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Prognostic significance of thermodilution-derived coronary flow capacity in patients with deferred revascularisation

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KEYWORDS

- fractional flow reserve
- ischaemic cardiomyopathy
- stable angina

Abstract

Aims: The aim of this study was to investigate the prognostic value of thermodilution-derived coronary flow capacity (T-CFC) in patients with stable coronary artery disease and deferred revascularisation.

Methods and results: We evaluated 308 lesions in 308 patients with deferred revascularisation, stratifying the cohort according to T-CFC. Ischaemic T-CFC was defined as a composite of mildly, moderately, and severely reduced T-CFC. Clinical outcomes were assessed by vessel-oriented composite endpoints (VOCE) and major adverse cardiac events (MACE). VOCE and MACE occurred in 19 and 28 patients, respectively. Ischaemic T-CFC was found in 88 lesions (28.6%). Kaplan-Meier analysis revealed that lesions with ischaemic T-CFC had a significantly higher risk of both VOCE and MACE. The net reclassification index and integrated discrimination improvement index were both significantly improved when ischaemic T-CFC was added to the clinical risk model (age, sex, prior stent implantation, and lesion length) for predicting VOCE and MACE. Furthermore, ischaemic T-CFC showed significant incremental predictive ability for VOCE and MACE when compared with the clinical risk model + fractional flow reserve ≤0.8, or with the clinical model + coronary flow reserve ≤2.0.

Conclusions: T-CFC categorisation improved the risk stratification for both VOCE and MACE and showed incremental prognostic value in patients with deferred revascularisation.

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Abbreviations

CFC	coronary flow capacity
CFR	coronary flow reserve
FFR	fractional flow reserve
IMR	index of microvascular resistance
MACE	major adverse cardiac events
PCI	percutaneous coronary intervention
TVR	target vessel revascularisation
VOCE	vessel-oriented composite endpoint

Introduction

Fractional flow reserve (FFR)-guided revascularisation is recommended in updated clinical guidelines[1]. The benefits of physiology-guided decision making in revascularisation are largely attributable to deferral of percutaneous coronary intervention (PCI)[2,3]. A recent meta-analysis by Zimmermann et al showed that FFR-guided PCI resulted in a reduction of the composite of cardiac death or myocardial infarction (MI) compared with medical therapy, which was driven by a decreased risk of MI[4]. For deferred lesions in one prospective large registry study, the risk of major adverse cardiac events (MACE) demonstrated a significant, inverse relationship with FFR when lesions were deferred after FFR measurements[5]. However, although FFR is highly reliable for physiological assessment of epicardial lesions, the severity and extent of microvascular dysfunction that occurs irrespective of epicardial stenosis could not be determined by FFR. A comprehensive diagnostic approach to coronary heart disease is warranted based on prior evidence indicating a strong link between adverse clinical outcomes and microcirculatory disturbance as well as epicardial flow impairment[6].

Coronary flow reserve (CFR), another index of coronary flow assessment, indicates integrated coronary vascular function, which is known to be associated with adverse cardiac events[7,8]. Several previous studies have evaluated the prognostic value of CFR, and CFR was consistently reported to be associated with clinical outcomes[9,10]. The problems when using CFR relate to unstable baseline haemodynamics, attenuated hyperaemic responses caused by various conditions, and a heterogeneous population with low CFR including patients with high coronary flow at baseline, limited flow with hyperaemia, or impaired vasodilatory response to adenosine. To overcome the limitations of CFR, coronary flow capacity (CFC) was introduced, which integrates CFR with hyperaemia coronary flow into a comprehensive platform of coronary flow characteristics[11]. CFC was first developed using non-invasive positron emission tomography (PET), subsequently verified using an invasive intracoronary Doppler flow wire[12], and recently evaluated using a pressure-temperature sensor-tipped wire[13]. Despite the strong theoretical fundamentals of CFC, validation of CFC for potential clinical use is needed to determine whether the prognostic implications are better than for CFR alone. In the present study, we investigated the prognostic efficacy of CFC obtained using a pressure-temperature sensor-tipped wire (thermodilution method [T-CFC]) in patients with deferred revascularisation based on FFR and clinical judgement. Of note, FFR can be determined with CFR and T-CFC categorisation using the same wire. Thus, we hypothesised that T-CFC could provide incremental prognostic information for subsequent adverse events compared with FFR or CFR alone.

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Methods

PATIENT POPULATION

From June 2012 to June 2017, patients with known or suspected coronary artery disease who underwent coronary physiological assessments using the PressureWire™ (St. Jude Medical, St. Paul, MN, USA) at Tsuchiura Kyodo General Hospital were identified from the institutional physiology database. We enrolled patients with deferred revascularisation after physiological examination of intermediate lesions documented in the institutional physiology data registry. A physiological study was indicated for vessels with intermediate coronary lesions (30%-80% diameter stenosis on visual assessment). With multiple coronary stenoses, we used a single vessel with the most severely decreased FFR value. The exclusion criteria are detailed in **Supplementary Appendix 1**.

This study was conducted in accordance with the Declaration of Helsinki; our institutional ethics committee approved the study protocol. Before catheterisation, all patients provided written informed consent for enrolment in the institutional database for potential future investigations. All patient data and procedural details were obtained from medical records, and prompt optimal medical therapy was initiated in all patients after coronary angiography (CAG).

CORONARY PHYSIOLOGICAL ASSESSMENT

FFR, mean transit time (Tmn), and index of microvascular resistance (IMR) were determined using a RadiAnalyzer™ Xpress instrument with a PressureWire™ Certus™ (St. Jude Medical) as previously described[14,15]. Details are shown in **Supplementary Appendix 1**.

DERIVATION OF CORONARY FLOW CAPACITY

Based on CFC values derived from PET or Doppler flow velocity, T-CFC categorises lesions into four ranges using CFR and the inverse of hyperaemic Tmn[11,12]. The inverse of hyperaemic Tmn (1/Tmn) can be a surrogate that correlates well with absolute hyperaemic coronary flow because shorter Tmn suggests higher coronary flow velocity[15]. Because thresholds or cut-off values for 1/Tmn have not been well established, we matched Tmn values according to the percentiles corresponding to CFR values as follows: normal T-CFC indicated no myocardial ischaemia and CFR ≥2.80 with corresponding 1/Tmn >3.70 (53th percentile)[16], mildly reduced T-CFC indicated CFR <2.80 and ≥2.20, which were the reported upper limits for inducible ischaemia, and a corresponding 1/Tmn <3.70 and ≥2.7 (72nd percentile each)[17], moderately reduced T-CFC indicated CFR <2.20 and ≥1.90, which reflected lower limits for inducible ischaemia, and 1/Tmn <2.70 and ≥2.30 (80th percentile each)[18], and severely reduced T-CFC indicated

definite ischaemia with CFR <1.90 and 1/Tmn <2.30[19]. We defined ischaemic T-CFC as a composite of mildly, moderately, and severely reduced T-CFC.

