ORIGINAL ARTICLE

Clinical Value of Computational Angiography-derived Fractional Flow Reserve in Stable Coronary Artery Disease

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Abstract

The utilization of FFR remains low. Our study evaluated the per-vessel prognostic value of computational pressure-flow dynamics-derived FFR (caFFR) among patients with stable coronary artery disease. A total of 3329 vessels from 1308 patients were included and analysed. They were stratified into ischaemic (caFFR ≤ 0.8) and non-ischaemic (caFFR > 0.8) cohorts, and the associations between PCI and outcomes were evaluated. The third cohort comprised all included vessels, and the associations between treatment adherent-to-caFFR (PCI in vessels with caFFR ≤ 0.8 and no PCI in vessels with caFFR > 0.8) and outcomes were evaluated. The primary outcome was VOCE, defined as a composite of vessel-related cardiovascular mortality, non-fatal myocardial infarction, and repeat revascularization. PCI was associated with a lower 3-year risk of VOCE in the ischaemic cohort (HR, 0.44; 95% CI, 0.26–0.74; $P = 0.002$) but not in the non-ischaemic cohort. The risk of VOCE was lower in the adherent-to-caFFR group ($n = 2649$) (HR, 0.69; 95% CI, 0.48–0.98; $P = 0.039$).

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Clinical Relevance This study, to the best of our knowledge, is the first to demonstrate a favourable clinical performance in patients with stable CAD by adhering to values derived by a non-wire-based per-vessel angiography-derived functional assessment. These findings support the use of caFFR and its potential for widespread application in clinical practice.

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Abbreviations

caFFR	Computational pressure-flow dynamics-derived fractional flow reserve
CFD	Computational fluid dynamics
CI	Confidence interval
CPFD	Computational pressure-flow dynamics
FFR	Fractional flow reserve
GEE	Generalized estimating equations
HR	Hazard ratio
VOCE	Vessel-oriented composite endpoint

Introduction

The evaluation of coronary artery disease (CAD) for any inducible myocardial ischaemia can be performed by fractional flow reserve (FFR) during coronary angiography. The Fractional Flow Reserve vs Angiography for Multivessel Evaluation 2 (FAME 2) trial revealed that percutaneous coronary intervention (PCI) in ischaemic lesions, defined by FFR ≤ 0.8, improved clinical outcomes compared with medical therapy alone [1]. On the contrary, PCI has not been recommended for non-ischaemic FFR lesions (defined by

FFR > 0.8) because it has not been shown to reduce adverse outcomes and may even be harmful [2, 3]. As a result, FFR has been incorporated in class IA international recommendations to guide decision-making during PCI [4]. A previous study further confirmed that the adoption of an FFR-guided revascularization strategy improved survival compared with an angiography-only revascularization strategy [5].

Of note, FFR has several limitations including the need to pass a pressure wire and hyperaemia induction. The advent of angiography-derived FFR, which circumvents these limitations, has therefore received considerable attention with several models correlating favourably with FFR [6–8]. A novel computational pressure-flow dynamics (CPFD)–derived FFR (caFFR) utilizes invasive aortic pressure coupled to computational fluid dynamics (CFD) at the time of angiography and has demonstrated a high degree of accuracy, sensitivity, and specificity compared with wire-based FFR [9, 10]. Recent results from the FAVOR III China trial showed improved 1-year clinical outcomes in CAD patients who underwent PCI guided by quantitative flow ratio (QFR), which utilizes CFD, compared with those who underwent PCI guided by angiography, suggesting a significant role for various angiography-derived FFR models [11]. Like all randomized trials, concerns exist when extrapolating results to routine clinical practice due to strict protocols and selective patient enrolment. The aim of our study was to determine whether the ischaemic status of a coronary vessel, derived by caFFR, could offer long-term prognostic information (up to 3 years) to help strategize revascularization decisions in patients with stable CAD in a routine clinical setting.

Methods

Study Population and Design

Patients aged ≥ 18 years with a clinical diagnosis of CAD who underwent coronary angiography at Queen Mary Hospital, Hong Kong between January 1, 2014, and December 31, 2016, were retrospectively included for caFFR analysis. Exclusion criteria included: acute coronary syndrome (ACS) or TIMI flow grade below 3 in at least 1 vessel, congenital heart disease, prior coronary artery bypass grafting (CABG) or CABG as preferred treatment, severe valvular heart disease, angiographically significant left main (LM) disease (> 70% diameter stenosis) or prior LM-PCI, and no lesions with ≥ 30% diameter stenosis in any vessel (Fig. 1). Angiographic data of patients who fulfilled the inclusion and exclusion criteria were retrieved and caFFR analysis was performed. Vessel-level exclusion criteria included the presence of chronic total occlusion, right coronary artery (RCA)

aorto-ostial lesion ≤ 3 mm from the aorta, left anterior descending artery (LAD), and left circumflex artery (LCx) ostial lesions, true bifurcation lesions (medina 1,0,1; 0,1,1 or 1,1,1) and non-measurable caFFR (Fig. 1) [12]. Baseline demographics and prescribed medication were retrieved from the inter-hospital electronic system. The scoring system of quantitative coronary angiography in the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) study was calculated by three independent operators (CKLL, LYL, KYL) to characterize the severity of CAD. This study was approved by the ethics committee of the West Cluster Hospital Authority of Hong Kong (UW 19–575).

