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Research paper

Derivation and validation of a novel functional FFR_{CT} score incorporating the burden of coronary stenosis severity and flow impairment to predict clinical events

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ABSTRACT

Background: A score combining the burden of stenosis severity on coronary computed tomography angiography (CCTA) and flow impairment by fractional flow reserve derived from computed tomography (FFR_{CT}) may be a better predictor of clinical events than either parameter alone.

Methods: The Functional FFR_{CT} Score (FFS) combines CCTA and FFR_{CT} parameters in an allocated point-based system. The feasibility of the FFS was assessed in cohort of 72 stable chest pain patients with matched CCTA and FFR_{CT} datasets. Validation was performed using 2 cohorts: (a) 4468 patients from the ADVANCE Registry to define its association with revascularization and major adverse cardiovascular events (MACE); (b) 212 patients from the FORECAST trial to determine predictors of MACE.

Results: The median calculation time for the FFS was 10 (interquartile range 6–17) seconds, with strong intra-operator and inter-operator agreement (Cohen's Kappa 0.89 ($\pm$0.37, $p < 0.001$) and 0.83 ($\pm$0.04, $p < 0.001$, respectively). The FFS correlated strongly with both the CT-SYNTAX and the Functional CT-SYNTAX scores ($rS = 0.808$ for both, $p < 0.001$).

In the ADVANCE cohort the FFS had good discriminatory abilities for revascularization with an area under the curve of 0.82, 95 % confidence interval (CI) 0.81–0.84, $p < 0.001$. Patients in the highest FFS tertile had significantly higher rates of revascularization (61 % vs 5 %, $p < 0.001$) and MACE (1.9 % vs 0.5 %, $p = 0.001$) compared with the lowest FFS tertile.

In the FORECAST cohort the FFS was an independent predictor of MACE at 9-month follow-up (hazard ratio 1.04, 95 % CI 1.01–1.08, $p < 0.01$).

Conclusion: The FFS is a quick-to-calculate and reproducible score, associated with revascularization and MACE in two distinct populations of stable symptomatic patients.

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Abbreviations

ADVANCE Registry	Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care Registry
AUC	area under the (ROC) curve
CABG	coronary artery by-pass graft
CAD	coronary artery disease
CAD-RADS	Coronary Artery Disease–Reporting and Data System
CCTA	coronary computed tomography angiography
CI	confidence interval
CV	cardiovascular
FFR	fractional flow reserve
FFR_{CT}	Fractional flow reserve derived from computed tomography
ICA	invasive coronary angiography
IHD	ischaemic heart disease
IQR	interquartile range
LMS	left main stem
MACE	major adverse cardiovascular events
MI	myocardial infarction
FFRCT	fractional flow reserve derived from computed tomography
FFR	fractional flow reserve
ROC curve	receiver operating characteristic curve
SD	standard deviation
SE	standard error

1. Introduction

Ischaemic heart disease (IHD) remains the leading cause of death and disability worldwide and generates substantial morbidity burden on healthcare systems.[1] Given the robust evidence that lifestyle changes and disease-modifying medical therapies are effective in improving prognosis,[2] tools to facilitate early identification of patients at risk of ischaemic events offer considerable clinical potential.

Large randomised trials, such as SCOTHEART, have demonstrated that coronary computed tomography angiography (CCTA) facilitates a management strategy based around optimal medical therapy, with an associated prognostic benefit.[3]Consequently, international guidelines recommend CCTA as the initial investigation for patients presenting with chronic coronary syndromes (CCS).[4]

Complementing the anatomical evaluation via CCTA, fractional flow reserve derived from computed tomography (FFR_{CT}) is a well validated test that provides physiological modelling of the epicardial coronary flow.[5] Importantly, a recent meta-analysis, including 5460 patients, shows that FFR_{CT} negative lesions (>0.8) pertained to a benign prognosis, whilst each 0.10-unit reduction in FFR_{CT} was associated with a greater risk of death and myocardial infarction (MI).[6]

There is a large body of evidence that atheroma burden is predictive of future ischaemic events.[7] Furthermore, there is evidence that both ischaemia[8] and a reduction in coronary flow[9,10] are associated with the risk of major adverse cardiovascular events (MACE). We postulate that a test providing a combined estimate of the burden of coronary stenosis severity and flow reduction may be more predictive of the risk of future clinical events than either parameter alone.

