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Fractional flow reserve and pressure-bounded coronary flow reserve to predict outcomes in coronary artery disease

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Aims Fractional flow reserve (FFR) has proven to its prognostic and therapeutic value. However, the additive prognostic value of coronary flow reserve (CFR) remains unclear. This study sought to investigate the clinical utility of combined FFR and CFR measurements to predict outcomes.

Methods and results Using the prospective, multicentre Interventional Cardiology Research Incooperation Society–FFR registry, a total of 2088 lesions from 1837 patients were included in this substudy. Based on baseline and hyperaemic pressure gradients, we computed physiologic limits of CFR [the so called pressure-bounded (pb) CFR] and classified lesions as low (<2) or high (≥2). The primary endpoint was major adverse cardiac events (MACE, a composite of cardiac death, myocardial infarction, and revascularization) analysed on a per-patient basis. During a median follow-up of 1.9 years (interquartile range: 1.0–3.0 years), MACE occurred in 5.7% of patients with FFR ≤0.80 vs. 2.8% of patients with FFR >0.80 [adjusted hazard ratio (aHR): 2.15, 95% confidence interval (CI): 1.19–3.89; $P = 0.011$. In contrast, the incidence of MACE did not differ between patients with pb-CFR < 2 vs. pb-CFR ≥ 2 (4.2% vs. 4.2%; aHR: 0.98, CI: 0.60 to 1.58; P = 0.92). Incorporation of FFR significantly improved model prediction of MACE (global χ^2 38.8–48.1, $P = 0.002$). However, pb-CFR demonstrated no incremental utility to classify outcomes (global χ^2 48.1–48.2, $P > 0.99$).

Conclusions In this large, prospective registry of over 2000 coronary lesions, FFR was strongly associated with clinical outcomes. In contrast, a significant association between pb-CFR and clinical events could not be determined and adding knowledge of pb-CFR did not improve prognostication over FFR alone.

Keywords Fractional flow reserve • Coronary flow reserve • Coronary artery disease • Prognosis

Introduction

During the last two decades, fractional flow reserve (FFR) has established itself as an invasive standard for identifying flow-limiting coronary artery disease. Several prospective randomized trials and observational studies have shown that FFR-guided percutaneous coronary intervention (PCI) outperforms angiography-guided PCI. Therefore, FFR receives strong recommendations in the current clinical guidelines.[1] FFR is characterized by a simple, practical, pressure-derived index specifically assessing the influence of epicardial coronary disease on myocardial perfusion, independent of microvascular (dys)function.[1–8]

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In contrast, coronary flow reserve (CFR) provides combined physiologic information on epicardial stenosis plus microvascular function, although a single distal measurement cannot discriminate their relative contributions.[9–11] Considering the frequent, multi-level involvement of coronary artery disease, CFR could remain advantageous and additive to FFR.[12–14] However, measurement of invasive CFR with the present techniques remains technically more challenging and less reproducible than FFR.[15] Due to the distinct physiologic nature of CFR and FFR, their integrated assessment might be helpful in more accurately identifying the risk and guide treatment.

Therefore, we used the large prospective Interventional Cardiology Research Incooperation Society–Fractional Flow Reserve (IRIS–FFR) registry to compare the incremental usefulness of CFR and FFR for predicting clinical outcomes. To overcome the technical limitations of the current invasive CFR techniques, we applied the novel concept of pressure-bounded CFR (pb-CFR), which enables robust classification of 'low' and 'high' CFR using only routine pressure measurements.[16]

Methods

Study design

The IRIS–FFR registry (clinicaltrials.gov NCT01366404) is a prospective, multicentre study designed to investigate the natural history of coronary stenosis assessed by FFR. A total of 30 heart centres in South Korea participated. The registry consecutively enrolled all patients who underwent FFR measurement of at least one coronary lesion between August 2009 and August 2015. Exclusion criteria were minimal, which included Thrombolysis in Myocardial Infarction (TIMI) flow <3, bypass graft lesion, severe heart failure, and technical unsuitability for FFR evaluation. The study protocol was approved by the institutional review board or ethical committee at each participating centre, and all patients provided written informed consent.

Fractional flow measurement and revascularization

Fractional flow reserve was measured with a commercially available coronary pressure wire during coronary angiography in standard fashion.[3] After administration of intracoronary nitrates (100–200μg), the pressure wire was positioned distal to the target lesion. Intravenous adenosine infusion (140 μg/kg/min) via a central line or large antecubital vein induced coronary hyperaemia. FFR was calculated from the proximal aortic pressure (Pa) and distal coronary pressure (Pd) during hyperaemia, as mean Pd/Pa. Revascularization was generally performed in coronary lesions with FFR ≤ 0.75 and deferred in those with FFR > 0.80. For FFR values between 0.75 and 0.80, the decision regarding revascularization was left to the operator's discretion.