Measurement of caFFR

The principles and procedures of caFFR analysis have been described previously [9]. Technical requirements for caFFR analysis include [1] contrast opacification of the entire vessel using standard manual force, without table movement during injection of contrast; and 2) ≥ 2 coronary angiograms with projections separated by ≥ 30°. Coronary angiograms were recorded at a standard frame number count of 15 frames per second. Along with mean aortic pressure, a simulated three-dimensional mesh reconstruction of the coronary artery of interest was generated and the analysis was completed using CPFD methods. In our study, caFFR was generated for the main branch of all three major coronary arteries in the patients undergoing caFFR analysis using FLASH software (Fig. 1). The 3D mesh reconstruction was done from the inlet of the vessel until the most distal point (at least 10 mm downstream of the most distal stenosis). In case the distal segment of the vessel had more than 2 daughter branches (e.g. the posterolateral branch and posterior descending artery in RCA), the branch with a larger diameter was considered part of the main vessel. The mean aortic pressure data required for caFFR analysis was computed based on arterial tracing records of coronary angiography sessions. Supplemental Fig. 1 illustrates an example of caFFR analysis. All caFFR analyses were performed by an independent investigator (YF), who was blinded to patient data and outcomes.

Despite a paucity of data regarding the optimal cut-off value of caFFR to predict adverse events, caFFR has been proven to be closely correlated with FFR [9]. In our study, caFFR was considered a surrogate of FFR and a threshold of 0.80 was adopted as the cut-off value for caFFR measurements. Subsequently, two separate cohorts of vessels were created for analysis: vessels with caFFR ≤ 0.80 formed the ischaemic cohort (cohort 1), and vessels with caFFR > 0.80 the non-ischaemic cohort (cohort 2). In cohort 1, vessels were assigned to ischaemic
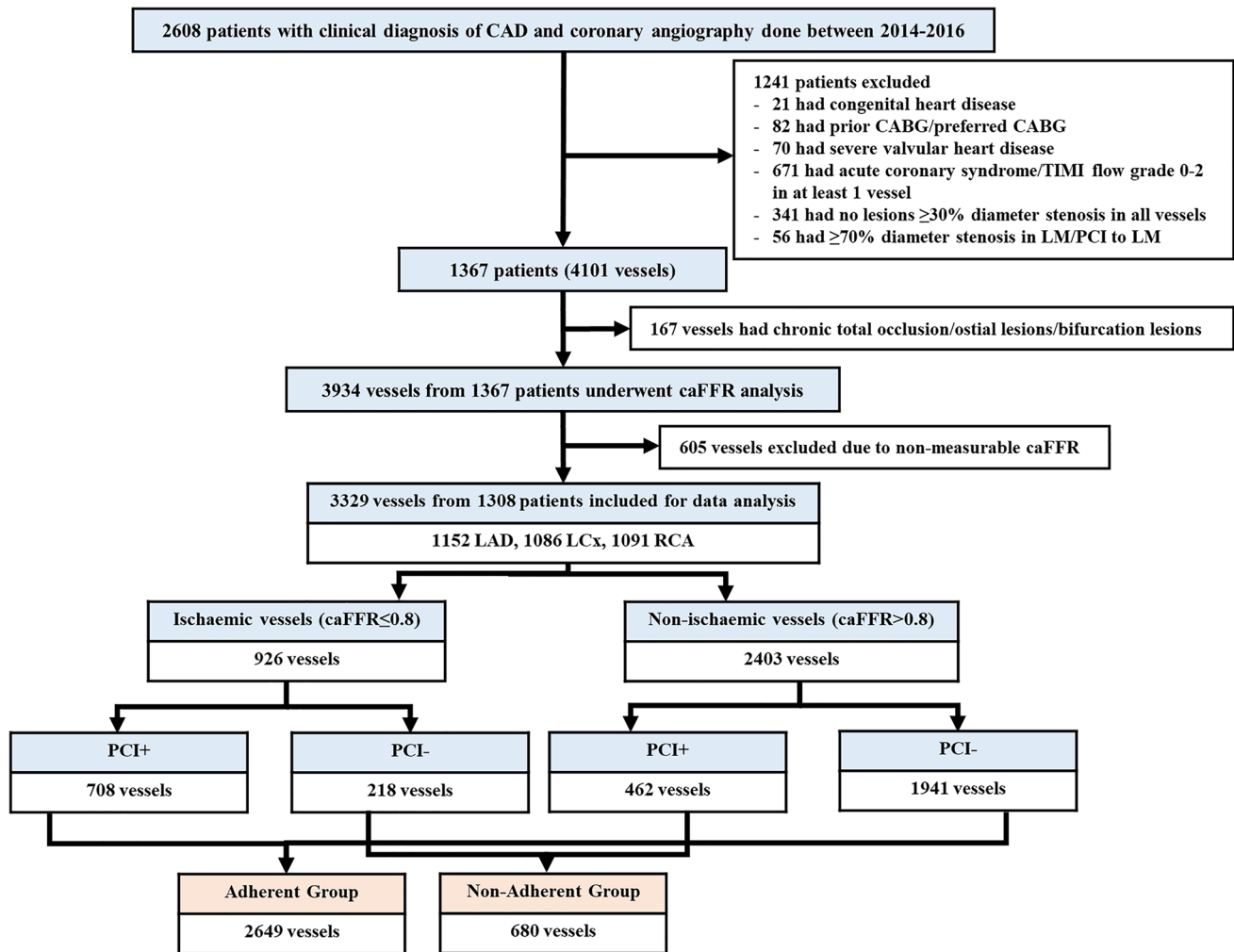
Fig. 1 Study design. Study flowchart with details of the cohorts. Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; caFFR, computational pressure-flow dynamics-derived fractional flow reserve; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LM, left main coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction

PCI + or ischaemic PCI- group based on whether PCI was performed on any lesion. Similarly, in cohort 2, vessels were assigned to non-ischaemic PCI + or non-ischaemic PCI- group accordingly.