CLINICAL FOLLOW-UP

The primary outcome was the vessel-oriented composite endpoint (VOCE), including cardiovascular death, vessel-related spontaneous MI, and ischaemia-driven target vessel revascularisation (TVR). The secondary endpoint was MACE, including VOCE, non-TVR, and heart failure requiring hospitalisation.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS, Version 23.0 (IBM Corp., Armonk, NY, USA). Categorical data were expressed as numbers and percentages and compared by χ^2 or Fisher's exact tests, as appropriate. Continuous biochemical or physiological data were expressed as median (interquartile range [IQR]) and analysed using the Mann-Whitney test and analysis of variance for variables with non-normal distribution and normal distribution, respectively. Correlations between the two parameters were evaluated using linear regression analysis. Receiver operating characteristic curves were analysed to assess the best cut-off values for the physiological indices and clinical characteristics to predict the occurrence of VOCE and MACE; the optimal cut-off was calculated using Youden's index **(Supplementary Figure 1)**. Event rates over time were estimated using the Kaplan-Meier method, and linear trends were tested with log-rank tests. A Cox proportional hazards regression model was used to identify independent predictors of VOCE and MACE, and the covariates used in multivariate analysis were selected using the criterion of p<0.10 in the univariate analysis. A collinearity index was used to evaluate linear combinations among covariates with the Akaike information criterion to avoid overfitting. Ten prediction models were constructed to determine the incremental discriminatory and reclassification performance of physiological parameters for VOCE or MACE by using relative integrated discrimination improvement (IDI) and category-free net reclassification index (NRI). Prediction models are detailed in **Supplementary Appendix 1**; p<0.05 indicated statistical significance.

Results

BASELINE PATIENT CHARACTERISTICS AND PROCEDURAL FINDINGS

A total of 308 patients with 308 lesions were included in the present analysis **(Figure 1)**. Median FFR and CFR values were 0.86 (IQR: 0.83–0.90) and 2.91 (IQR: 2.11–4.00), respectively. We created the T-CFC map using CFR and the inverse of hyperaemic Tmn, and categorised patients into four T-CFC categories **(Figure 2)**. Normal, mildly, moderately, and severely reduced T-CFC categories constituted 220 (71.2%), 48 (15.5%), 18 (5.8%), and 22 (7.1%) vessels, respectively. Next, we defined the composite of mildly, moderately, and severely reduced T-CFC as ischaemic T-CFC (n=88, 28.5%). Clinical outcomes are summarised in **Table 1**. The baseline clinical characteristic and physiological parameters for each T-CFC group are summarised in **Table 2**. Compared with normal T-CFC, the prevalence of patients with diabetes mellitus was significantly greater in ischaemic T-CFC. The physiological properties of the lesions differed significantly between the normal T-CFC and ischaemic T-CFC groups, although a non-significant difference in FFR was seen **(Table 3)**. Ischaemic T-CFC vessels were significantly associated with microvascular dysfunction.

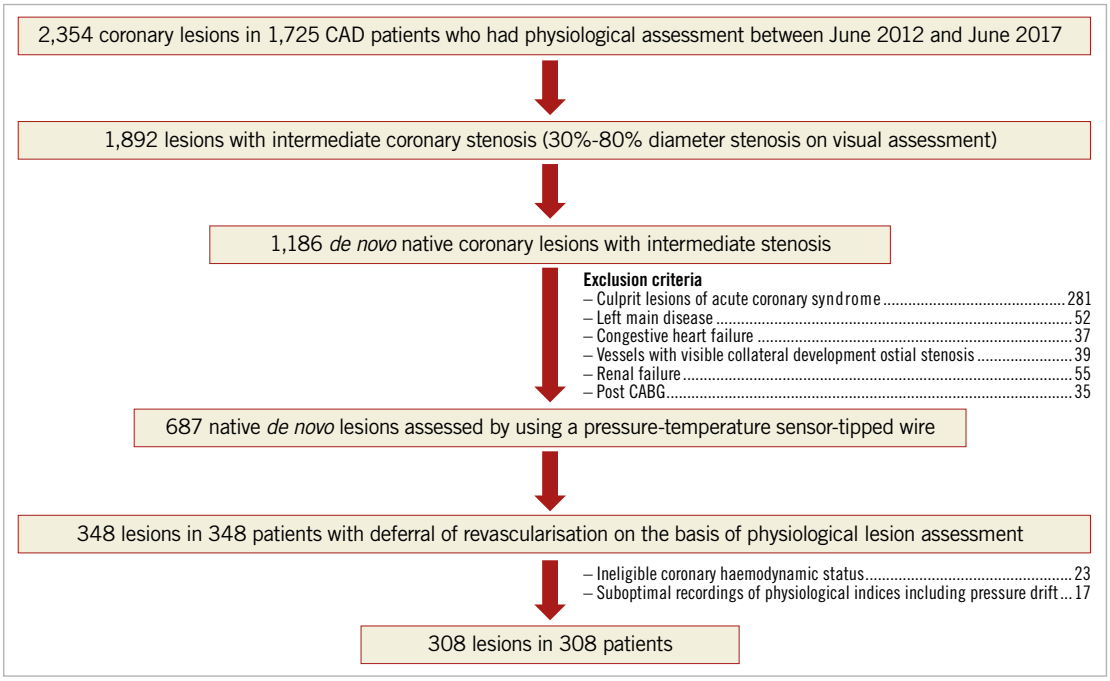

Figure 1. *Study population. CABG: coronary artery bypass graft; CAD: coronary artery disease*

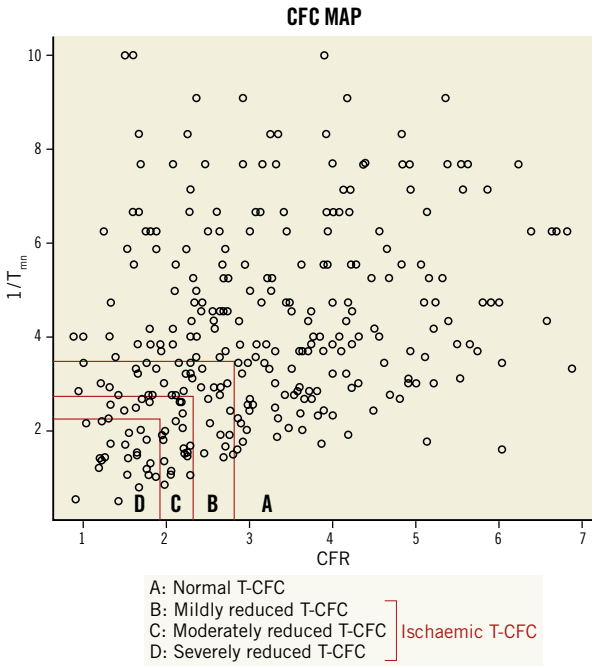

Figure 2. *Distribution of 308 lesions across the two-dimensional map of CFR versus $1/T_{mn}$ values with four categories. A) A total of 220 lesions (71.2%) showed normal T-CFC. B) 45 (15.5%) showed mildly reduced T-CFC. C) 18 (5.8%) showed moderately reduced T-CFC. D) 22 (7.1%) showed severely reduced T-CFC. CFR: coronary flow reserve; T-CFC: thermodilution-derived coronary flow capacity; T_{mn}: mean transit time*

Table 2. Patient characteristics.