The aims of this study were (1) to develop a novel scoring tool that describes the combined burden of coronary stenosis severity and physiological flow impairment, named Functional FFR_{CT} Score (FFS) and (2) to assess whether the FFS is associated with future revascularization and adverse clinical events in two distinct populations of symptomatic stable patients.

2. Methods

2.1. Population

There were three cohorts included in this study: 1) the feasibility cohort of 72 patients from a single centre included in the FORECAST trial[11] upon whom the FFS was designed and refined, 2) the first validation cohort of 4468 patients from the ADVANCE Registry[12] upon whom the performance of the score in relation to revascularization and adverse clinical events was assessed and the optimum single cut-off point and FFS tertiles were determined, 3) the second validation cohort of 212 patients from the FORECAST trial[11] upon which the prognostic value of the FFS was assessed.

The feasibility cohort consisted of 72 consecutive patients with suspected coronary artery disease (CAD) who underwent CCTA and FFR_{CT} in a single centre (University Hospital Southampton NHS Foundation Trust, Southampton, UK) as part of the FORECAST trial.

The first validation cohort was comprised of 4468 patients who underwent CCTA and FFR_{CT} in the ADVANCE Registry. The ADVANCE Registry (NCT02499679) methodology and 1-year follow-up results have been previously published.[12]

The second validation cohort included all 212 patients who underwent CCTA and FFR_{CT} as part of the FORECAST trial in all 10 UK participating centres and completed 9-month follow-up. The FORECAST Trial (NCT03187639) methodology and 9 month follow up results have been previously published.[11]

2.2. Functional FFR_{CT} score (FFS) feasibility

Several scoring models were initially devised by combining, in an allocated point-based system, parameters of the CCTA, such as stenosis segment location and severity, and the FFR_{CT} values. These models were then compared with the previously validated CT-SYNTAX(13), Functional CT-SYNTAX scores,[14] Coronary Artery Disease–Reporting and Data System (CAD-RADS)[15] and Agatston calcium score.[16] One candidate model, labelled the Functional FFR_{CT} Score (FFS), was chosen based upon ease of use, reproducibility and correlation with comparator risk scores, and was then applied to the ADVANCE and FORECAST validation cohorts.

The FFS comprises two components: (i) an anatomical score and (ii) a physiology score, which are calculated separately and then added up to obtain the total FFS (Table 1 and Supplementary Figure 1). The anatomical score is derived in each main vessel according to the most severe stenosis in that vessel, as assessed by a visual estimate of luminal diameter stenosis, with a number allocated accordingly as shown in Table 1. The anatomical component of FFS represents the sum of the scores for each vessel, with the addition of 1 point if the left main stem (LMS) is involved. Each vessel is also allocated a score according to the value of the FFR_{CT} in the distal third of that vessel. The physiology component of FFS represents the sum of physiology scores for all allocated vessels.

The principles for calculating the FFS are as follows: 1) include main coronary vessels and all branches of a diameter of sufficient calibre to be potentially suitable for stents or bypass grafts (>/=2.25 mm); 2) a non-dominant right coronary artery is excluded, co-dominant vessels are included if their calibre is /= 2.25 mm; 3) for each vessel, only the most severe stenosis is scored; 4) FFR_{CT} readings are derived from the distal third of the vessel, at a similar point at which intracoronary invasive FFR would be measured, practically within the proximal-mid portion of the distal coronary segment; 5) patients with previous revascularization by stent or CABG are excluded. No further assessment of anatomical complexity is required, for example about bifurcations or diffuse disease.

Table 1
The methodology for calculating the functional FFR_{CT} score.