To further assess the association of treatment adherence to the caFFR threshold with clinical outcomes, cohort 3 was formed to include all vessels from cohorts 1 and 2. The adherent-to-caFFR group (hereinafter called the adherent group) included the ischaemic PCI + and non-ischaemic PCI- groups. The term 'adherent-to-caFFR' refers to the treatment of the vessel being adherent to its caFFR value, that is vessels with caFFR ≤ 0.8 being treated with PCI and those with caFFR > 0.8 not. Correspondingly, the group non-adherent-to-caFFR (hereinafter called the non-adherent group) included the ischaemic PCI- group and the non-ischaemic PCI + group (Fig. 1).

Endpoints and Follow-Up

The primary endpoint was the vessel-oriented composite endpoint (VOCE) at 3 years, defined as a composite of vessel-related cardiovascular mortality, vessel-related nonfatal myocardial infarction (MI), and any repeat revascularization [13–15]. Secondary endpoints included individual components of the primary endpoint. All deaths were considered cardiovascular mortality unless a non-cardiovascular cause was indisputable. In cases of single index vessel stenosis, cardiovascular mortality was designated as index vessel related. In cases of stenoses in multiple index vessels, cardiovascular mortality was assigned to each stenotic index vessel [15]. In cases where only side branch(es) had stenoses but not in any main vessels and an outcome event occurred, the caFFR was re-measured in

the side branch(es) by reconstruction from its ostium to its most distal part, and during data analysis, it would replace the main vessel where it originated from. Endpoint events would be considered related to the relevant side branch(es). The fourth universal definition of MI was used as the definition of MI, based on a significant increase in cardiac troponin, symptoms, new electrocardiographic changes, and imaging findings of myocardium viability loss [16]. Electrocardiograms and coronary angiograms performed during the episode of MI were reviewed to designate the event as vessel-related or non-vessel-related. Any repeat revascularization was defined as subsequent PCI or CABG to the vessel that occurred after index admission. All clinical outcomes were ascertained from the inter-hospital centralized electronic medical records that contain detailed clinical data of patients, including clinical notes, procedural records, and radiological and laboratory investigation results. These clinical data were used for adjudication of endpoints and the follow-up rate was complete in our cohort of patients.

Statistical Analysis

The primary purpose of data analysis was to evaluate the 3-year probability of VOCE in the three cohorts. Categorical variables were expressed as proportions and compared using the chi-square test or Fisher exact test. Continuous variables were expressed as mean ± standard deviation.

Survival curves were constructed using Kaplan–Meier estimates and differences between groups were tested using the log-rank test [17]. Cox proportional hazards models were used to evaluate the association of PCI + vs. PCI- group (cohort 1 and cohort 2) and adherence-to-caFFR (cohort 3) with the risk of VOCE [18]. The following parameters were entered into the model for univariate analysis: age, gender, Charlson comorbidity index (CCI), hypertension, diabetes mellitus, hyperlipidaemia, ever-smoker, prior PCI, SYNTAX score, presence of multivessel disease and PCI (cohort 1 and cohort 2) or adherence-to-caFFR (cohort 3). Parameters with $P < 0.1$ upon univariate analysis were entered into multivariable Cox models. To account for a possible significant interaction between vessels, generalized estimating equations (GEE) were used to further evaluate the predictive value of clinical parameters and PCI (ischaemic and non-ischaemic cohorts) or adherence-to-caFFR (adherent-to-caFFR cohort) for VOCE, with adjustment for within-patient vessel non-independence [19, 20]. The proportionality assumption was verified by a non-significant interaction between exposure variables and time. A robust variance estimator was used to estimate the standard error for all regression models [21]. Effect estimates from Cox proportional hazards models were reported as hazard ratios (HRs) with the associated

95% confidence interval (CIs). A two-sided P value < 0.05 indicated statistical significance. All statistical analyses were performed with R (v.4.0.4) and SPSS (v.26.0).

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, outcomes, or dissemination of this study.

Results

Baseline Characteristics

A total of 1367 patients were eligible for caFFR analysis. Among all vessels analysed, 772 (18.8%) were excluded based on vessel-level exclusion criteria. Ultimately, 3329 vessels from 1308 patients were included for data analysis (Fig. 1). There was no side branch included among the 3329 vessels. The median follow-up duration was 1693 days (interquartile range: 1583 to 1897 days). Baseline characteristics at both the patient-level and the vessel-level are listed in Table 1 and Supplemental Table 1. Vessel-level baseline characteristics within each cohort are listed in Table 2, and noteworthily, vessels treated without adherence to caFFR were more likely left anterior descending arteries and have lesions with ≥ 70% diameter stenosis. Table 3 shows the stent characteristics of the vessels with PCI done. Almost half of the vessels were the LAD, and drug-eluting stents were used in most cases (92.1%). The endpoint event rates at 3 years are shown in Table 4. The detailed distribution of caFFR measurements is shown in Supplemental Table 2.