	Overall (n=308)	Ischaemic T-CFC (n=88)	Normal T-CFC (n=220)	*p*-value
Age, years	69.0 (61.0-74.0)	72.5 (61.8-75.0)	68.0 (61.0-74.0)	0.078
Male	160 (79.6)	71 (80.7)	175 (79.5)	0.946
Hypertension	212 (68.6)	65 (73.9)	147 (66.8)	0.285
Dyslipidaemia	194 (62.8)	57 (64.8)	137 (62.3)	0.780
Diabetes mellitus	133 (43.0)	49 (55.7)	84 (38.2)	<0.001
Current smoker	77 (24.9)	28 (31.8)	49 (22.3)	0.109
Prior PCI	77 (24.9)	17 (19.3)	60 (27.3)	0.190
Prior MI	72 (23.3)	17 (19.3)	55 (25.0)	0.360
LDL cholesterol, mg/dl	94.0 (76.0-111.0)	91.0 (69.0-108.8)	94.5 (78.3-112.0)	0.186
eGFR, mL/min/1.73 m²	69.2 (57.4-83.4)	65.9 (55.5-77.5)	71.5 (58.1-84.2)	0.134
Ejection fraction, %	63.0 (57.0-69.0)	62.0 (56.0-68.0)	63.0 (58.0-69.0)	0.402
Medication				
Statin	208 (67.5)	63 (71.6)	145 (65.9)	0.414
ACE-I/ARB	200 (64.7)	59 (67.0)	141 (64.1)	0.720
ß-blocker	143 (46.3)	42 (47.7)	101 (45.9)	0.871

Data are presented as n (%), mean SD, or median (interquartile range). ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; MI: myocardial infarction; PCI: percutaneous coronary intervention; T-CFC: thermodilution-derived coronary flow capacity

CLINICAL OUTCOMES

During the median follow-up of 30 months (range, 20-61 months), VOCE occurred in 19 (6.2%) patients and MACE occurred in 28 (9.1%) patients. Demographics, angiographic and procedural characteristics according to the presence or absence of VOCE and MACE are shown in **Supplementary Table 1**. There were no significant differences in baseline characteristics in the two patient groups regarding the presence or absence of VOCE (19 events) or MACE (28 events).

Table 1. Clinical events during follow-up period.

VOCE	**19 (6.2%)**
Cardiac death	2
Non-fatal myocardial infarction	2
Vessel-oriented TVR	15
MACE	**28 (9.1%)**
Cardiac death	2
Non-fatal myocardial infarction	2
Vessel-oriented TVR	15
Non-target vessel TVR	6
Heart failure	3

Data are presented as n (%). MACE: major adverse cardiac events; TVR: target vessel revascularisation; VOCE: vessel-oriented composite endpoint

Lesions with FFR ≤0.8 predicted both VOCE and MACE, while CFR ≤2.0 predicted MACE, specifically **(Figure 3, Figure 4)**. Kaplan-Meier analysis revealed that lesions with ischaemic T-CFC had a significantly higher risk of both VOCE and MACE **(Figure 5)**. Kaplan-Meier curves showing survival from MACE according to all four T-CFC categories appear in **Supplementary Figure 2**. Multivariate Cox proportional hazards analysis demonstrated that ischaemic T-CFC and FFR ≤0.8 were independent predictors of VOCE **(Supplementary Table 2)**. Multivariate Cox proportional hazards analysis demonstrated that age, prior stent implantation, and ischaemic T-CFC were independent predictors of MACE **(Supplementary Table 3)**. IMR was not a significant factor for predicting VOCE or MACE. NRI and IDI index were both significantly improved when ischaemic T-CFC was added to the clinical risk model 1 for predicting VOCE and MACE. Furthermore, ischaemic T-CFC showed significant incremental predictive ability when compared with the clinical risk model + FFR ≤0.8 or the clinical model + CFR ≤2.0 **(Figure 6)**. In the subgroup analysis of deferred patients with FFR >0.8, ischaemic CFC was also significantly associated with poor prognosis **(Supplementary Figure 3)**, whereas CFR ≤2.0 showed no significant predictive information **(Supplementary Figure 4)**. Furthermore, ischaemic T-CFC showed significant incremental predictive ability when compared with the clinical risk model + CFR ≤2.0 **(Supplementary Figure 5)**.

Table 3. Angiographic and physiological findings.

		Overall (n=308)	Ischaemic T-CFC (n=88)	Normal T-CFC (n=220)	*p*-value
Quantitative coronary angiography data					
Reference diameter, mm		2.80 (2.42-3.25)	2.79 (2.37-3.18)	2.84 (2.44-3.28)	0.237
Minimum lumen diameter, mm		1.59 (1.32-1.88)	1.60 (1.32-1.87)	1.59 (1.32-1.88)	0.830
Diameter stenosis, %		44.8 (33.7-52.6)	43.9 (33.6-52.3)	45.2 (33.9-53.0)	0.820
Lesion length, mm		17.7 (12.0-23.3)	17.9 (13.5-24.2)	17.6 (11.5-22.8)	0.180
Coronary location (RCA/LAD/LCX)		57/219/32 (18.5/71.1/10.4)	19/62/7 (21.6/70.5/8.0)	38/157/25 (17.3/71.4/11.4)	0.536
Physiological data					
FFR		0.86 (0.83-0.90)	0.86 (0.83-0.90)	0.85 (0.82-0.90)	0.611
Aorta pressure, mmHg		81.0 (74.0-91.0)	81.0 (72.8-90.0)	82.0 (74.0-92.0)	0.374
Distal pressure, mmHg		69.0 (63.0-78.3)	67.0 (61.0-77.0)	70.0 (63.0-79.0)	0.179
CFR		2.91 (2.11-4.00)	1.97 (1.61-2.30)	3.58 (2.71-4.38)	<0.001
IMR		18.6 (12.6-27.4)	30.8 (23.7-42.0)	15.0 (11.2-21.4)	<0.001
IMR (corrected)		17.9 (12.4-26.8)	30.2 (23.2-40.5)	14.6 (10.9-21.0)	<0.001
Tmn	At rest, s	0.82 (0.56-1.22)	0.88 (0.66-1.34)	0.77 (0.51-1.22)	0.015
	At hyperaemia, s	0.27 (0.18-0.38)	0.43 (0.34-0.65)	0.22 (0.16-0.28)	<0.001

Data are presented as n (%), mean SD, or median (interquartile range). CFR: coronary flow reserve; FFR: fractional flow reserve; IMR: index of microcirculatory resistance; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; T-CFC: thermodilution-derived coronary flow capacity; Tmn: mean transit time

Discussion

To our knowledge, this is the first study demonstrating that categorisation based on coronary flow capacity improved risk stratification and showed incremental prognostic value for both VOCE and MACE compared with FFR or CFR alone in patients with deferred revascularisation for stable coronary lesions. Patients with deferred lesions with ischaemic T-CFC showed a significantly higher risk of VOCE and MACE than patients with lesions with normal T-CFC.

Although FFR has become the standard in decision making for revascularisation, FFR >0.8 does not necessarily mean the absence of ischaemia or that a patient is free from the risk of adverse events[20]. In the FAME 2 trial, patients with stenoses and FFR >0.8 who were treated by optimal medical therapy