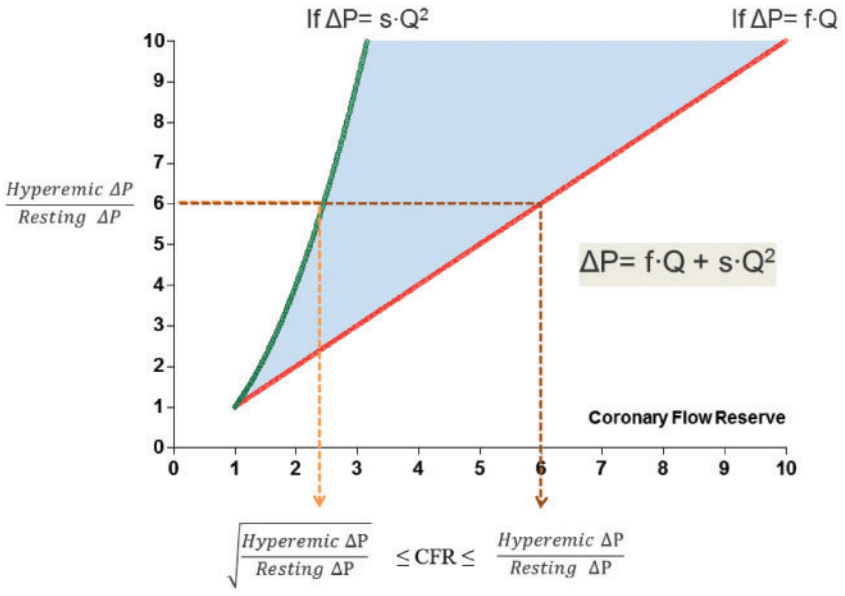

Figure 1 Theory of pressure-bounded coronary flow reserve. Fundamental fluid dynamics demonstrate that the pressure gradient (ΔP) induced by an epicardial coronary stenosis can be described as $\Delta P = f \cdot Q + s \cdot Q^2$. If all of the pressure gradient is caused by frictional loss, then $\Delta P = f \cdot Q$(red line); conversely, if all of the pressure gradient is caused by separation loss, then $\Delta P = s \cdot Q^2$(green line). Therefore, for any resting and hyperaemic pressure gradient, coronary flow reserve (CFR) is bounded between $\sqrt{\text{hyperaemic } \Delta P / \text{resting } \Delta P}$ and hyperaemic ΔP/resting ΔP (blue area). Accordingly, if the upper bound of CFR estimated from resting and hyperaemic pressure gradient is < 2, then CFR is definitely <2 (low CFR group); and if the lower bound of CFR estimated from resting and hyperaemic pressure gradient is ≥ 2, then CFR is definitely ≥2 (high CFR group). In the remaining patients, CFR cannot be classified with certainty in this way and so is called indeterminate. CFR denotes coronary flow reserve; *f*, friction coefficient; s, separation coefficient; ΔP, pressure gradient; *Q*, coronary blood flow.

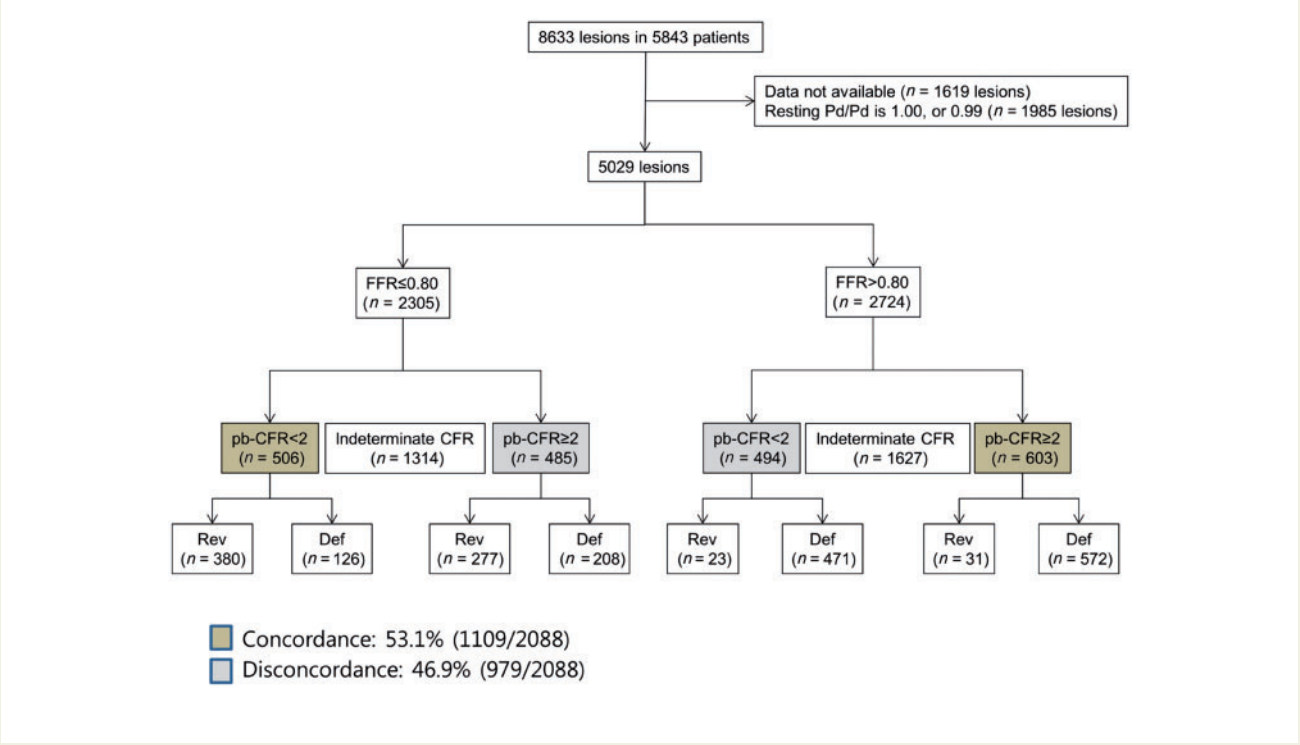

Figure 2 Flow chart. pb-CFR denotes pressure-bounded coronary flow reserve; Def, deferral of revascularization; FFR, fractional flow reserve; REV, revascularization.