Clinical Outcomes

Ischaemic Cohort (Cohort 1)

The ischaemic cohort comprised 926 vessels, with 708 treated with PCI and 218 not treated with PCI. The 3-year rate of VOCE was lower in the PCI + group than in the PCI- group (4.8% vs. 11.5%, $P < 0.001$) (Table 4, Fig. 2). After multivariable adjustment, PCI was associated with a 56% lower risk of VOCE than no PCI (HR, 0.44; 95% CI, 0.26–0.74; $P = 0.002$) (Table 5). The GEE analysis further showed that PCI was an independent negative predictor of VOCE, whereas the male gender was an independent predictor of VOCE (Table 6). For secondary endpoints, PCI was associated with a lower rate of vessel-related cardiovascular mortality, vessel-related non-fatal MI, and any repeat revascularization (Supplemental Table 3, Supplemental Figs. 2–4).

Table 1 Baseline characteristics (abridged)[a]

Patients (n = 1308)	
Demographics	
Age, years	66.3 ± 10.8
Male, no. (%)	945 (72.2)
Female, no. (%)	363 (27.8)
Medical history	
Charlson comorbidity index	3.2 ± 2.0
Ever-smoker, no. (%)	251 (19.2)
History of myocardial infarction, no. (%)	203 (15.5)
History of PCI, no. (%)	178 (13.6)
Peripheral vascular disease, no. (%)	51 (3.9)
Hypertension, no. (%)	590 (45.1)
Diabetes mellitus, no. (%)	275 (21.0)
Hyperlipidaemia, no. (%)	562 (43.0)
Chronic kidney disease, no. (%)	79 (6.0)
Heart failure, no. (%)	80 (6.1)
Cerebrovascular disease, no. (%)	115 (8.8)
Chronic pulmonary disease, no. (%)	53 (4.1)
Dialysis, no. (%)	35 (2.7)
Family history of CAD, no. (%)	32 (2.4)
Creatinine, μmol/L	110.6 ± 138.6
Haemoglobin, g/dL	13.8 ± 1.7
CAD characteristics	
≥ 1 vessel with caFFR ≤ 0.8, no. (%)	701 (53.6)
SYNTAX score	13.5 ± 9.7
Vessels (n = 3329)	
Location	
LAD, no. (%)	1152 (34.6)
LCx, no. (%)	1086 (32.6)
RCA, no. (%)	1091 (32.8)
caFFR	0.83 ± 0.15
caFFR ≤ 0.8, no. (%)	926 (27.8)
Treated with PCI, no. (%)	1170 (35.1)
Adherence-to-caFFR, no. (%)	2649 (79.6)

Categorical variables are reported as n (%). Continuous variables are reported as median ± standard deviation

[a]The complete table of baseline characteristics including baseline medication use at the patient-level is shown in Supplemental Table 1

Abbreviations: *CAD*, coronary artery disease; *caFFR*, computational pressure-flow dynamics-derived fractional flow reserve; *LAD*, left anterior descending coronary artery; *LCx*, left circumflex coronary artery; *PCI*, percutaneous coronary intervention; *RCA*, right coronary artery

Non-Ischaemic Cohort (Cohort 2)

The non-ischaemic cohort comprised 2403 vessels, with 462 receiving PCI and 1941 not receiving PCI. The 3-year rate of VOCE was similar in the PCI + and PCI- groups (3.9% vs. 3.8%, P = 0.891) (Table 4, Supplemental Fig. 5). In univariate analysis, PCI was not associated with a significant

change in risk of VOCE (HR, 1.04; 95% CI, 0.62–1.79; P = 0.888) (Table 5). The GEE analysis showed CCI ≥ 3 and ever-smoker status were independent predictors of VOCE (Table 6). There were no associations between PCI and all three secondary endpoints (Table 4, Supplemental Table 4, Supplemental Figs. 6–8).

Adherent Group vs. Non-Adherent Group (Cohort 3)

The adherent-to-caFFR cohort comprised 3329 vessels, with 2649 receiving treatment adherent-to-caFFR and 680 receiving treatment non-adherent-to-caFFR. The 3-year rate of VOCE was lower in the adherent group than in the non-adherent group (4.0% vs. 6.3%, P = 0.010) (Table 4, Fig. 3). After multivariable adjustment, treatment adherent-to-caFFR was associated with a 31% reduction in VOCE compared with the non-adherent group (HR, 0.69; 95% CI, 0.48–0.98; P = 0.039) (Table 5). The GEE analysis further confirmed that treatment adherent-to-caFFR was an independent negative predictor of VOCE, while male gender, Charlson comorbidity index ≥ 3, and ever-smoker status were independent predictors (Table 6). In the analysis of secondary outcomes, the reduction in VOCE was mainly driven by a reduction in vessel-related non-fatal MI, but not vessel-related cardiovascular mortality or any repeat revascularization (Table 4, Supplemental Table 5, Supplemental Figs. 9–11).

Discussion

In the present study, we characterized coronary artery ischaemic status by caFFR, an angiography-derived index, in a large population of patients with stable CAD. Our results showed that among ischaemic lesions (caFFR ≤ 0.8) (cohort 1), PCI was associated with a lower incidence of VOCE at 3 years, compared with those without PCI. Conversely, in vessels with non-ischaemic lesions (caFFR > 0.8) (cohort 2), no reduction of VOCE was observed in those that underwent PCI compared with no PCI. Finally, using a caFFR threshold of 0.8, PCI performed only in vessels with caFFR-defined ischaemia had a significantly lower risk of VOCE than those that did not adhere to their ischaemic status (cohort 3). The present study, conducted in a routine clinical setting, demonstrates favourable long-term clinical performance (up to 3 years) for adherence to non-wire-based angiography-derived functional assessment in patients with stable CAD lesions.