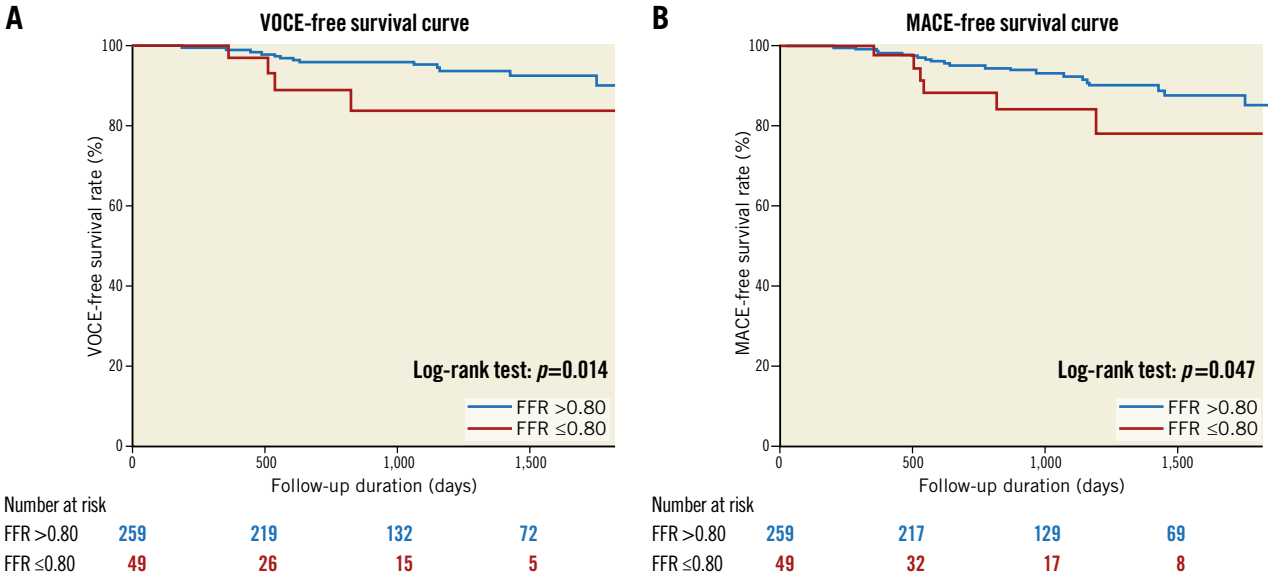

Figure 3. *Survival from cardiac events in patients based on an FFR value of 0.8. A) Kaplan-Meier curves demonstrating survival from VOCE in patients based on an FFR value of 0.8. B) Kaplan-Meier curves demonstrating survival from MACE in patients based on an FFR value of 0.8. FFR: fractional flow reserve; MACE: major adverse cardiac events; VOCE: vessel-oriented composite endpoint*

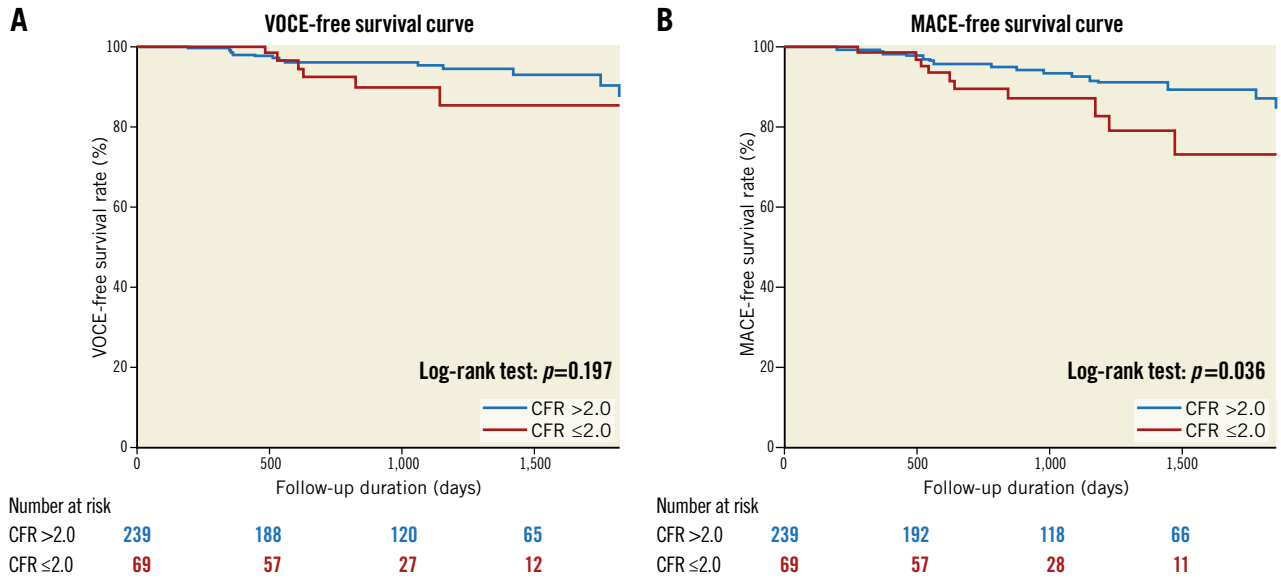

Figure 4. *Survival from cardiac events in patients based on a CFR value of 2.0. A) Kaplan-Meier curves demonstrating survival from VOCE in patients based on a CFR value of 2.0. B) Kaplan-Meier curves demonstrating survival from MACE in patients based on a CFR value of 2.0. CFR: coronary flow reserve; MACE: major adverse cardiac events; VOCE: vessel-oriented composite endpoint*

alone still suffered MACE in more than 10% of evaluated vessels[3]. Although FFR measurement is highly feasible and valuable in daily clinical practice, findings suggest that comprehensive assessment of coronary artery disease including diffuse arterial narrowing and microvascular dysfunction, which indicate risk of future clinical adverse outcomes, is needed to predict subsequent adverse events after revascularisation deferral based on FFR[21]. Johnson and Gould[11] first proposed CFC, based on the rationale that combining CFR with hyperaemic flow comprehensively captures all relevant flow characteristics of the evaluated vasculature. Despite the strong theoretical fundamentals of CFC, validation is necessary for potential clinical use to determine whether the prognostic implications are better than with FFR or CFR alone. To date, the clinical usefulness of CFC obtained by pressure-temperature sensor-tipped wire-derived coronary flow capacity in patients with deferred revascularisation has not been evaluated

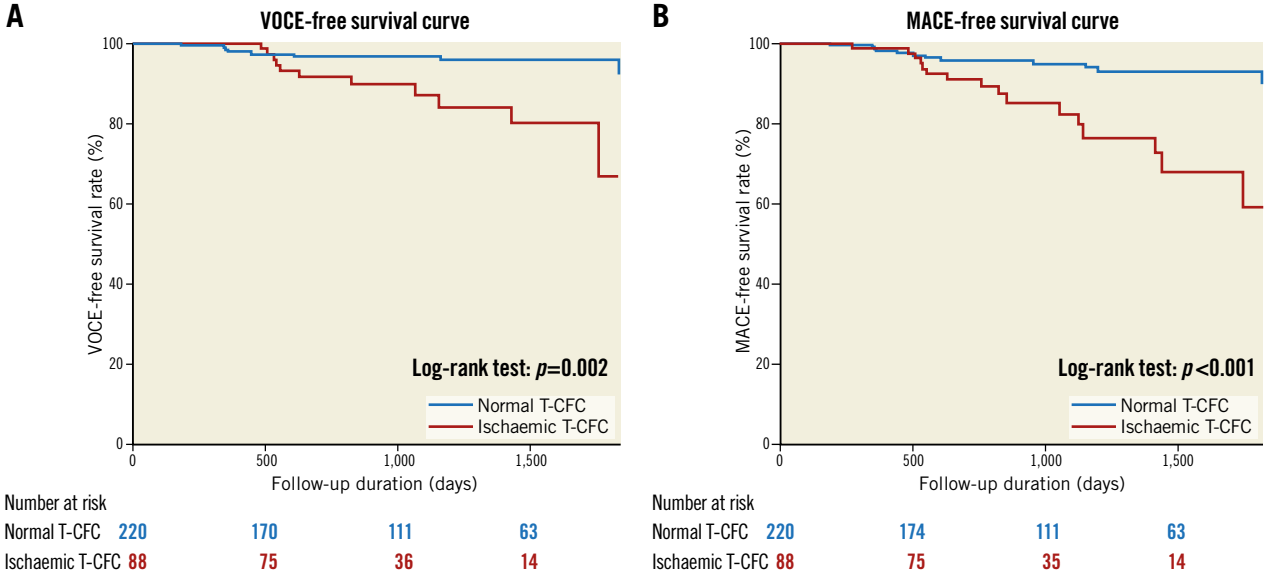

Figure 5. *Survival from cardiac events in patients divided into two groups by T-CFC. A) Kaplan-Meier curves demonstrating survival from VOCE in patients divided into two groups by T-CFC. B) Kaplan-Meier curves demonstrating survival from MACE in patients divided into two groups by T-CFC. MACE: major adverse cardiac events; T-CFC: thermodilution-derived coronary flow capacity; VOCE: vessel-oriented composite endpoint*