Pressure-bounded coronary flow reserve

A well-established fluid dynamics equation quantifies the pressure gradient induced by an epicardial coronary artery stenosis[11]:

$$\Delta P = f \cdot Q + s \cdot Q^2,$$

where f is friction or viscous coefficient, s is separation or expansion coefficient, ΔP is pressure gradient, and Q is coronary blood flow.

If all the pressure gradient was caused by frictional loss, then $\Delta P = f \cdot Q$; conversely, if all pressure gradient was caused by separation loss, then $\Delta P = s \cdot Q^2$. Therefore, for any given combination of resting and hyperaemic pressure gradients, CFR (the ratio of hypearemic flow to resting flow) is bounded as follows (*Figure 1*)[16]:

$$\sqrt{\frac{\text{Hyperaemic } \Delta P}{\text{Resting } \Delta P}} \leq \text{CFR} \leq \frac{\text{Hyperaemic } \Delta P}{\text{Resting } \Delta P} \quad (1)$$

We classified lesions into three distinct pb-CFR groups based on *Equation 1*: low when the upper boundary of CFR (i.e. hyperaemic ΔP/resting ΔP) was <2; high when lower boundary of CFR (i.e. $\sqrt{\text{hyperaemic } \Delta P/\text{resting } \Delta P}$) was ≥2; and indeterminate when the boundary crossed the value of 2. To make the calculation more straightforward since only Pd/Pa was available, *Equation 1* can also be rewritten as:

$$\sqrt{\frac{\text{1-Hyperaemic Pd/Pa}}{\text{1-Resting Pd/Pa}}} \leq \text{CFR} \leq \frac{\text{1-Hyperaemic Pd/Pa}}{\text{1-Resting Pd/Pa}} \quad (2)$$

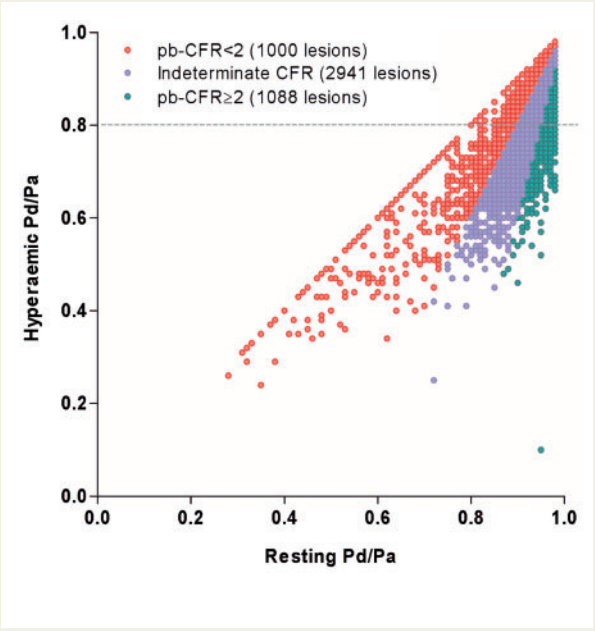

Figure 3 Distribution of pressure-bounded coronary flow reserve.

Table 1 Patient and lesion characteristics among combinations of fractional flow reserve and pressure-bounded coronary flow reserve