Functional FFR_{CT} Score			
Anatomical Score (per vessel)		Physiology Score (per vessel)	
Stenosis severity	Score	Distal vessel FFR_{CT}	Score
0%	0	>0.8	0
1–29 %	1	0.71–0.8	1
30–69 %	2	0.61–0.7	2
70–99 %	3	≤0.6	3
100 %	4		
Anatomical Score = Sum of individual vessel anatomical scores Add 1 point if any left main stem stenosis		Physiology Score = Sum of individual vessel physiology scores	
Functional FFR_{CT} Score = Anatomical Score + Physiology Score			

In the feasibility phase, comprising of a single centre cohort of patients included in the FORECAST trial (n = 72 patients), each CCTA was assessed visually for luminal stenosis severity and FFR_{CT} in the main coronary vessels and all large branches as per the principles listed above. The FFS was calculated manually and independently by two operators (LG and JH) for each dataset. As a comparator, the CT-SYNTAX score was calculated[13] using the online calculator (www.syntaxscore.com, SYNTAX I extension). The time in seconds required exclusively for calculating each score manually was measured for the FFS and CT-SYNTAX. Other comparators included the calculated Functional CT-SYNTAX score,[14] CAD-RADS and Agatston calcium scores, which were extracted from the CCTA datasets and reports.

2.3. Application of FFS: validation cohorts

In the first validation cohort, the FFS was calculated retrospectively using CTCA and FFR_{CT} data from patients in the ADVANCE Registry. This was achieved using an automated algorithm based upon the manually derived scoring tool described above, with the exception that only the main coronary arteries were included due to data availability. The FFR_{CT} values represented the coronary vessel nadir as per the ADVANCE registry methodology.[10] The FFS output was then correlated with revascularization events and major adverse cardiac events (MACE; a composite of death, myocardial infarction (MI), and acute coronary syndrome leading to urgent revascularization).

In the second validation cohort the FFS was applied retrospectively to all 212 patients included in the FORECAST trial with available matched CCTA and FFR_{CT} data. As per the FORECAST trial methodology the coronary stenosis severity was determined visually, at site level, and recorded in the electronic Case Report Form. Two cardiologists (LG and MK), blinded to other patient details and to each other's opinion, assessed FFR_{CT} in the distal third of all coronary arteries of a diameter suitable for revascularization (>/=2.25mm). The FFS was then correlated with the rate of invasive coronary angiography (ICA), revascularization and clinical events (MACE; a prespecified composite of all cause death, non-fatal MI, stroke, and cardiovascular hospitalization).

2.4. Statistical analysis

Continuous data are presented as mean (standard deviation, SD) or median (interquartile range, IQR), as appropriate. Categorical data are presented as frequency and percentage. Comparative statistics for speed of calculation used the Mann–Whitney test, due to non-normally distributed data. Bland-Altman plots are used to assess intra- and inter-operator variability, including 95 % levels of agreement. Intra-observer and inter-observer agreement for the FFS in its entirety was determined with Cohen's kappa statistics. Correlation between the newly calculated FFS model (and individual components) and the established risk scores (CAD-RADS, CT-SYNTAX and Functional CT-SYNTAX) was assessed using a Spearman rank correlation, when both variables were not normally distributed, and a Pearson correlation if at least one variable was normally distributed.