Although recommended as a class IA indication, wire-based FFR is underutilized in clinical practice, with a substantial proportion (> 80%) of patients with intermediate obstructive coronary lesions not undergoing FFR assessment [22]. As a result, coronary angiography-derived FFR

Table 2 Comparison of vessel-level baseline characteristics within each Cohort

Ischaemic cohort (n = 926)	PCI+ (n = 708)	PCI- (n = 218)	P value
LAD, no. (%)	329 (46.5)	105 (48.2)	0.661
LCx, no. (%)	213 (30.1)	83 (38.1)	0.027
RCA, no. (%)	166 (23.4)	30 (13.8)	0.002
≥ 70% diameter stenosis, no. (%)	585 (82.6)	154 (70.6)	< 0.001
caFFR	0.61 ± 0.14	0.65 ± 0.13	< 0.001
Non-ischaemic cohort (n = 2403)	PCI+ (n = 462)	PCI- (n = 1941)	P value
LAD, no. (%)	232 (50.2)	486 (25.0)	< 0.001
LCx, no. (%)	91 (19.7)	699 (36.0)	< 0.001
RCA, no. (%)	139 (30.1)	756 (38.9)	< 0.001
≥ 70% diameter stenosis, no. (%)	363 (78.6)	1123 (57.9)	< 0.001
caFFR	0.88 ± 0.04	0.92 ± 0.04	< 0.001
Adherent-to-caFFR cohort (n = 3329)	Adherence-to-caFFR (n = 2649)	Non-adherence-to-caFFR (n = 680)	P value
LAD, no. (%)	815 (30.8)	337 (49.6)	< 0.001
LCx, no. (%)	912 (34.4)	174 (25.6)	< 0.001
RCA, no. (%)	922 (34.8)	169 (24.9)	< 0.001
≥ 70% diameter stenosis, no. (%)	1708 (64.5)	517 (76.0)	< 0.001
caFFR	0.83 ± 0.16	0.80 ± 0.13	< 0.001
caFFR ≤ 0.8, no. (%)	708 (26.7)	218 (32.1)	0.006
Treated with PCI, no. (%)	708 (26.7)	462 (67.9)	< 0.001

Categorical variables are reported as n (%). Continuous variables are reported as median ± standard deviation

Abbreviations: *caFFR*, computational pressure-flow dynamics derived fractional flow reserve; *LAD*, left anterior descending coronary artery; *LCx*, left circumflex coronary artery; *PCI*, percutaneous coronary intervention; *RCA*, right coronary artery

Table 3 Stent characteristics for vessels with PCI done

Vessels with PCI done (n = 1170)[a]	
Vessel location	
LAD, no. (%)	561 (47.9)
LCx, no. (%)	304 (26.0)
RCA, no. (%)	305 (26.1)
Number of stents per vessel (n)	1.44 ± 0.66
Type of stents	
Drug eluting stent, no. (%)	1077 (92.1)
Bare metal stent, no. (%)	42 (3.6)
Bioresorbable vascular scaffold, no. (%)	32 (2.7)
Mixed, no. (%)	6 (0.5)
Total length of stents used per vessel (mm)	33.9 ± 17.6
Smallest stent diameter per vessel (mm)	2.79 ± 0.53

Categorical variables are reported as *n* (%). Continuous variables are reported as median ± standard deviation

Abbreviations: *LAD*, left anterior descending artery; *LCx*, left circumflex artery; *PCI*, percutaneous coronary intervention; *RCA*, right coronary artery

[a]Data on stent characteristics were missing in 12 vessels (1.0%)

has gained considerable attention, as it precludes the need for wire manipulation and hyperaemia stimulus essential in wire-based FFR, and avoids wire-related technical inadequacies, potentially overcoming certain limitations that may have impacted the utilization of FFR [23–25].

Importantly, these non-wire-based angiography-derived measurements have been shown to have comparable diagnostic accuracy to conventional FFR [26, 27]. For instance, QFR had a diagnostic accuracy of over 90% compared with wire-based FFR [6], while FFR$_{angio}$, another coronary angiography-based technology, was validated to have 92% accuracy against wire-based FFR [7]. CPFD-derived caFFR [9], utilized in the present study, employs invasive aortic pressure coupled to computational flow modelling, eliminating the convective and diffusive energy losses associated with the lumped model used by FFR$_{angio}$ and QFR. The diagnostic performance of caFFR is excellent with 96% accuracy compared with wire-based FFR, and its clinical utility is further strengthened by its short operating time with a total operation time below 5 min and computational time below 1 min. Consequently, these advantages point towards the potential widespread adoption of caFFR to guide PCI and utilization of functional assessment in routine clinical settings.

Clinically, the incorporation of angiography-derived FFR measurements into PCI strategies may improve patient outcomes. The recent FAVOR III China trial confirmed that a QFR-guided PCI strategy, compared with a standard angiography-guided PCI strategy, resulted in improved