	FFR>0.80; pb-CFR≥2	FFR>0.80; pb-CFR<2	FFR≤0.80; pb-CFR≥2	FFR≤0.80; pb-CFR<2	*P*-value
Patient characteristics	*n* = 513	*n* = 425	*n* = 434	*n* = 465	
Age	63.0 ± 9.5	65.5 ± 10.0	60.7 ± 9.5	64.4 ± 10.3	<0.001
Gender	380 (74.1)	240 (56.5)	373 (85.9)	330 (71.0)	<0.001
Clinical presentation					<0.001
Stable angina	418 (81.5)	347 (81.6)	359 (82.7)	334 (71.8)	
Unstable angina	74 (14.4)	61 (14.4)	69 (15.9)	85 (18.3)	
NSTEMI	15 (2.9)	14 (3.3)	5 (1.2)	34 (7.3)	
STEMI	6 (1.2)	3 (0.7)	1 (0.2)	12 (2.6)	
Hypertension	319 (62.2)	299 (70.4)	278 (64.1)	313 (67.3)	0.047
Diabetes	136 (26.5)	150 (35.3)	99 (22.8)	196 (42.2)	<0.001
Current smoking	138 (26.9)	79 (18.6)	122 (28.1)	102 (21.9)	0.003
Hyperlipidaemia	338 (65.9)	218 (51.3)	279 (64.3)	305 (65.6)	<0.001
Previous MI	24 (4.7)	26 (6.1)	23 (5.3)	24 (5.2)	0.81
Previous PCI	98 (19.1)	83 (19.5)	79 (18.2)	89 (19.1)	0.97
Family history	72 (14.0)	37 (8.7)	43 (9.9)	58 (12.5)	0.045
Previous congestive heart failure	9 (1.8)	5 (1.2)	5 (1.2)	6 (1.3)	0.84
Previous stroke	32 (6.2)	24 (5.6)	29 (6.7)	39 (8.4)	0.39
Peripheral vascular disease	13 (2.5)	7 (1.6)	12 (2.8)	17 (3.7)	0.32
Chronic renal failure	11 (2.1)	13 (3.1)	3 (0.7)	29 (6.2)	<0.001
Chronic obstructive lung disease	13 (2.5)	14 (3.3)	11 (2.5)	6 (1.3)	0.26
Lesion characteristics	*n* = 603	*n* = 494	*n* = 485	*n* = 506	
Resting Pd/Pa	0.97 ± 0.01	0.93 ± 0.03	0.95 ± 0.02	0.74 ± 0.13	<0.001
Hyperaemic Pd/Pa (FFR)	0.86 ± 0.03	0.89 ± 0.04	0.73 ± 0.07	0.65 ± 0.12	<0.001
Lower limit of pb-CFR	2.42 ± 0.29	1.23 ± 0.12	2.41 ± 0.46	1.20 ± 0.14	<0.001
Higher limit of pb-CFR	5.47 ± 1.44	1.54 ± 0.28	6.04 ± 2.55	1.45 ± 0.33	<0.001
Revascularization	31 (5.1)	23 (4.7)	277 (57.1)	380 (75.1)	<0.001
Lesion territory					<0.001
Left main	14 (2.3)	17 (3.4)	39 (8.0)	58 (11.5)	
Left anterior descending artery	255 (42.3)	352 (71.3)	233 (48.0)	310 (61.3)	
Right coronary artery	206 (34.2)	58 (11.7)	117 (24.1)	59 (11.7)	
Left circumflex artery	91 (15.1)	46 (9.3)	70 (14.4)	53 (10.5)	
Others	37 (6.1)	21 (4.3)	26 (5.4)	26 (5.1)	
Lesion location					<0.001
Proximal	298 (49.4)	188 (38.1)	279 (57.5)	306 (60.5)	
Mid	175 (29.0)	222 (44.9)	112 (23.1)	129 (25.5)	
Distal	130 (21.6)	84 (17.0)	94 (19.4)	71 (14.0)	
Diameter stenosis					<0.001
≥70%	63 (10.4)	45 (9.1)	217 (44.7)	302 (59.7)	
50–69%	347 (57.5)	243 (49.2)	228 (47.0)	185 (36.6)	
30–49%	193 (32.0)	206 (41.7)	40 (8.2)	19 (3.8)	
AHA/ACC lesion B2C lesion	327 (54.2)	227 (46.0)	346 (71.3)	403 (79.6)	<0.001
Long lesion (>20 mm)	247 (41.0)	185 (37.4)	268 (55.3)	333 (65.8)	<0.001
Moderately to severely calcified lesion	13 (2.2)	20 (4.0)	15 (3.1)	21 (4.2)	0.21
Thrombus containing lesion	5 (0.8)	2 (0.4)	4 (0.8)	7 (1.4)	0.42
Angiographic ulcerated lesion	7 (1.2)	1 (0.2)	2 (0.4)	3 (0.6)	0.21

Mean ± SD and number (%).
FFR, fractional flow reserve; NSTEMI, non–ST-segment–elevated myocardial infarction; pb-CFR, pressure bounded coronary flow reserve; STEMI, ST–segment–elevated myocardial infarction; AHA/ACC, American Heart Association/American College of Cardiology; PCI, percutaneous coronary intervention.

under the assumption that aortic pressure does not change. We excluded lesions with missing resting Pd/Pa and lesions with resting Pd/Pa of 0.99 or 1, because the intrinsic error of a pressure measurement is 2%.[17,18] For the latter group, we performed a sensitivity analysis to evaluate the impact of this exclusion criterion on overall findings, hypothesizing that for FFR ≥ 0.99, CFR will frequently be > 2.

Endpoints and definitions

The primary endpoint was a major adverse cardiac event (MACE) consisting of composite cardiac death, myocardial infarction (MI), and subsequent revascularization. MACE was analysed on a per-lesion and per-patient basis. For per-patients analysis, the lowest value of FFR and its pb-CFR was selected as the representative value of patient. Cardiac death was defined as any death due to cardiac causes including cardiac arrest, MI, low output failure, or fatal arrhythmia. Myocardial infarction was defined as follows: (i) within the first 48 h after revascularization, ischaemic symptoms with an elevation of creatinine kinase-MB (CK-MB) fraction concentration >5 times normal or (ii) 48 or more hours after revascularization, any CK-MB or troponin increase above the upper range plus ischaemic signs or symptoms. Subsequent revascularization was defined as any PCI or coronary artery bypass surgery of an index lesion. All outcomes of interest were confirmed by source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee.

Data and follow-up

Baseline characteristics and outcome data were collected using a dedicated, electronic case report form by specialized personnel at each centre. Monitoring and verification of registry data were periodically performed in participating hospitals by members of the academic coordinating centre (Clinical Research Center, Asan Medical Center, Seoul, Korea). Clinical follow-up was conducted during the index hospitalization and at 30 days, 6 months, and 12 months, then every 6 months thereafter. During these visits, data pertaining to the patient's clinical status, all interventions, and adverse events were recorded.

