocedural complications, and thus worse longer term complications may be anticipated. Besides, given that vessels with diffuse disease may not be good candidates for PCI, post-PCI physiological assessment, although it has prognostic value for the detection of residual disease burden, is too late for the decision of intervention strategy. Therefore, evaluation of baseline atherosclerosis patterns before PCI may be a potential supplement of QFR-guided strategy and deserves more attention.

Recently, PPG index derived from a motorized pressure pullback tracing was proposed to quantify the distribution of coronary atherosclerosis and discriminate focal from diffuse disease.[9] However, inherent technical difficulties with pressure wire pullback, including the need for motorized pullback device and prolonged adenosine infusions, may counteract its advantages. In contrast, QFR virtual pullback curve can be derived from angiographic images and does not require an additional procedure.[10] In the current study, QFR-derived PPG was calculated to evaluate the coronary disease patterns before PCI and a higher risk of VOCO was observed in the low pre-PCI QFR-PPG group, indicating that diffuse disease carries a poorer prognosis compared with focal disease.

However, prognostic implication of the baseline disease patterns after successful stent implantation has rarely been investigated. In the current study, included vessels were classified according to pre-PCI QFR-PPG and post-PCI QFR. In low post-PCI QFR group, the risk of VOCO at 2 years was significantly higher regardless of the pre-PCI QFR-PPG. This is in line with that reported in HAWKEYE (Prospective Validation of the Angio-based Fractional Flow Reserve [Quantitative Flow Ratio] System to Discriminate Patients at Risk of Adverse Events After Stent Implantation) study,[7] the presence of lower QFR values predicted an increased risk for adverse events attributed to several different underlying mechanisms. Interestingly, what our study has added to current findings is that in the high post-PCI QFR group, those with



Model	AUC (95% CI)	Difference in AUC	P value	NRI	P value	IDI	P value
Model1	0.72 (0.65-0.78)	Reference		Reference		Reference	
Model2	0.77 (0.71-0.83)	0.05	0.03	0.33	0.02	0.93%	0.04

Figure 5. Comparison of discrimination and reclassification ability of predictive models for VOCO at 2 years.
Discriminant functions to predict 2-year VOCO are presented. The reference model included clinical risk factors only, including age, hypertension, diabetes, creatinine clearance, family history of CAD, previous PCI, peripheral vascular disease, acute myocardial infarction, residual SYNTAX score. The model with post-PCI QFR and pre-PCI QFR-PPG index significantly increased discriminant and reclassification abilities for predicting clinical outcomes than the reference model. AUC indicates area under curve; CAD, coronary artery disease; IDI, integrated discrimination improvement; NRI, net reclassification index; PCI, percutaneous coronary intervention; QFR, quantitative flow reserve; QFR-PPG, quantitative flow reserve derived pullback pressure gradient; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery; and VOCO, vessel-oriented composite outcome.

low pre-PCI QFR-PPG demonstrated significantly higher VOCO risk than those with high pre-PCI QFR-PPG, indicating that the prognostic impact of baseline functional disease pattern retained despite stent implantation and good physiological results achieved. When assessed as a continuous index, post-PCI QFR showed different prognostic power between groups divided by pre-PCI QFR-PPG. In addition, the mediation analysis showed that the size of the direct prognostic effect of pre-PCI QFR-PPG index not mediated by post-PCI QFR was larger than that of the indirect effect mediated by post-PCI QFR. These results indicate that the independent prognostic value of baseline disease patterns reserved even after successful stent implantation and benefit of PCI was lesser in diffuse lesions causing gradual pressure drop pattern.

Our current study does not undermine the prognostic value of post-PCI physiology but highlights the prognostic value of pre-PCI disease patterns (diffuse or focal) retained even after PCI, indicating that the poor prognosis due to diffused atherosclerosis, represented as low PPG index, may not be reversed by successful PCI.