Table 4 Primary and secondary endpoint event rates at 3 years in each cohort

Ischaemic cohort (n = 926)			
	PCI + (n = 708)	PCI- (n = 218)	P value
VOCE, no. (%)	34 (4.8)	25 (11.5)	< 0.001
Vessel-related cardiovascular mortality, no. (%)	11 (1.6)	12 (5.5)	0.001
Vessel-related non-fatal MI, no. (%)	4 (0.6)	5 (2.3)	0.038
Any repeat revascularization, no. (%)	22 (3.1)	15 (6.9)	0.013
Non-ischaemic cohort (n = 2403)			
	PCI + (n = 462)	PCI- (n = 1941)	P value
VOCE, no. (%)	18 (3.9)	73 (3.8)	0.891
Vessel-related cardiovascular mortality, no. (%)	5 (1.1)	15 (1.3)	0.720
Vessel-related non-fatal MI, no. (%)	4 (0.9)	7 (0.3)	0.239
Any repeat revascularization, no. (%)	11 (2.4)	47 (2.4)	0.959
Adherent-to-caFFR cohort (n = 3329)			
	Adherence-to-caFFR (n = 2649)	Non-adherence-to-caFFR (n = 680)	P value
VOCE, no. (%)	107 (4.0)	43 (6.3)	0.010
Vessel-related cardiovascular mortality, no. (%)	36 (1.4)	17 (2.5)	0.034
Vessel-related non-fatal MI, no. (%)	11 (0.4)	9 (1.3)	0.011
Any repeat revascularization, no. (%)	69 (2.6)	26 (3.8)	0.089

Abbreviations: *caFFR*, computational pressure-flow dynamics-derived fractional flow reserve; *MI*, myocardial infarction; *VOCE*, vessel-oriented composite endpoint
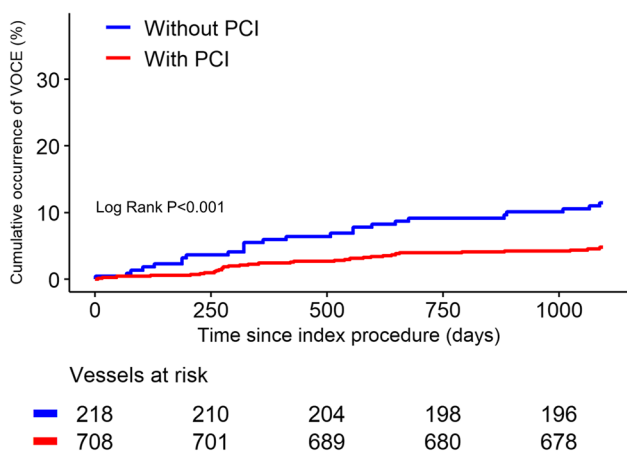

Fig. 2 Ischaemic Cohort: Cumulative Occurrence of VOCE. In the ischemic cohort, a significantly higher cumulative occurrence of VOCE was observed in vessels without PCI done. Abbreviations: PCI, percutaneous coronary intervention; VOCE, vessel-oriented composite endpoint

one-year outcomes among patients with CAD [11]. Our data, derived from patients in the routine clinical setting and with extended follow-up, provide additional unique information that supports the adoption of angiography-derived FFR. The current results confirm that PCI was associated with significantly fewer VOCE in vessels with ischaemic lesions, defined by a caFFR ≤ 0.8, while no association between PCI and clinical outcomes was seen in vessels with non-ischaemic lesions, defined by a caFFR > 0.8. Furthermore,

we demonstrated that adherence to caFFR-guided PCI was associated with a 31% reduction in VOCE, compared with those that were non-adherent to caFFR. Our findings corroborate those of the IRIS-FFR registry, which demonstrated that major adverse cardiac events (MACE) were similar between deferred and revascularized lesions with FFR ≥ 0.76, but a significant benefit of PCI was observed only in those with FFR < 0.75. The neutral effect of PCI in non-ischaemic lesions was likewise observed in the DEFER study. Conversely, a population-based study demonstrated that PCI in non-ischaemic lesions, compared with no PCI, was associated with a higher MACE [3]. The discrepant observation in their study may have been due to the adoption of a single vessel FFR assessment, unlike our study which included a multivessel assessment. Irrespective of these differences, supported by the current class III recommendation [4], revascularization in non-ischaemic lesions, either by wire-based FFR or angiography-derived FFR, does not provide clinical benefit and should be avoided.

In our study, where revascularization strategies were angiography-guided, the frequency of PCI in non-ischemic vessels (defined by caFFR > 0.8) was 19.2%. Observations in other FFR-based studies have demonstrated that physicians tend to opt for PCI when the decision is clinically driven, rather than FFR guided, with the frequencies of PCI in non-ischaemic vessels ranging from 4 to 13% [3, 28, 29]. Perhaps due to a low FFR utilization rate, it is possible that PCI in non-ischaemic lesions (unnecessary coronary stenting) is not uncommon in clinical practice. The FAVOR 3