Statistical analysis

Continuous variables were expressed as means ± 1 SD; categorical variables were shown as counts and percentages. Continuous variables were compared using unpaired *t*-tests, non-parametric Mann–Whitney tests, or one-way analysis of variance; categorical variables were compared using χ^2 statistics or Fisher's exact test, as appropriate. Time-to-event data were presented as Kaplan–Meier estimates and compared using the log-rank test. Baseline variables that were considered clinically relevant or that showed significant univariate relationships with MACE were entered into multivariable Cox proportional hazards regression models.[19] Variables for inclusion were carefully chosen, given the number of events, to ensure parsimony of the final models. A marginal Cox model was used to account for patients with multiple lesions.[20] A nested Cox proportional hazard regression analysis was used to investigate the incremental prognostic value of the predictors. Statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute). Applicable *P*-values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Between August 2009 and August 2015, 8633 lesions from 5843 patients were prospectively enrolled, of which pb-CFR could be calculated in 5029 lesions. Excluding 2941 lesions with indeterminate CFR, 1000 lesions were classified as low pb-CFR <2 and 1088 as high pb-CFR ≥2 within 1837 patients (*Figure 2*). The concordance and discordance rates between FFR and pb-CFR were 53.1% and 46.9%, respectively, using traditional thresholds of FFR = 0.80 and pb-CFR = 2. *Figure 3* depicts the distribution of pb-CFR, resting Pd/Pa, and hyperaemic Pd/Pa.

Baseline patient characteristics in low and high pb-CFR groups are shown in Supplementary material online, *Tables S1 and S2*. Significant associations with low pb-CFR included older age, female sex, acute coronary syndrome, hypertension, diabetes, and chronic renal failure. In contrast, low FFR was significantly associated with older age, male sex, and hyperlipidaemia. *Table 1* describes the patient and lesion characteristics of the 4 groups of binary FFR and pb-CFR. In general, the group with low pb-CFR and low FFR had the most cardiac risk factors.

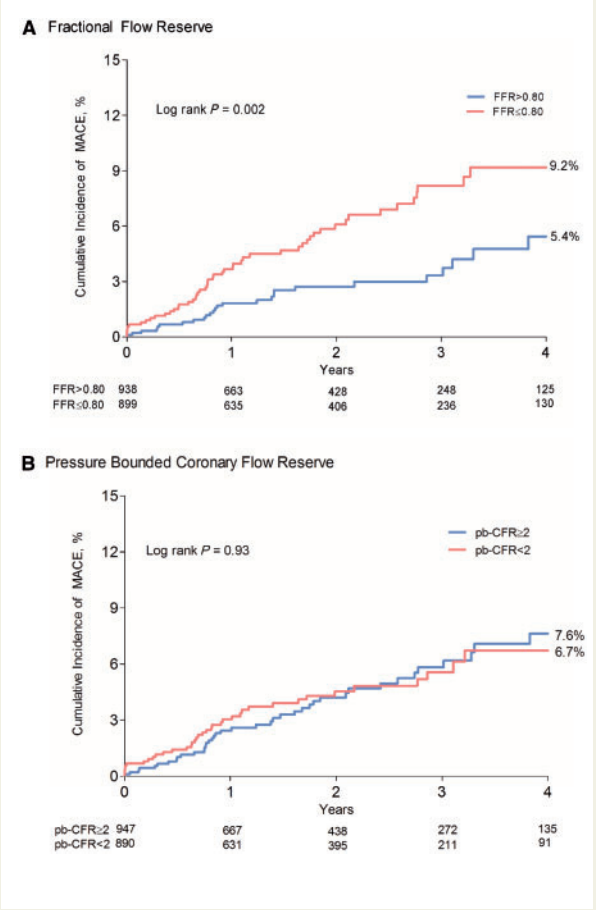

Figure 4 Kaplan–Meier curves for major adverse cardiac events when using (*A*) fractional flow reserve and (*B*) coronary flow reserve in all patients independent of chosen treatment.

Table 2 Clinical outcomes according to fractional flow reserve

	Total no. of events (%)		*P*-value[a]	aHR[b]	95% CI	*P*-value
	Low FFR (≤0.80)	High FFR (>0.80)				
Per-patient analysis	*n* = 899	*n* = 938				
Primary endpoint (MACE): the composite of cardiac death, myocardial infarction, or subsequent revascularization						
All lesion	51 (5.7)	26 (2.8)	0.002	2.15	1.19–3.89	0.011
Deferred lesion	20 (6.9)	25 (2.8)	0.002	2.14	1.15–3.99	0.017
Revascularized lesion	31 (5.1)	1 (2.3)	0.72	1.37	0.18–10.2	0.76
Secondary endpoint:						
Cardiac death or myocardial infarction	11 (1.2)	4 (0.4)	0.06	1.89	0.38–9.38	0.44
Repeat revascularization	43 (4.8)	22 (2.3)	0.005	2.29	1.22–4.28	0.01
Per-lesion analysis[c]	*n* = 991	*n* = 1097				
Primary endpoint						
All lesion	57 (5.8)	27 (2.5)	NA	2.46	1.40–4.31	0.002
Deferred lesion	23 (6.9)	26 (2.5)	NA	2.38	1.32–4.30	0.004
Revascularized lesion	34 (5.2)	1 (1.9)	NA	1.88	0.25–14.0	0.54
Secondary endpoint:						
Cardiac death or myocardial infarction	14 (1.4)	4 (0.4)	NA	3.61	0.90–14.5	0.07
Repeat revascularization	48 (4.8)	23 (2.1)	NA	2.62	1.44–4.75	0.002

aHR, adjusted hazard ratio; CFR, coronary flow reserve; CI, confidence interval; MACE, major adverse cardiac event; NA, not available.
[a]Log-rank *P*-value.
[b]Adjusted for age, male sex, clinical presentation, hypertension, diabetes, current smoking, hyperlipidaemia, revascularization, lesion territory, lesion location, and diameter stenosis.
[c]The models accounted for the clustering of lesions in patients.