Considering the fact that QFR is more readily adopted into the workflow of angiography-based diagnostic and interventional procedures with no need of pressure wire and hyperemic agents, and QFR-PPG index can be easily calculated from virtual QFR pullback curves, it can be anticipated that integrated disease burden (QFR) and pattern (QFR-PPG index) assessment might facilitate physiological assessment in clinical practice and further improve the clinical outcomes compared with QFR-guided strategy. Nevertheless, this concept requires prospective validation in future trials. In addition, as the validation of QFR against FFR in its early days, QFR-PPG should also be validated against FFR derived PPG prospectively.

Limitations

There are several limitations in this study. First, this is a post hoc analysis of a published research cohort, and thus inherent limitations of residual confounding factors should be considered. Further studies are needed to confirm our findings. Second, there is no definite cutoff value for PPG index to discriminate focal from diffuse disease. We

used 0.78 as the cutoff, which is derived from our previous report.[15] Further studies with a larger sample size, clinical outcomes, and imaging data are required to validate the most reasonable cutoff value for the QFR-PPG index. Third, the current cohort has a high post-PCI QFR, with relatively low overall adverse events, which may represent low-risk patients included; prospective studies with high-risk patients and complex lesions will be helpful to confirm our findings. Fourth, QFR is theoretically more dependent on anatomical stenosis severity than FFR,[22] and though the prognostic value of post-PCI QFR as well as pre-PCI QFR-PPG has been demonstrated, our study results still need to be checked with invasive pressure wire measurements. Fifth, more than a quarter of the vessels in this study were unanalyzable for QFR, and thus QFR-PPG index could not be calculated, which may bias the results. However, this could be addressed in prospective situations.

CONCLUSIONS

The prognostic implication of pre-PCI functional disease pattern assessed by QFR-PPG index is retained even after successful PCI, and this prognostic value is mostly explained by its direct effect, which is independent of the mediation effect of post-PCI QFR. Integration of pre-PCI QFR-PPG and post-PCI QFR enables better discrimination of high-risk patients after stent implantation.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1–S5
Figure S1–S4

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Supplemental Material

Table S1. Patient Characteristics.

Patient characteristics	Total (N=1,395)	High pre-PCI QFR-PPG (N=664)	Low pre-PCI QFR-PPG (N=731)	*p*
Demographics				
Age (years)	61.3 ± 10.5	60.5 ± 10.5	61.9 ± 10.4	0.013
Male	960 (68.8)	431 (64.9)	529 (72.4)	0.003
Body mass index (kg/m^2)	24.9 ± 3.4	25.0 ± 3.4	24.8 ± 3.5	0.403
Ejection fraction (%)	59.7 ± 8.4	59.6 ± 8.1	59.8 ± 8.7	0.699
Cardiovascular risk factors				
Diabetes mellitus	326 (23.4)	147 (22.1)	179 (24.5)	0.331
Hypertension	891 (63.9)	405 (61.0)	486 (66.5)	0.038
Hyperlipidemia	426 (30.5)	196 (29.5)	230 (31.5)	0.466
Smoking	682 (48.9)	310 (46.7)	372 (50.9)	0.130
Family history of coronary artery disease	64 (4.6)	29 (4.4)	35 (4.8)	0.805
Previous myocardial infarction	236 (16.9)	107 (16.1)	129 (17.6)	0.490
Previous stroke	164 (11.8)	68 (10.2)	96 (13.1)	0.112
Previous PCI	163 (11.7)	68 (10.2)	95 (13.0)	0.129
Peripheral vascular disease	51 (3.7)	20 (3.0)	31 (4.2)	0.281
Creatine clearance, ml/min	91.2 ± 51.0	93.8 ± 63.0	88.8 ± 36.9	0.068
Clinical presentation				
Chronic coronary syndrome	248 (17.8)	117 (17.6)	131 (17.9)	0.939
Acute coronary syndrome	1,147 (82.2)	547 (82.4)	600 (82.1)	0.939
Unstable angina	786 (56.3)	371 (55.9)	415 (56.8)	
NSTEMI	193 (13.8)	92 (13.9)	101 (13.8)	
STEMI	168 (12.0)	84 (12.7)	84 (11.5)	
Multivessel disease	797 (57.1)	296 (44.6)	501 (68.5)	<0.001
Anatomic SYNTAX score	13.7 ± 8.7	10.7 ± 7.3	16.3 ± 9.0	<0.001
Residual SYNTAX score	3.0 [0.0, 7.5]	1.0 [0.0, 6.0]	4.0 [0.0, 9.0]	<0.001