Table 5 Cox Proportional Hazards Model for VOCE

	Univariate		Multivariate[a]	
	HR [95% CI][b]	*P* value	HR [95% CI][b]	*P* value
Ischaemic cohort (*n* = 926)				
Age ≥ 66[c]	1.23 [0.73–2.05]	0.437		
Male gender	2.11 [1.04–4.29]	0.040	2.27 [1.11–4.64]	0.025
Charlson comorbidity index ≥ 3[c]	1.71 [0.98–2.98]	0.058	1.70 [0.97–2.98]	0.065
Hypertension	0.97 [0.58–1.63]	0.919		
Diabetes mellitus	1.30 [0.74–2.29]	0.359		
Hyperlipidaemia	0.62 [0.36–1.07]	0.084	0.69 [0.40–1.19]	0.180
Ever-smoker	1.55 [0.88–2.73]	0.126		
Prior PCI	0.88 [0.40–1.93]	0.746		
SYNTAX score ≥ 17[c]	1.47 [0.87–2.50]	0.151		
PCI	0.40 [0.24–0.68]	0.001	0.44 [0.26–0.74]	0.002
Non-ischaemic cohort (*n* = 2403)				
Age ≥ 66[c]	1.11 [0.73–1.67]	0.636		
Male gender	2.22 [1.26–3.93]	0.006	2.03 [1.13–3.66]	0.018
Charlson comorbidity index ≥ 3[c]	2.44 [1.49–4.01]	< 0.001	2.13 [1.26–3.58]	0.005
Hypertension	1.62 [1.07–2.45]	0.022	1.33 [0.87–2.03]	0.195
Diabetes mellitus	2.25 [1.46–3.46]	< 0.001	1.68 [1.06–2.66]	0.026
Hyperlipidaemia	1.16 [0.77–1.76]	0.475		
Ever-smoker	2.41 [1.56–3.72]	< 0.001	1.94 [1.23–3.03]	0.004
Prior PCI	1.68 [1.00–2.82]	0.048	1.17 [0.68–2.01]	0.561
SYNTAX score ≥ 11.5[c]	1.53 [1.01–2.30]	0.044	1.31 [0.87–1.99]	0.198
PCI	1.04 [0.62–1.74]	0.888		
Adherent-to-caFFR cohort (*n* = 3329)				
Age ≥ 66[c]	1.14 [0.82–1.57]	0.436		
Male gender	2.19 [1.41–3.42]	0.001	2.14 [1.35–3.39]	0.001
Charlson comorbidity index ≥ 3[c]	2.08 [1.44–3.00]	< 0.001	1.94 [1.32–2.86]	0.001
Hypertension	1.35 [0.98–1.86]	0.067	1.14 [0.82–1.58]	0.438
Diabetes mellitus	1.87 [1.33–2.63]	< 0.001	1.48 [1.03–2.12]	0.035
Hyperlipidaemia	0.92 [0.66–1.27]	0.612		
Ever-smoker	2.08 [1.47–2.93]	< 0.001	1.73 [1.21–2.46]	0.002
Prior PCI	1.35 [0.88–2.07]	0.174		
SYNTAX score ≥ 12[c]	1.48 [1.07–2.05]	0.019	1.30 [0.93–1.81]	0.124
Adherence-to-caFFR	0.63 [0.44–0.90]	0.011	0.69 [0.48–0.98]	0.039

Abbreviations: *caFFR*, computational pressure-flow dynamics-derived fractional flow reserve; *CI*, confidence interval; *HR*, hazard ratio; *VOCE*, vessel-oriented composite endpoint; *PCI*, percutaneous coronary intervention

[a]Covariates with $P < 0.1$ in univariate analysis were entered into multivariable analysis

[b]Hazard ratios and 95% CI were estimated from cox proportional hazards models

[c]Continuous variables were converted into categorical variables using median of the respective cohort as cut-off

trial demonstrated that 445 (23.3%) patients had an initial angiography-based revascularization plan that differed from the eventual QFR-guided revascularization strategy [11]. Similarly, 680 (20.4%) vessels in our study that were treated according to angiographic considerations were nonadherent-to-caFFR. This highlights the importance of physiological testing to identify any mismatch between angiographic severity and haemodynamic consequences of coronary artery lesions. Without the need for pressure wire introduction and hyperaemic stimulation, caFFR may also encourage functional assessment of multivessel disease. These compelling advantages of angiographic-based FFR assessment may further improve adherence to evidence-based strategies and improve the clinical outcome of patients with stable CAD.

Table 6 Generalized Estimating Equations for VOCE[a]

	Standardized β [95% CI][b]	P value
Ischaemic cohort (n = 926)		
Male gender	0.41 [0.01 to 0.81]	0.045
Charlson comorbidity index ≥ 3[c]	0.27 [−0.03 to 0.58]	0.079
Hyperlipidaemia	−0.18 [−0.48 to 0.12]	0.232
PCI	−0.43 [−0.72 to −0.15]	0.003
Non-ischaemic cohort (n = 2403)		
Male gender	0.32 [−0.07 to 0.70]	0.107
Charlson comorbidity index ≥ 3[c]	0.34 [0.07 to 0.61]	0.015
Hypertension	0.14 [−0.12 to 0.39]	0.290
Diabetes mellitus	0.23 [−0.04 to 0.51]	0.092
Ever-smoker	0.32 [0.002 to 0.64]	0.048
Prior PCI	0.10 [−0.24 to 0.44]	0.575
SYNTAX score ≥ 11.5[c]	0.13 [−0.11 to 0.37]	0.297
Adherent-to-caFFR cohort (n = 3329)		
Male gender	0.35 [0.04 to 0.65]	0.026
Charlson Comorbidity Index ≥ 3[c]	0.31 [0.08 to 0.54]	0.009
Hypertension	0.07 [−0.15 to 0.29]	0.526
Diabetes mellitus	0.18 [−0.07 to 0.43]	0.157
Ever-smoker	0.27 [0.002 to 0.53]	0.048
SYNTAX score ≥ 12[c]	0.12 [−0.09 to 0.34]	0.260
Adherence-to-caFFR	−0.19 [−0.37 to −0.007]	0.041

Abbreviations: *caFFR*, computational pressure-flow dynamics-derived fractional flow reserve; *CI*, confidence interval; *VOCE*, vessel-oriented composite endpoint; *PCI*, percutaneous coronary intervention

[a]Variables included in multivariable cox proportional hazards model were entered into generalized estimating equations

[b]Standardized intercepts and 95%CI were estimated by generalized estimating equations

[c]Continuous variables were converted into categorical variables using median value of the respective cohort as the cut-off