Prediction model for VOCE

Prediction model	IDI	*p*-value	NRI	*p*-value
Clinical model 1	Reference	–	Reference	–
Clinical model 2	0.006	0.388	0.222	0.283
Clinical model 3	0.001	0.834	0.196	0.371
Clinical model 4	0.041	0.024	0.625	0.007
Clinical model 2	Reference	–	Reference	–
Clinical model 5	0.043	0.026	0.625	0.007
Clinical model 3	Reference	–	Reference	–
Clinical model 6	0.047	0.015	0.625	0.007

Prediction model for MACE

Prediction model	IDI	*p*-value	NRI	*p*-value
Clinical model 1	Reference	–	Reference	–
Clinical model 2	0.005	0.496	0.200	0.237
Clinical model 3	0.010	0.277	0.293	0.118
Clinical model 4	0.057	0.003	0.629	0.001
Clinical model 2	Reference	–	Reference	–
Clinical model 5	0.055	0.005	0.629	0.001
Clinical model 3	Reference	–	Reference	–
Clinical model 6	0.046	0.015	0.629	0.001

Clinical model 1 (Age, sex, prior stent implantation, lesion length)
Clinical model 2 (Clinical model 1+FFR ≤0.8)
Clinical model 3 (Clinical model 1+CFR ≤2.0)
Clinical model 4 (Clinical model 1+ischaemic T-CFC)
Clinical model 5 (Clinical model 2+ischaemic T-CFC)
Clinical model 6 (Clinical model 3+ischaemic T-CFC)

Figure 6. *Comparison of discriminant and reclassification ability of predictive models to determine incremental discriminatory and reclassification capacities of FFR, CFR and T-CFC for cardiac events. Red numbers indicate statistical significance. CFR: coronary flow reserve; FFR: fractional flow reserve; IDI: relative integrated discrimination improvement; MACE: major adverse cardiac events; NRI: net reclassification index; T-CFC: thermodilution-derived coronary flow capacity; VOCE: vessel-oriented composite endpoint*

and, to our knowledge, our results are the first to demonstrate the superiority of T-CFC to predict VOCE or MACE compared with FFR or CFR alone in these patients. Worse prognoses in the ischaemic T-CFC group in the present study may be related to the prevalent microvascular dysfunction that is not evaluated by FFR, described as high IMR in patients with ischaemic T-CFC **(Table 3)**. Regarding the underlying mechanism of clinical events despite functionally insignificant epicardial coronary stenosis, previous studies have suggested a link between the presence of microvascular disease, endothelial dysfunction, subclinical inflammation, unexpected rapid atherosclerotic progression, and coronary vasomotor dysfunction with subsequent adverse events[22-24]. Lee et al recently reported that, in patients with functionally non-significant stenoses (FFR >0.8, n=230), clinical outcomes were the worst in those with both elevated IMR and low CFR[25]. In our study, IMR was not a significant factor for predicting VOCE or MACE, whereas T-CFC did identify high-risk patients for both VOCE and MACE. Of note, T-CFC effectively stratified both CFR and IMR in our population **(Table 3)**, and lesions in the ischaemic T-CFC group showed significantly higher IMR compared with those in the normal T-CFC group, similar to results in the study by Lee et al. Both in the study by Lee et al and in our studies, outcome events were driven mainly by unplanned remote revascularisation in patients with ischaemic T-CFC. These results suggest that microvascular dysfunction and other vascular functional impairment, including diffuse coronary disease and endothelial dysfunction potentially represented by reduced T-CFC, may be a marker of subsequent epicardial lesion progression requiring PCI in deferred patients with lesions showing non-ischaemic FFR values. Our results showing that T-CFC could discriminate patients at high risk of both VOCE and MACE suggest that T-CFC may be a marker of both target lesion information and global atherosclerotic burden susceptible to adverse events or stenosis progression.

The specific aspects and aims of the present study which were different from our previously published paper[13] are detailed in **Supplementary Appendix 2**.

In the original CFC classification based on average peak flow velocity (APV)[12], the ischaemic T-CFC is considered as the moderately and severely reduced T-CFC. On the other hand, we defined "ischaemic" T-CFC as the T-CFC from mild to severe impairment. The details of difference between the original one and our definition are in **Supplementary Appendix 2**. Comparison of Doppler techniques and thermodilution method are also detailed in **Supplementary Appendix 2**.

Study limitations

Our results should be interpreted bearing in mind several important limitations. First, this study included a relatively small number of patients from a single centre, which may not allow extensive subgroup analysis or more reliable multivariable analyses. Second, rigorous exclusion criteria limited the number of included patients. The small number of events precludes the differentiation of hard endpoints, including death and MI, which may be more important than emergent revascularisation, considering prevention. With no established cut-off values for hyperaemic Tmn, the proposed cut-off values were derived from the percentiles of hyperaemic Tmn corresponding to CFR cut-offs defined by the present population. The use of Tmn had an important intrinsic limitation which showed the wider distribution of T-CFC compared with APV-based CFC. Furthermore, 1/Tmn is a surrogate index of absolute flow, which depends on the size of the perfused myocardial territory, being larger in proximal locations and smaller in distal segments. Theoretically, Doppler flow velocity-derived T-CFC is more accurate, because the decrease in flow velocity from proximal to distal segments is much smaller than the decrease in volumetric flow. Although obtaining high-quality Doppler flow velocity data remains challenging, Doppler flow

velocity showed superior agreement of CFR with [^{15}O] H_2O PET compared with thermodilution[26]. The thermodilution-derived CFC concept accompanies these several limitations and might show different features compared with Doppler APV-based CFC or PET-based CFC. Moreover, CFC may not differentiate flow impairment between the epicardial and microcirculatory domains of the coronary circulation.

Conclusions

T-CFC mapping provided accurate predictions of coronary flow impairment. Categorisation by T-CFC was associated with the incidence of VOCE and MACE independently from FFR or CFR in patients with deferred revascularisation lesions. Further studies are needed to validate our hypothesis and results regarding the implications of T-CFC.

Impact on daily practice

T-CFC categorisation improved the risk stratification for both VOCE and MACE in patients with deferred revascularisation. T-CFC categorisation showed incremental predictive value compared with FFR or CFR alone in patients with deferred revascularisation.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

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Supplementary Appendix 2. Discussion.

Supplementary Figure 1. ROC analysis of physiological indices to predict MACE.

Supplementary Figure 2. MACE incidence according to T-CFC category.

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Supplementary Table 1. Patient characteristics.

Supplementary Table 2. Univariate and multivariate Cox proportional hazards analysis for VOCE.

Supplementary Table 3. Univariate and multivariate Cox proportional hazards analysis for MACE.

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Supplementary data

Supplementary Appendix 1. Methods

Exclusion criteria

We excluded patients with angiographically significant left main disease, previous coronary artery bypass surgery, renal insufficiency with baseline creatinine >2.0 mg/dl, unstable symptoms (worsening angina or rest angina within one month), myocardial infarction episode within 30 days before coronary angiography, decompensated heart failure, cardiogenic shock, extremely tortuous or calcified coronary arteries, and vessels with visible collateral development or ostial stenosis. Revascularisation was indicated based on patients' symptoms as well as non-invasive test results and FFR, although the final decision for revascularisation was at the interventionalists' discretion.