Values are mean ± SD or n (%). N, number of patients; PCI, percutaneous coronary intervention; QFR, quantitative flow ratio; QFR-PPG: QFR derived pullback pressure gradient; SYNTAX, Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

Table S2. Multivariable adjustment for Pre-PCI QFR-PPG Index Predicting 2-Year VOCO.

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	***p* Value**	**HR (95% CI)**	***p* Value**
Age	1.06 (1.03-1.09)	<0.001	1.05 (1.02-1.09)	0.001
Male	0.96 (0.53-1.75)	0.90	1.43 (0.71-2.85)	0.32
Hypertension	1.91 (0.98-3.74)	0.06	1.66 (0.83-3.29)	0.15
Diabetes mellitus	1.05 (0.55-2.01)	0.88	0.94 (0.48-1.83)	0.86
Hyperlipidemia	1.31 (0.73-2.34)	0.36	1.32 (0.73-2.39)	0.36
Smoking	0.77 (0.44-1.36)	0.37	0.79 (0.41-1.52)	0.47
Pre-PCI SYNTAX score	1.03 (1.00-1.06)	0.10	1.02 (0.98-1.06)	0.38
In-stent %DS (per 10% increase)	0.78 (0.46-1.32)	0.35	0.74 (0.44-1.24)	0.25
Residual SYNTAX score	1.00 (0.95-1.05)	0.92	0.96 (0.91-1.02)	0.22
Pre-PCI QFR-PPG index (per 0.1 decrease)	1.28 (1.07-1.54)	0.007	1.23 (1.01-1.51)	0.04

CI, confidence interval; DS, diameter stenosis; HR, hazard ratio; Other abbreviations as in Table S1.

Table S3. Multivariable adjustment for Post-PCI QFR Predicting 2-Year VOCO.

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	***p* Value**	**HR (95% CI)**	***p* Value**
Age	1.06 (1.03-1.09)	<0.001	1.05 (1.02-1.09)	0.001
Male	0.96 (0.53-1.75)	0.90	1.27 (0.63-2.57)	0.51
Hypertension	1.91 (0.98-3.74)	0.06	1.62 (0.82-3.23)	0.17
Diabetes mellitus	1.05 (0.55-2.01)	0.88	0.98 (0.50-1.91)	0.95
Hyperlipidemia	1.31 (0.73-2.34)	0.36	1.34 (0.74-2.43)	0.33
Smoking	0.77 (0.44-1.36)	0.37	0.86 (0.44-1.68)	0.66
Pre-PCI SYNTAX score	1.03 (1.00-1.06)	0.10	1.03 (0.99-1.06)	0.19
In-stent %DS (per 10% increase)	0.78 (0.46-1.32)	0.35	0.79 (0.47-1.32)	0.36
Residual SYNTAX score	1.00 (0.95-1.05)	0.92	0.94 (0.89-1.00)	0.07
Post-PCI QFR (per 0.1 decrease)	1.66 (1.34-2.06)	<0.001	1.60 (1.26-2.02)	<0.001

Abbreviations as in Table S2.

Table S4. Multivariable adjustment for Groups by Pre-PCI QFR-PPG and Post-PCI QFR Predicting 2-Year VOCO.