In the ADVANCE validation cohort, to ascertain the discriminative ability for clinical outcomes at 1-year, the optimal FFS threshold for predicting each binary outcome was identified via a Receiver Operating Characteristic (ROC) Curve via the closest to (0,1) criteria. The FFS value with the optimum combination of sensitivity and specificity was further investigated in both validation cohorts. The ADVANCE validation cohort was divided into tertiles by the FFS value and these values were further used for dividing the FORECAST validation cohort. For all binary outcome data with status at 1-year follow-up, binary logistic regression modelling was calculated, with corresponding odds ratios (OR) presented with 95 % confidence intervals (CI). The chi-squared test was used to assess the differences in clinical events and revascularizations between the FFS strata (>6/≤6 and FFS tertiles); in cases of low (expected cell count <5) or zero cell counts, the Fisher's exact test was used. Continuous variables were compared between tertiles by using the 1-way ANOVA. Cumulative event rates were shown as Kaplan–Meier survival curves and compared using the log-rank test. ROC analysis was used to calculate the AUC for FFS and CAD-RADS, respectively. Univariable and multivariable Cox regression analysis was used to identify independent predictors of MACE by 9-month follow-up in the FORECAST validation cohort. 4 additive multivariable Cox models were assessed, and ROC analysis was used to calculate the area under the curve (AUC) for MACE for each model. Hazard ratios were assessed as an estimation of risk with 95 % confidence intervals (95 % CIs). Differences were considered statistically significant when the 2-sided p values were ≤0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 28 (IBM Corp., Armonk, N.Y., USA).

3. Results

3.1. Feasibility analysis

Out of the 72 patients in this cohort, 17 % of patients had single vessel CAD, 30 % had two vessel CAD and 53 % had three vessel CAD. The median CT-SYNTAX was 14 (IQR 3.5–24.5) and the median Functional CT-SYNTAX was 4.5 (IQR 0–18.7). The distribution and severity of coronary stenoses and the CAD-RADS and CT-SYNTAX scores are depicted in Figs. 2–4 in the Supplementary Appendix.

The median FFS was 8.5 (IQR 4–15), whilst the median anatomical FFS component was 7 (IQR 4–10) and the median physiology FFS component was 1.5 (IQR 1.5–4), see Figs. 5–7 in the Supplementary Appendix.

There was a strong correlation between the FFS and both the CT-SYNTAX and the Functional CT-SYNTAX scores (r_S = 0.80 for both, p < 0.001) (Fig. 1). Taken separately, the anatomical component of the FFS showed a weaker correlation with the anatomical CT-SYNTAX (r_S = 0.77, p < 0.001). By contrast, the physiology component of the FFS showed a stronger correlation with the Functional CT-SYNTAX (r_S = 0.88, p < 0.001). The relationship between the FFS and CAD-RADS and Agatston calcium score is shown in Figs. 8 and 9 in the Supplementary Appendix.

The FFS was significantly quicker to calculate, with an overall median time required for manual calculation of 10 (IQR 6.5–17) seconds, compared to a median time for calculating the CT-SYNTAX score of 97 (IQR 37–186) seconds, p < 0.001. The median time for calculating the