Coronary physiological assessment

Continuous infusion of adenosine via a central vein was used to induce hyperaemia for physiological measurements. FFR was calculated by dividing the mean distal pressure by the mean aortic pressure during stable hyperaemia. For IMR measurements, hyperaemic thermodilution curves (measured three times each using a 3 ml saline bolus injection) and hyperaemic Tmn were obtained. IMR was calculated as the product of the mean distal coronary pressure during stable hyperaemia and mean hyperaemic Tmn [14] and corrected using Yong's formula. CFR was measured simultaneously with FFR and IMR using the thermodilution method and expressed as a ratio: basal Tmn divided by hyperaemic Tmn [15]. After physiological measurements, the pressure wire was retracted into the guiding catheter to evaluate pressure drift. Our institutional standard protocol mandated repeat assessment if pressure drift was >3 mmHg. All waveform tracing and pressure data were transferred and validated at the institutional laboratory in a blinded fashion. Waveform tracings with phase adjustments meeting the following criteria were excluded from the analysis: 1) loss of pressure

signal at any point during the measurement phase (other than during saline flush injection), 2) significant arrhythmia, including atrial fibrillation that might preclude appropriate waveform analysis or pressure drift >3 mmHg, and 3) inferior waveform quality.

In the present study, patients, interventionalists, and outpatient physicians were aware of individual FFR values but blinded to the results of other physiological indices including CFR, transit time, and IMR, during follow-up.

Statistical analysis

Clinical prediction models were constructed to determine the incremental discriminatory and reclassification performance of physiological parameters for VOCE or MACE by using relative integrated discrimination improvement (IDI) and category-free net reclassification index (NRI). As a baseline reference, model 1 included clinical characteristics such as age, gender, prior PCI, and lesion length, then we tested an FFR model (model 2: model 1 + FFR ≤0.8), a CFR model (model 3: model 1 + CFR ≤2.0), and a T-CFC model (model 4: model 1 + T-CFC), in which T-CFC classification was converted into a binary variable (normal T-CFC vs ischaemic T-CFC). Model 5 included model 2 + T-CFC, and model 6 included model 3 + T-CFC. The discriminatory abilities of these models were assessed by the reclassification performance of each model and compared using relative integrated discrimination improvement (IDI) and category-free net reclassification index (NRI). In the subgroup analysis of deferred patients with FFR >0.8, as a baseline reference, model 7 included clinical characteristics such as age, gender, prior PCI, and lesion length, then we tested a CFR model (model 8: model 7 + CFR ≤0.8) and a T-CFC model (model 9: model 7 + T-CFC). Model 10 included model 8 + T-CFC.

Supplementary Appendix 2. Discussion

There were specific aspects and aims of the present study which were different from our previously published paper [13]. Since clinical events occur even in patients deferred on the basis of high FFR values [20], further stratification of FFR-guided deferred patients may be considered. Our previous report showed that the T-CFC categorisation could discriminate MACE in the total cohort, but it could not show significant predictive information in the severely reduced T-CFC group. To avoid underpower of the analysis by limiting CFC categorisations by one cut-off point and to limit the analysis in revascularisation deferral, we evaluated the predictive ability of T-CFC in the deferred population after FFR measurements. Since the thresholds of Tmn or CFR for CFC derivations have not been well established, we sought to investigate if a specific CFC cut-off point can better stratify deferred patients at risk for subsequent cardiac events with an incremental predictive ability in comparison with FFR or CFR alone. Furthermore, since FFR has been suggested to be the current standard index for the prediction of the vessel-oriented composite endpoint, we sought to evaluate if T-CFC could provide prognostic information for both vessel-level and patient-level events in comparison with FFR/CFR.

The difference between the original CFC classification based on APV and our T-CFC classification

When ischaemic T-CFC was defined as a composite of the moderately and severely reduced T-CFC, the discrimination efficacy of T-CFC was similarly significant for long-term adverse events (log-rank test; χ^2=6.0, p=0.015). Non-negligible numbers of cardiac events were observed in the mildly reduced CFC (VOCE: 6/48 [12.5%], MACE: 9/48 [18.8%]) category in the total study population. Discriminatory efficacy of T-CFC for predicting future events was higher when ischaemic T-CFC was defined as a composite of the mildly, moderately and severely reduced T-CFC on the basis of

ROC analysis (AUC: 0.657 vs 0.584, p=0.101). Thus, in the present study, we termed ischaemic T-CFC as normal T-CFC. This is the first study in which the deferred lesions were evaluated by ischaemic and non-ischaemic T-CFC categories for predicting cardiac events by the dichotomous cut point.

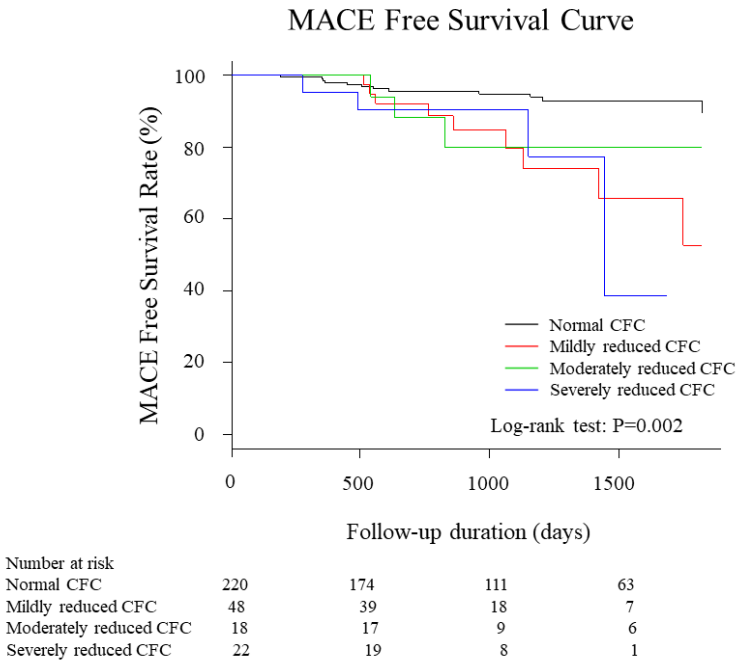
Comparison of Doppler techniques and thermodilution method

Doppler flow velocity-derived CFR showed superior agreement with CFR obtained by using [^{15}O] H_2O PET in comparison with the thermodilution technique-derived CFR [26]. CMR-derived microvascular obstruction has been reported to be better correlated with that by the velocity technique compared with the thermodilution method [27]. On the other hand, Fearon et al reported that thermodilution CFR correlates better with absolute flow-derived CFR than Doppler wire-derived CFR. From the prognostic point of view, Lee et al reported that thermodilution-derived CFR provided significant prognostic information in a relatively large population study [28]. On the basis of the previous reports, the Doppler technique for CFR appears superior to the thermodilution method, whereas it remains elusive if CFR by the Doppler technique provides better prognostic information compared with that by the thermodilution technique.

Supplementary Figure 1. ROC analysis of physiological indices to predict MACE.

Receiver operating characteristic (ROC) curve analyses were used to assess the best cut-off values of the physiological indices to predict MACE in FFR or CFR.