Table 3 Clinical outcomes according to pressure bounded coronary flow reserve

	Total no. of events (%)		*P*-value[a]	aHR[b]	95% CI	*P*-value
	Low pb-CFR (<2)	High pb-CFR (≥2)				
Per-patient analysis	*n* = 890	*n* = 947				
Primary endpoint (MACE): the composite of cardiac death, myocardial infarction, or subsequent revascularization						
All lesion	37 (4.2)	40 (4.2)	0.93	0.98	0.60–1.58	0.92
Deferred lesion	18 (3.5)	27 (4.1)	0.85	0.84	0.46–1.55	0.57
Revascularized lesion	19 (5.1)	13 (4.6)	0.88	1.32	0.64–2.72	0.45
Secondary endpoint						
Cardiac death or myocardial infarction	12 (1.3)	3 (0.3)	0.012	2.60	0.69–9.85	0.16
Repeat revascularization	27 (3.0)	38 (4.0)	0.33	0.85	0.50–1.45	0.55
Per-lesion analysis[c]	*n* = 1000	*n* = 1088				
Primary endpoint						
All lesion	40 (4.0)	44 (4.0)	NA	0.93	0.59–1.48	0.76
Deferred lesion	20 (3.4)	29 (3.7)	NA	0.84	0.46–1.55	0.57
Revascularized lesion	20 (5.0)	15 (4.9)	NA	1.32	0.64–2.72	0.45
Secondary endpoint						
Cardiac death or myocardial infarction	15 (1.5)	3 (0.3)	NA	3.77	1.04–13.7	0.044
Repeat revascularization	29 (2.9)	42 (3.9)	NA	0.79	0.47–1.32	0.37

aHR, adjusted hazard ratio; pb-CFR, pressure-bounded coronary flow reserve; CI, confidence interval; MACE, major adverse cardiac event; NA, not available.
[a]Log-rank *P*-value.
[b]Adjusted by age, gender, clinical presentation, hypertension, diabetes, current smoking, hyperlipidemia, revascularization, lesion territory, lesion location, and diameter stenosis.
[c]The models accounted for the clustering of lesions in patients.

Overall clinical outcomes

During a median follow-up of 1.9 years (inter-quartile range: 1.0–3.0 years), MACE occurred in 84 lesions in 77 patients (cardiac death or MI in 18 lesions in 15 patients, repeat revascularization in 71 lesions in 65 patients).

Association of fractional flow reserve with clinical outcomes

A significantly higher incidence of MACE occurred in lesions with low FFR (≤0.80) than those with high FFR (>0.80) (*Figure 4A*). In addition, the risk of MACE in lesions with low FFR remained significantly higher even after adjustment for other significant covariates or multiple potential confounders (*Table 2*). The risk of revascularization also remained significantly higher in lesions with FFR ≤ 0.80.

Association of pressure-bounded coronary flow reserve with clinical outcomes

The risk of MACE was similar between patients with low (<2) and high (≥2) pb-CFR (*Table 3*). The Kaplan–Meier curves are presented in *Figure 4B*. Regarding the composite of cardiac death or MI, patients with low pb-CFR had higher risk compared with patients with high pb-CFR in univariate analysis (see Supplementary material online, *Figure S2B*).

Incremental value of coronary physiology for predicting major adverse cardiac events

Figure 5 visually summarizes the improvement in predicting MACE by adding FFR or pb-CFR to a model including conventional clinical and lesion factors. When FFR was incorporated into the model, the global χ^2 increased significantly. However, the addition of pb-CFR did not significantly improve the global χ^2 for predicting MACE.

Figure 6 shows Kaplan–Meier curves of cumulative events by groupings of physiologic (FFR and pb-CFR subsets) and treatment status (medical or revascularization). For deferred lesions, there was a continuous separation of the event curves according to low vs. high pb-CFR in lesions with low FFR; however, in lesions with high FFR, the overall event rate for low and high pb-CFR was low and not different ($P = 0.05$ for interaction). In contrast, for all lesions and for revascularized lesions, pb-CFR did not separate event rates between high and low FFR.

Sensitivity analysis

We performed a sensitivity analysis by including lesions with resting Pd/Pa ratio of 1.0 and 0.99 in the high pb-CFR group. These lesions were excluded from the original analysis, because pb-CFR is theoretically limited in cases with no or mild resting pressure gradients. We hypothesized that for lesions with FFR ≥0.99, CFR will frequently be > 2. This sensitivity analysis increased the number of lesions from 2088 to 4073 (from 1837 to 3032 patient) adding about 2000 functionally completely normal arteries to the analysis. By doing so, the event rates for patients with the 'normal' CFR group decreased from 7.6% to 5.5% and was slightly lower now than the event rate in lesions with pb-CFR < 2 (see Supplementary material online, *Figure S3*).