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	***p* Value**	**HR (95% CI)**	***p* Value**
Age	1.06 (1.03-1.09)	<0.001	1.05 (1.02-1.09)	0.001
Male	0.96 (0.53-1.75)	0.90	1.38 (0.69-2.78)	0.37
Hypertension	1.91 (0.98-3.74)	0.06	1.71 (0.86-3.39)	0.13
Diabetes mellitus	1.05 (0.55-2.01)	0.88	1.01 (0.52-1.96)	0.98
Hyperlipidemia	1.31 (0.73-2.34)	0.36	1.30 (0.72-2.36)	0.38
Smoking	0.77 (0.44-1.36)	0.37	0.80 (0.41-1.55)	0.80
Pre-PCI SYNTAX score	1.03 (1.00-1.06)	0.10	1.01 (0.95-1.06)	0.86
In-stent %DS (per 10% increase)	0.78 (0.46-1.32)	0.35	0.74 (0.44-1.25)	0.26
Residual SYNTAX score	1.00 (0.95-1.05)	0.92	0.97 (0.92-1.02)	0.21
Groups by pre-PCI QFR-PPG and post-PCI QFR*				
Group 1	Reference		Reference	
Group 2	2.03 (1.09-3.76)	0.03	1.95 (1.02-3.71)	0.04
Group 3	5.54 (2.17-14.2)	<0.001	5.28 (1.89-14.81)	0.002

* Groups: group 1, high post-PCI QFR with high pre-PCI QFR-PPG; group 2, high post-PCI QFR with low pre-PCI QFR-PPG; and group 3: low post-PCI QFR.

Abbreviations as in Table S2.

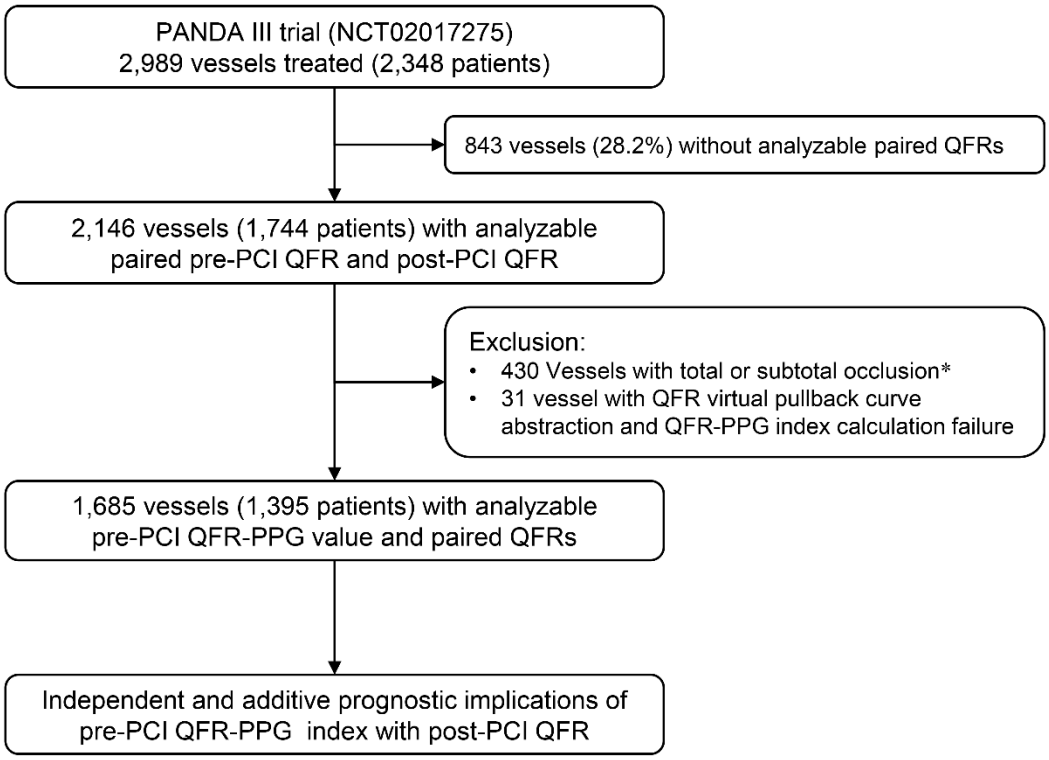
Table S5. Subgroup Analysis of Two-year Clinical Outcomes According to Pre-PCI QFR-PPG and Post-PCI QFR.