AUC: area under the curve; CFC: coronary flow capacity; CFR: coronary flow reserve; FFR: fractional flow reserve; MACE: major adverse cardiac events

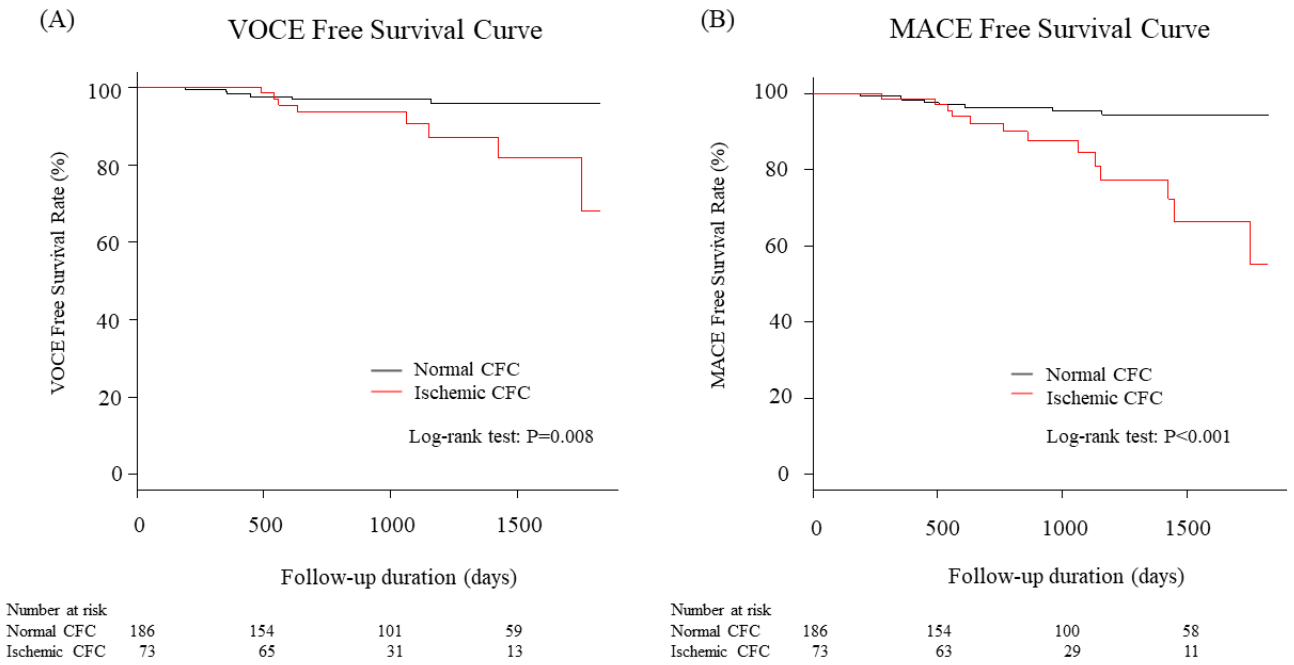


Number at risk				
Normal CFC	220	174	111	63
Mildly reduced CFC	48	39	18	7
Moderately reduced CFC	18	17	9	6
Severely reduced CFC	22	19	8	1

Supplementary Figure 2. MACE incidence according to T-CFC category.

Kaplan-Meier curves demonstrating survival from major adverse cardiac events (MACE) in patients with normal (A), mildly reduced (B), moderately reduced (C), or severely reduced T-CFC in the investigated coronary arteries. T-CFC categorisation significantly discriminated the incidence of MACE (p=0.002).

AUC: area under the curve; CFR: coronary flow reserve; MACE: major adverse cardiac events; T-CFC: thermodilution-derived coronary flow capacity

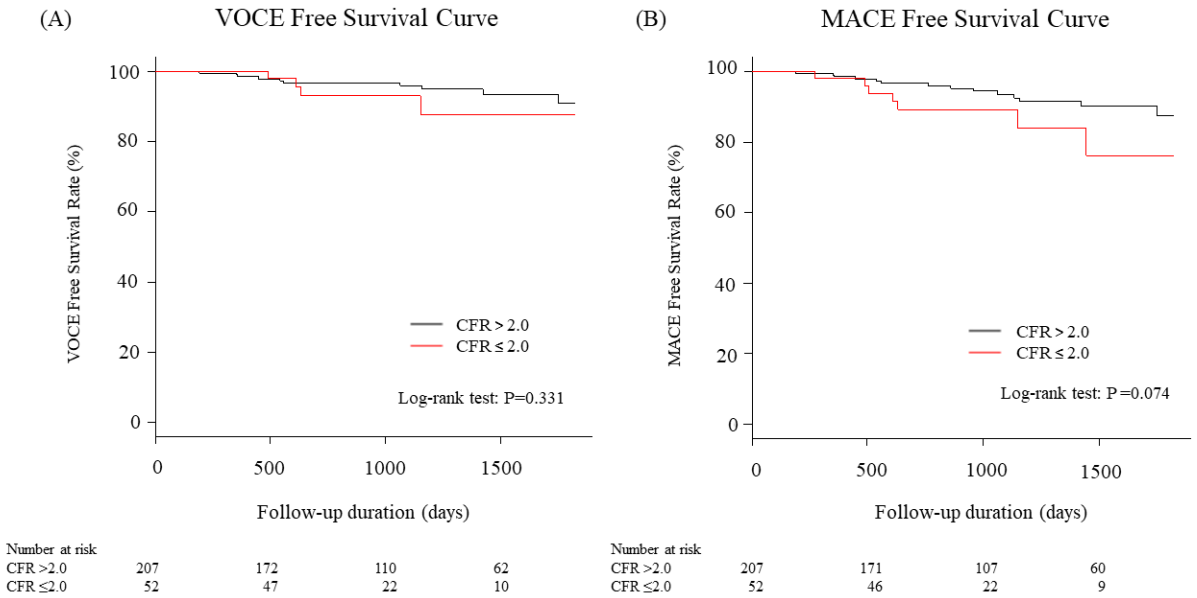


Supplementary Figure 3. Survival from cardiac events divided into two groups by T-CFC in patients with FFR >0.8.

A) Survival from VOCE in patients divided into two groups by T-CFC in patients with FFR >0.8. Kaplan-Meier curves demonstrating survival from VOCE in patients divided into two groups by T-CFC.

B) Survival from MACE in patients divided into two groups by T-CFC in patients with FFR >0.8. Kaplan-Meier curves demonstrating survival from MACE in patients divided into two groups by T-CFC.

CFC: coronary flow capacity; FFR: fractional flow reserve; MACE: major adverse cardiac events; T-CFC: thermodilution-derived coronary flow capacity; VOCE: vessel-oriented composite endpoint



Supplementary Figure 4. Survival from cardiac events based on a CFR value of 2.0 in patients with FFR >0.8.

A) Survival from VOCE in patients based on a CFR value of 2.0 in patients with FFR >0.8. Kaplan-Meier curves demonstrating survival from VOCE in patients based on a CFR value of 2.0.

B) Survival from MACE in patients based on a CFR value of 2.0 in patients with FFR >0.8. Kaplan-Meier curves demonstrating survival from MACE in patients based on a CFR value of 2.0.