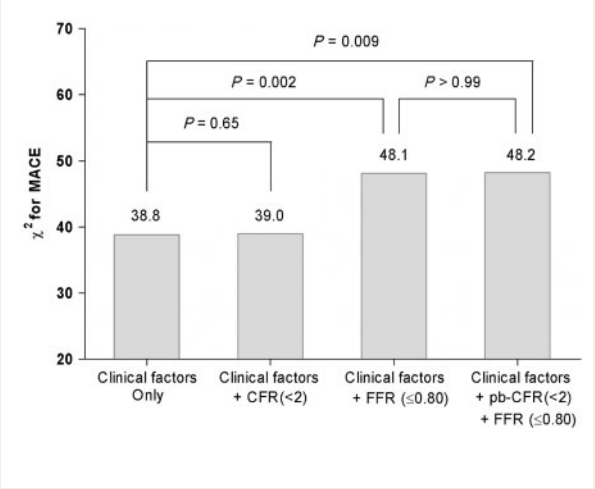

Figure 5 Incremental utility to predict MACE by adding coronary flow reserve and fractional flow reserve to traditional risk factors. Included clinical factors for model construction were clinical presentation, smoking, hyperlipidaemia, previous percutaneous coronary intervention, peripheral vascular disease, chronic renal failure, chronic obstructive lung disease, revascularization, lesion location, percent diameter stenosis, American Heart Association/American College of Cardiology lesion B2C lesion, and moderate-to-severe lesion calcification. MACE denotes major adverse cardiac events as a composite of cardiac death, myocardial infarction, and subsequent revascularization.

However, even with this sensitivity analysis, pb-CFR showed no incremental value to predict MACE in the multiple risk factor model (see Supplementary material online, *Figure S4*).

Discussion

This large, prospective registry confirmed that FFR is significantly associated with MACE (composite of cardiac death, MI, and revascularization). In contrast, pb-CFR failed to predict adverse cardiac events. Additionally, regardless of pb-CFR, for lesions with FFR > 0.80, clinical outcomes were excellent and performance of PCI did not improve them. Incorporation of FFR into a model with clinical factors improved prediction of MACE. However, pb-CFR demonstrated no incremental utility. Therefore, despite the value of pb-CFR to understand coronary physiology, FFR remains the more useful index for prognosis and revascularization decisions.

To overcome the well-recognized technical challenges of invasive CFR measurement,[9] there have been several attempts to derive CFR from coronary pressure.[17,18,21] By refining such a concept, we estimated the upper and lower boundaries of CFR from resting and hyperaemic trans-lesional coronary pressure gradients based on fundamental fluid dynamics[11] and discriminated groups as low (<2) and high (≥2) CFR.[16] A unique strength of this study arises from our *post hoc* analysis of pb-CFR that was blinded from operators and patients, implying that it did not affect clinical decision-making, thereby reducing bias.