	AMI		Non-AMI		*p* for interaction
	HR (95% CI)	*p*	HR (95% CI)	*p*	
Group 1	Reference		Reference		
Group 2	1.81 (0.64, 5.09)	0.260	2.16 (1.00, 4.67)	0.051	0.257
Group 3	1.82 (0.22, 15.08)	0.581	8.39 (2.87, 24.56)	<0.001	

*Group 1, high post-PCI QFR & high pre-PCI QFR-PPG; Group 2, high post-PCI QFR & low pre-PCI QFR-PPG; Group 3, low post-PCI QFR-QFR.

AMI, acute myocardial infarction. Other abbreviations as in Table S2.

Figure S1. Study Flowchart.

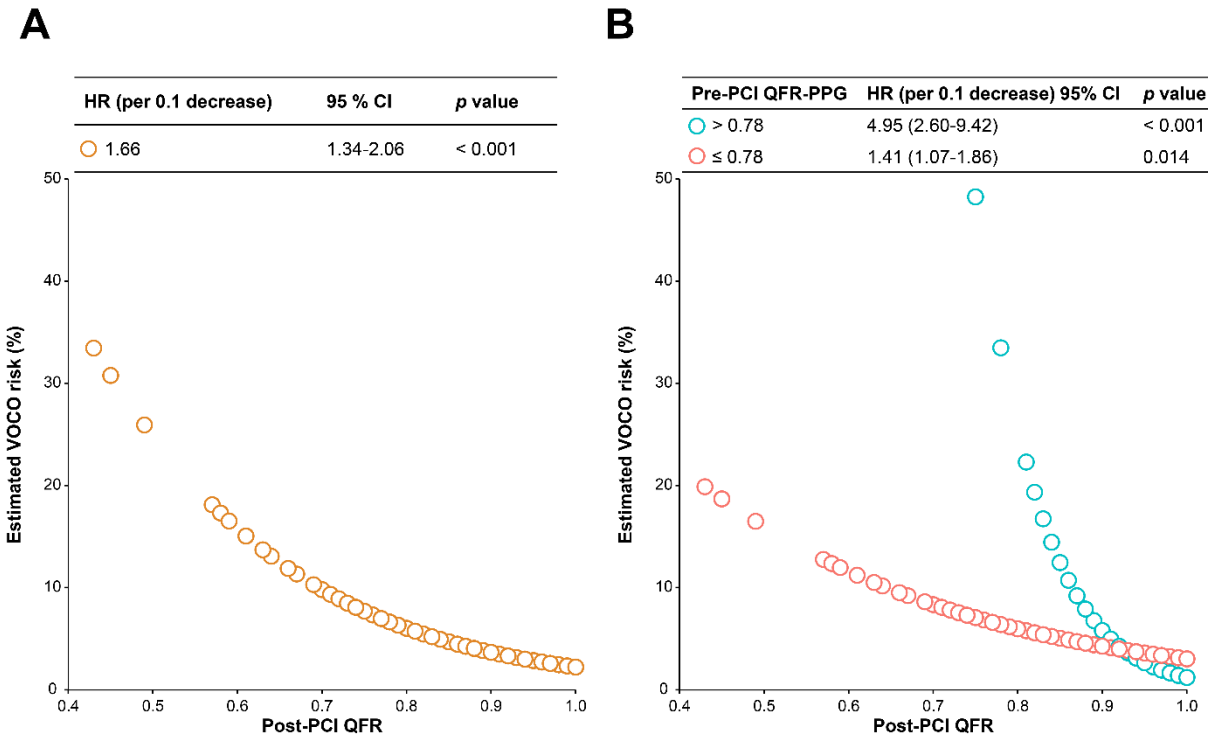


* Subtotal occlusion defined as vessels with diameter stenosis (%) >90% and Thrombolysis in Myocardial Infarction (TIMI) flow < 3

Study flow is presented. * Subtotal occlusion defined as vessels with diameter stenosis (%) >90% and Thrombolysis in Myocardial Infarction (TIMI) flow < 3.

PCI, percutaneous coronary intervention; QFR, quantitative flow reserve; QFR-PPG, QFR derived pullback pressure gradient.