CFR: coronary flow reserve; FFR: fractional flow reserve; MACE: major adverse cardiac events; VOCE: vessel-oriented composite endpoint

Prediction model for VOCE

Prediction Model	IDI	P value	NRI	P value
Clinical model 7	Reference	-	Reference	-
Clinical model 8	0.007	0.892	0.147	0.552
Clinical model 9	0.039	0.032	0.612	0.024
Clinical model 8	Reference	-	Reference	-
Clinical model 10	0.041	0.036	0.612	0.024

Prediction model for MACE

Prediction Model	IDI	P value	NRI	P value
Clinical model 7	Reference	-	Reference	-
Clinical model 8	0.011	0.356	0.230	0.280
Clinical model 9	0.082	0.002	0.734	<0.001
Clinical model 8	Reference	-	Reference	-
Clinical model 10	0.070	0.010	0.734	<0.001

Clinical model 7 (Age, sex, prior stent implantation, lesion length)
Clinical model 8 (Clinical model 1 + CFR ≤ 2.0)
Clinical model 9 (Clinical model 1 + ischemic CFC)
Clinical model 10 (Clinical model 2 + ischemic CFC)

Supplementary Figure 5. Comparison of discriminant and reclassification ability of predictive models in patients with FFR >0.8 to determine incremental discriminatory and reclassification capacities of CFR and T-CFC for cardiac events. Red numbers indicate statistical significance.

CFC: coronary flow capacity; CFR: coronary flow reserve; FFR: fractional flow reserve; IDI: relative integrated discrimination improvement; MACE: major adverse cardiac events; NRI: net reclassification index; T-CFC: thermodilution-derived coronary flow capacity; VOCE: vessel-oriented composite endpoint

Supplementary Table 1. Patient characteristics.

	VOCE (n=19)	No VOCE (n=289)	*p*-value	MACE (n=28)	No MACE (n=280)	*p*-value
Age, yrs	72.0 (64.5-72.0)	69.0 (61.0-74.0)	0.438	73.0 (67.3-75.0)	69.0 (61.0-74.0)	0.053
Male	17 (89.5)	229 (79.2)	0.384	26 (92.9)	220 (78.6)	0.085
Hypertension	14 (73.7)	198 (68.5)	0.800	20 (71.4)	192 (68.6)	0.923
Dyslipidaemia	13 (68.4)	181 (62.6)	0.794	17 (60.7)	177 (63.2)	0.955
Diabetes mellitus	11 (57.9)	122 (42.2)	0.272	14 (50.0)	119 (42.5)	0.573
Current smoker	4 (21.1)	73 (25.3)	0.791	5 (17.9)	72 (25.7)	0.493
Prior PCI	9 (47.4)	68 (23.5)	0.040	12 (42.9)	65 (23.2)	0.039
Prior MI	6 (31.6)	84 (32.4)	1.000	9 (33.3)	81 (32.3)	1.000
LDL cholesterol, mg/dl	90.5 (79.0-105.3)	94.0 (76.0-111.0)	0.564	85.0 (76.5-107.0)	94.0 (76.0-111.0)	0.285
eGFR, mL/min/1.73 m^2	74.5 (66.9-79.9)	68.9 (56.2-83.7)	0.272	68.4 (59.3-78.3)	69.8 (57.4-83.7)	0.833
Ejection fraction, %	66.5 (62.0-69.0)	63.0 (57.0-68.0)	0.217	63.0 (53.0-68.0)	63.0 (57.0-69.0)	0.509
Medication						

Statin	12 (63.2)	196 (71.5)	0.606	19 (67.9)	189 (71.3)	0.869
ACE-I/ARB	12 (63.2)	188 (65.1)	1.000	20 (71.4)	180 (64.3)	0.584
β-blocker	11 (57.9)	132 (45.7)	0.347	14 (50.0)	129 (46.1)	0.843
QCA						
RD, mm	2.66 (2.39-3.13)	2.80 (2.42-3.27)	0.466	2.69 (2.41-3.15)	2.81 (2.42-3.27)	0.571
MLD, mm	1.40 (1.17-1.70)	1.60 (1.32-1.88)	0.111	1.49 (1.21-1.96)	1.59 (1.32-1.87)	0.546
DS, %	49.8 (38.5-57.7)	44.4 (33.8-52.0)	0.091	48.0 (29.7-56.3)	44.6 (34.3-52.0)	0.508
Lesion length, mm	18.3 (14.4-22.6)	17.6 (11.9-23.3)	0.623	10.8 (7.2-13.9)	9.9 (7.1-13.8)	0.791
Coronary location (RCA/LAD/LCX)	2/15/2	55/204/30	0.739	3/22/3	54/197/29	0.593
Physiological data						
FFR	0.85 (0.80-0.88)	0.86 (0.83-0.90)	0.101	0.85 (0.81-0.88)	0.86 (0.83-0.90)	0.123
CFR	2.36 (1.92-3.47)	2.96 (2.11-4.00)	0.123	2.31 (1.78-3.23)	2.98 (2.18-4.02)	0.019
IMR	20.1 (15.2-31.7)	17.9 (12.5-27.3)	0.436	20.5 (13.1-32.1)	17.8 (12.6-27.1)	0.247
IMR (corrected)	19.8 (14.6-27.4)	17.5 (12.2-26.7)	0.497	20.2 (12.6-28.3)	17.5 (12.4-26.3)	0.319
Ischaemic T-CFC	11 (57.9)	77 (26.6)	0.008	16 (57.1)	72 (25.7)	<0.001

Data are presented as n (%), mean SD, or median (interquartile range).

ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CFR: coronary flow reserve; DS: diameter stenosis; eGFR: estimated glomerular filtration rate; FFR: fractional flow reserve; IMR: index of microcirculatory resistance; LAD: left anterior descending artery; LCX: left circumflex coronary; LDL: low-density lipoprotein; MACE: major adverse cardiac events; MI: myocardial infarction; MLD: minimum lumen diameter; PCI: percutaneous coronary intervention; QCA: quantitative coronary angiography; RCA: right coronary artery; RD: reference diameter; T-CFC: coronary flow capacity; VOCE: vessel-oriented composite endpoint

Supplementary Table 2. Univariate and multivariate Cox proportional hazards analysis for VOCE.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.04	0.98-1.10	0.222			
Male	1.66	0.38-7.20	0.500			
Diabetes mellitus	1.86	0.75-4.63	0.181			
Prior PCI	2.77	1.12-6.83	0.027			
Diameter stenosis	1.03	0.99-1.07	0.093			
Lesion length	1.05	1.00-1.10	0.062			
FFR ≤0.80	3.24	1.16-9.04	0.025	3.00	1.07-8.39	0.037
CFR ≤2.0	1.88	0.71-5.00	0.205			
Ischaemic CFC	3.84	1.53-9.65	0.004	3.70	1.47-9.33	0.005

CFC: coronary flow capacity; CFR: coronary flow reserve; CI: confidence interval; FFR: fractional flow reserve; HR: hazard ratio; PCI: percutaneous coronary intervention; VOCE: vessel-oriented composite endpoint

Supplementary Table 3. Univariate and multivariate Cox proportional hazards analysis for MACE.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	1.07	1.01-1.12	0.014	1.05	1.00-1.11	0.048
Male	2.48	0.59-10.48	0.216			
DM	1.37	0.65-2.88	0.403			
Prior PCI	2.26	1.07-4.78	0.034	2.42	1.14-5.14	0.022
Diameter stenosis	1.01	0.98-1.04	0.533			
Lesion length	1.03	0.98-1.08	0.301			
FFR ≤0.80	2.33	0.99-5.50	0.053			
CFR ≤2.0	2.25	1.03-4.90	0.041			
Ischaemic CFC	3.83	1.80-8.14	<0.001	3.57	1.66-7.67	0.001

CFC: coronary flow capacity; CFR: coronary flow reserve; CI: confidence interval; DM: diabetes mellitus; FFR: fractional flow reserve; HR: hazard ratio; MACE: major adverse cardiac events; PCI: percutaneous coronary intervention