Clinical Implications

Current guidelines recommend FFR-guided PCI in the management of patients with stable CAD, but its adoption has been exceedingly low due to a myriad of limitations. Non-invasive FFR assessment by computed tomography (FFR_{CT}) has been validated and shows considerable promise for patients with CAD [30]. Nonetheless, it requires patient data transfer offsite to be post-processed, introducing a delay of approximately 24 h. Furthermore, raw data acquired by CT may be of insufficient quality due to artefacts and raises the possibility of high rejection rates. The use of caFFR provides instant ischaemic assessment and usually requires less than 10 min with the advantage of re-evaluation by additional angiography images if the calculation is considered inadequate. Importantly, our study demonstrated that
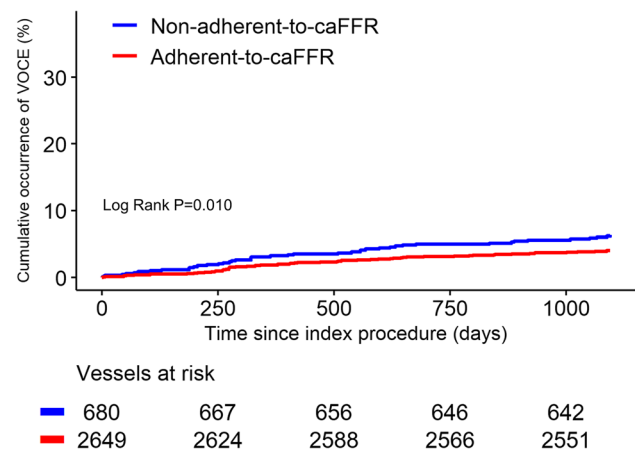

Fig. 3 Adherent-to-caFFR Cohort: Cumulative Occurrence of VOCE. In the adherent-to-caFFR cohort, a significantly higher cumulative occurrence of VOCE was observed in vessels that were treated without adherence to caFFR treatment threshold. Abbreviations: caFFR, computational pressure-flow dynamics-derived fractional flow reserve; VOCE, vessel-oriented composite endpoint

adherence to caFFR-guided PCI (as a surrogate of FFR) reduced the risk of adverse outcomes, without the necessity for wire introduction or hyperaemia induction. Furthermore, offline calculation of caFFR was performed by an investigator blinded to patient clinical characteristics and outcomes. We were also able to comprehensively evaluate the outcomes at 3 years, providing unique long-term prognostic information offered by caFFR. Our findings will be further supported by an ongoing nationwide prospective randomized study to compare the clinical outcome of caFFR vs. wire-based FFR strategy.

Study Limitations

Several limitations should be considered in the present study. First, like most retrospective observational studies, selection bias and confounding factors may have existed, although minimised by our large study population relative to other studies that evaluated coronary physiological indices at a per-vessel level. Future prospective trials will further provide robust clinical data to validate the use of caFFR. Second, the present study included patients with single-vessel and multi-vessel disease compared with a recent study that included only single-vessel FFR assessment and intervention. (3) Nevertheless, we evaluated the use of caFFR at the per-vessel level, which, alongside its ease in multi-vessel assessment, provides generalizable results to patients with multi-vessel disease. Third, the data regarding the reasons to or not to perform PCI, such as the use of other assessment modalities (e.g. intravascular imaging) and chest pain severity, were unknown or inadequate. In our study, 277 (29.9%)

vessels with ≥ 70% diameter stenosis in the ischaemic cohort did not receive PCI, whereas 1222 (50.9%) vessels in the non-ischaemic cohort received PCI despite not having ≥ 70% diameter stenosis. This was likely to be driven by multiple factors including the interventionists' clinical judgement and the patient's comorbidities, such that the exact decision for revascularization may not be fully illustrated due to the retrospective nature of our study. Fourth, data on periprocedural MI was unavailable from the inter-hospital electronic medical records, leading to possibly lowered event rates and our limited ability to perform multivariable adjustments for study endpoints. Nonetheless, our study focused on evaluating the long-term prognostic value of caFFR and showed significant results at a 3-year follow-up. Fifth, post-PCI caFFR data was not included in this study and there is a lack of quantification of improvement in vessel ischemia. However, the primary aim of this study was to evaluate the prognostic role of treatment adherence to caFFR, which refers to suitable use of PCI based on caFFR, and the benefit of assessing post-PCI residual ischemic burden was not the main focus of this study. Future trials focusing on the clinical value of post-PCI caFFR will be beneficial to further expand the data supporting the clinical use of caFFR in various settings. Sixth, caFFR was treated as a surrogate of FFR and an optimal cutoff value of caFFR per se was not evaluated. However, with a high diagnostic accuracy of caFFR compared with FFR, we believe the ischaemic and non-ischaemic cohorts were correctly identified. Future multicentre prospective trials are warranted and will be in a better position to define the optimal cutoff value of caFFR. Finally, caFFR could not be ascertained in a number of vessels due to several reasons (Supplemental Table 6). Most of them were due to the inability to fulfilling the technical criteria of caFFR analysis, namely inadequate angiographic angulation, unsuitable angiographic projection, and poor angiogram quality. Furthermore, angiographic data of some vessels were missing owing to the incomplete storage of images in the retrospective context of this study. To optimize the use of caFFR in the future, standardized protocols of angiographic image acquisition are needed for maximizing the success rate of caFFR analysis.

Conclusion

In this retrospective analysis of patients with stable CAD, angiography-derived caFFR provided valuable long-term prognostic information, and in the future may assist decision-making about revascularization in clinical practice. The prognostic information provided by caFFR, which precludes pressure wire introduction and hyperaemia induction, has the potential for widespread clinical application.

Declarations

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