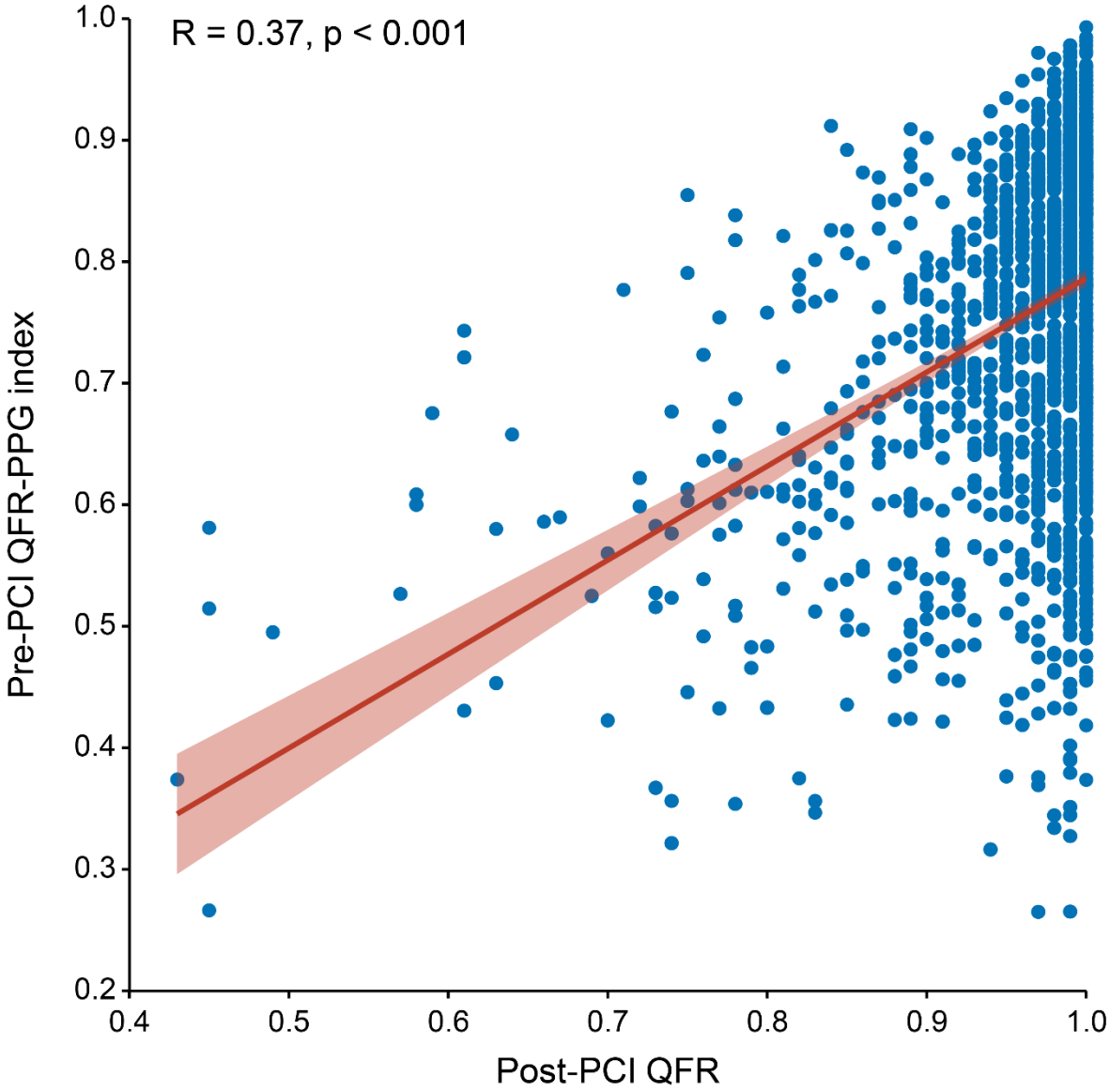
Figure S2. Association between the estimated risk of VOCO and post-PCI QFR in all vessels as well as subgroups divided by pre-PCI QFR-PPG index.