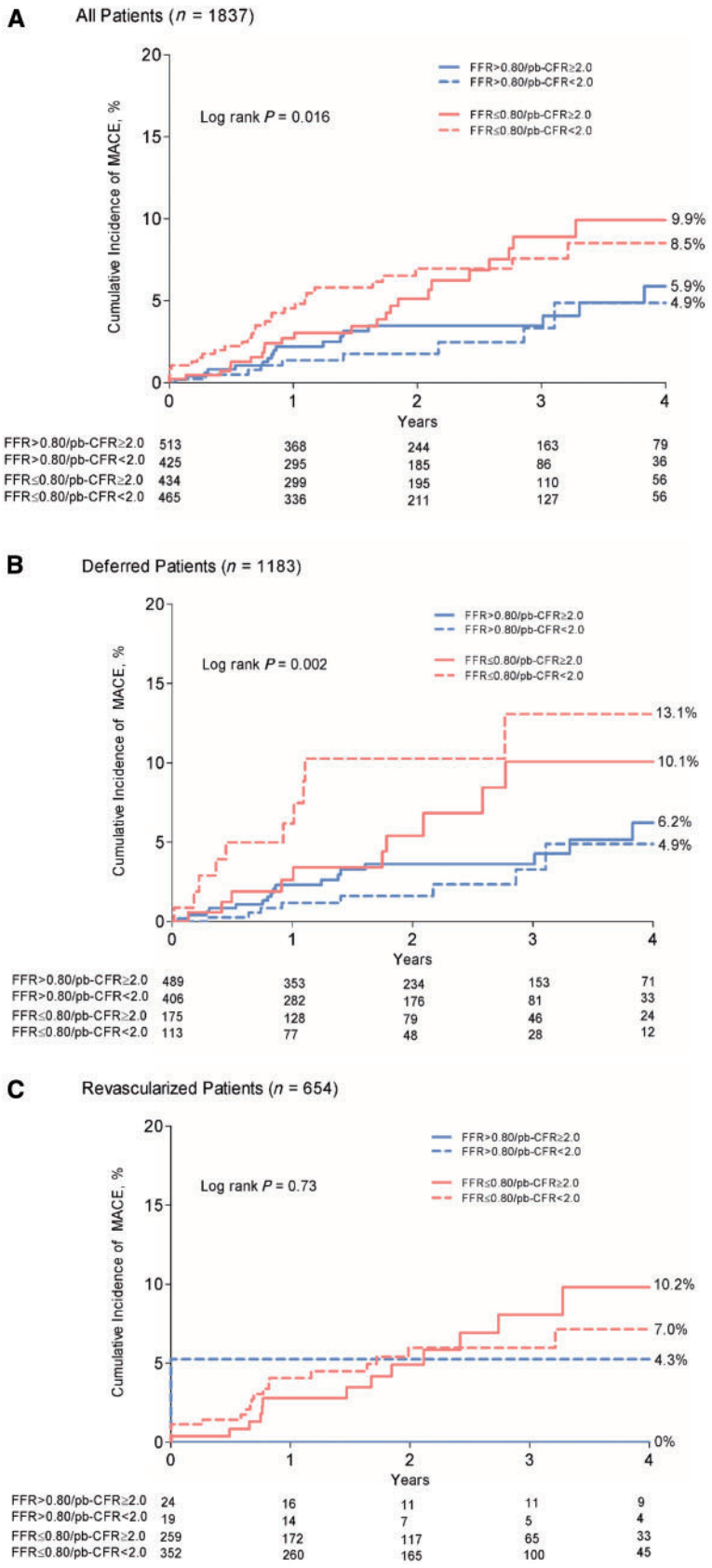

Figure 6 Kaplan–Meier curves for major adverse cardiac events by FFR > 0.80/≤0.80 and pb-CFR ≥ 2/<2, (*A*) for all patients, (*B*) deferred patients, and (*C*) revascularized patients.

Previous studies into prognostic value of invasively measured CFR have been comparatively small and had conflicting results.[10,12] In one recent retrospective study, low CFR and high FFR showed worse outcomes than high CFR with low FFR, suggesting that CFR might be more important than FFR in predicting clinical events.[12] However, that conclusion was based on a small number of patients and events, essentially driven completely by subsequent revascularization within 1 year after the unblinded index measurement.

In the present study, pb-CFR did not demonstrate independent prognostic value with respective to clinical outcome. In addition, a *post hoc* sensitivity analysis assigning lesions and patients with no or mild pressure gradients to the high pb-CFR group showed consistent findings and did not change the results. Furthermore, pb-CFR did not provide incremental value for predicting MACE in addition to FFR. In contrast, and in agreement with previous findings,[7,22] FFR itself was strongly associated with MACE. Therefore, our study favours FFR measurement for guiding clinical decision-making and predicting outcomes in daily practice.

Despite the lack of independent prognostic value for pb-CFR in this study, combined pb-CFR and FFR assessment provided several important insights. First, we found that the event rate of lesions with FFR >0.80 was very low regardless of pb-CFR, suggesting that the presence of microvascular disease, although it may cause angina, plays a limited role regarding hard outcomes in the presence of a patent epicardial coronary artery. Second, lesions with a low pb-CFR in addition to a low FFR showed the highest clinical risk and benefited the most from revascularization. The event rate for revascularized lesions was lower in that subgroup than was the case for deferred lesions in that group. The ongoing Distal Evaluation of Functional performance with Intravascular sensors to assess the Narrowing Effect–combined pressure and Doppler FLOW velocity measurements (DEFINE–FLOW, clinicaltrials.gov NCT02328820) study will provide more detailed information about the prognostic value of the different combinations of FFR and CFR, not only as binary indices but also as continuous variables.

This study also confirms epidemiologic links between low CFR and traditional risk factors. Low pb-CFR were associated with old age, female sex, hypertension, diabetes, previous MI, and chronic renal failure. As those risk factors also associate with microvascular disease, our findings favour pb-CFR as an index of flow decrease in the complete coronary circulation rather than the epicardial coronary artery. In addition, such clustering would explain the observed worse outcomes for low CFR.[12,23]

This study has several limitations. First, there are the inherent limitations of any observational study. Second, in cases with a small pressure gradient at rest or hyperaemia, the estimation of pb-CFR might become inaccurate. Therefore, such lesions were excluded from the primary analysis. Nevertheless, when we included lesions with resting Pd/Pa of 1.0 and 0.99 (worst-case scenario), the sensitivity analysis showed that the overall results were not greatly changed. Third, because of low event rates, our study was underpowered to assess the impact of FFR and pb-CFR regarding hard endpoints of cardiac death or MI, separately. Finally, slightly more than half of lesions were not included in the analysis due to being assigned to the indeterminate pb-CFR group due to the intrinsic limitation of using pb-CFR instead of measuring CFR directly.

In conclusion, this large, prospective, multicentre registry showed that FFR was strongly associated with long-term outcomes, whereas CFR failed to independently predict the risk of cardiac events. As such, our results confirmed the primacy of FFR for risk stratification and clinical decision-making in patients with coronary artery disease. Nevertheless, the technique of pb-CFR appears useful to study the clinical impact of FFR/CFR discordances.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: N.P.J received internal funding from the Weatherhead PET Center; has an institutional licensing and consulting agreement with Boston Scientific for the smart minimum FFR algorithm; and has received significant institutional research support from St. Jude Medical/Abbott (CONTRAST, NCT02184117) and Volcano/Philips Corporation (DEFINE-FLOW, NCT02328820). N.H.J.P. is consultant for St. Jude Medical, Boston Scientific, and Opsens Medical and holds equity interest in Philips, General Electric, Heartflow, and ASML. Others have nothing to disclosure related to this work.

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