The estimated risks of clinical events at 2 years were plotted according to the post-PCI QFR. The risk of VOCO in all vessels (A) and subgroups divided by pre-PCI QFR-PPG index (B) decreased along with the increase of post-PCI QFR. However, this association attenuated in vessels with low pre-PCI QFR-PPG index.

CI: confidence interval; HR, hazard ratio; other abbreviations as in Figures S1.

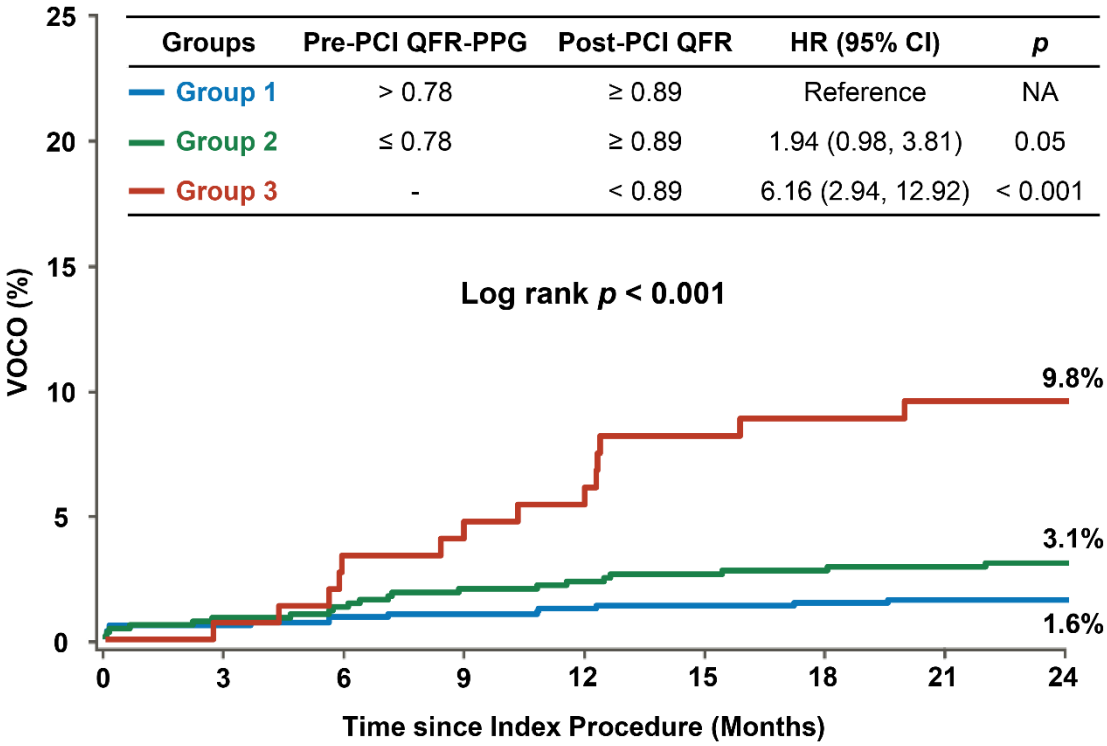
Figure S3. Correlation between pre-PCI QFR-PPG and post-PCI QFR.



Scatter plot between pre-PCI QFR-PPG index and post-PCI QFR is presented.

Abbreviations as in Figure S1.

Figure S4. Cumulative incidence of VOCO at 2 years From Index Procedure According to pre-PCI QFR-PPG index and post-PCI QFR levels.



Number at Risk:

Group 1	864	856	853	849	844	839	836	834	833
Group 2	674	667	664	657	649	643	641	640	638
Group 3	147	144	142	137	134	128	127	125	125

The vessels were classified according to pre-PCI QFR-PPG index (> 0.78) and post-PCI QFR (≥ 0.89). Kaplan-Meir estimates of 3 groups (Group1, high pre-PCI QFR-PPG index and high post-PCI QFR; Group2, low pre-PCI QFR-PPG index and high post-PCI QFR; Group3, low post-PCI QFR regardless of pre-PCI QFR-PPG index) are presented.

Abbreviations as in Figures 1 and 2.