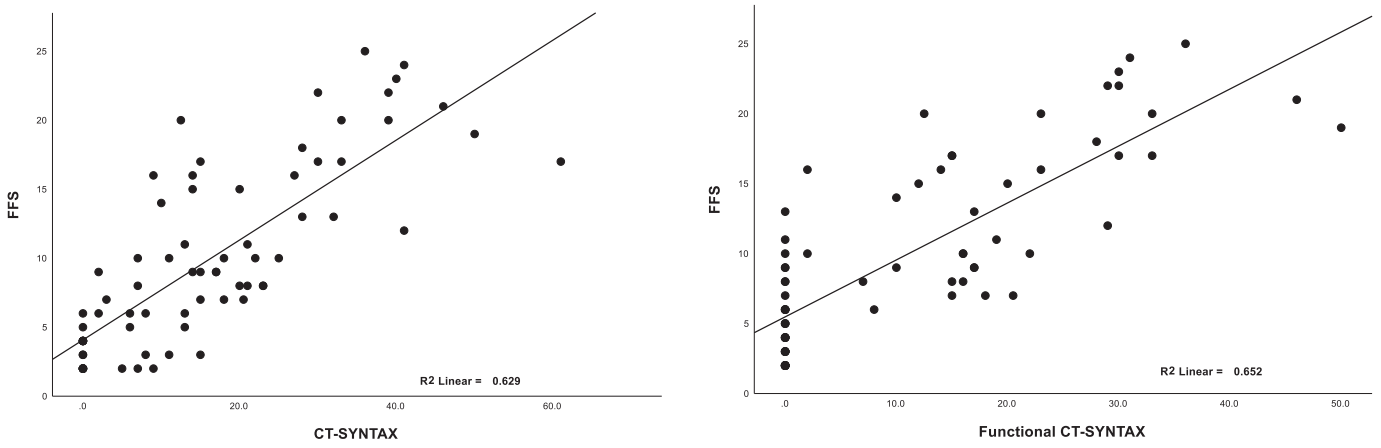


Fig. 1. Scatter Plots of the Functional FFR_{CT} Score (FFS) versus CT-SYNTAX and Functional CT-SYNTAX scores, respectively.

FFS was 8 (IQR 5–12) seconds for operator 1 and 15 (IQR 9–23) seconds for operator 2 (Table 2 and Fig. 10 in the Supplementary Appendix).

The reproducibility analysis demonstrated a high correlation between two FFS calculations performed by the same operator (r_S 0.999, $p < 0.001$) and between calculations performed by two independent operators (r_S 0.998, $p < 0.001$). Both intra-operator and inter-operator variability showed very strong agreement with Cohen's Kappa of 0.89 (Standard Error (SE) = 0.03, $p < 0.001$) and 0.83 (SE 0.04, $p < 0.001$), respectively. The mean intra- and inter-operator differences were 0.05(±0.73) and 0.04(±0.76), with Bland-Altman plot analysis displayed in Figs. 11 and 12 in the Supplementary Appendix.

3.2. *First validation cohort: ADVANCE registry*

The validation analysis included a cohort of 4468 patients from the ADVANCE Registry. The demographics of this cohort are published elsewhere.[12] At a median follow up of 1-year, 1220 patients underwent revascularization (27.3 %) and 915 patients underwent invasive coronary angiography (ICA) only (20.4 %). There were 50 MACE (1.1 %; 32 deaths, 11 myocardial infarctions and 7 hospitalizations for ACS leading to urgent revascularization).

The median FFS was 6 (IQR 4–8), with a median anatomical FFS component of 4 (IQR 3–6) and a median physiology FFS component of 1 (IQR 0–3), see Fig. 13 in the Supplementary Appendix.

The FFS receiver operating characteristic curve for revascularization showed an area under the curve (AUC) of 0.82 (95 % CI: 0.81–0.84, $P < 0.001$). The FFS AUCs for clinical events were: 0.66 for total MACE (95 % CI 0.58–0.74, $P < 0.001$), 0.69 for non-fatal MI (95 % CI 0.55–0.84, $p = 0.007$) and 0.65 for all cause death (95 % CI 0.55–0.74, $p = 0.003$), see Fig. 14 in the Supplementary Appendix.

The optimum cut-off point for FFS was 6, associated with sensitivities of 86 % for revascularization and 72 % for MACE.

Binary logistic regression analysis demonstrated that the FFS was associated with significantly higher rates of revascularization, MACE, all cause death, cardiovascular death and non-fatal MI, but no significant differences in the rates of ICA only and urgent revascularization (Table 3 in Supplementary Appendix).

Upon dividing the validation cohort by intervals of FFS (Fig. 2), there was a progressive increase in the rate of revascularization from 0 % for patients with FFS of 0, to 80 % if the FFS was above 12. The rate of ICA only was 0 % for FFS of 0, and it did not vary significantly with the FFS intervals (11–24 %).

The validation cohort was divided into tertiles of the FFS as follows: Tertile 1 - Low FFS (0–4) - 1498 patients (33.5 %); Tertile 2- Intermediate FFS[5–7] - 1634 patients (36.6 %) and Tertile 3 - High FFS[8–22] - 1336 patients (29.9 %). Patients in the high FFS tertile had a significantly higher rate of revascularization (61 % vs 5 %, $p < 0.001$), MACE (1.9 % vs 0.5 %, $p = 0.001$), all cause death (1.2 vs 0.3 %, $p = 0.007$) and CV death (0.60

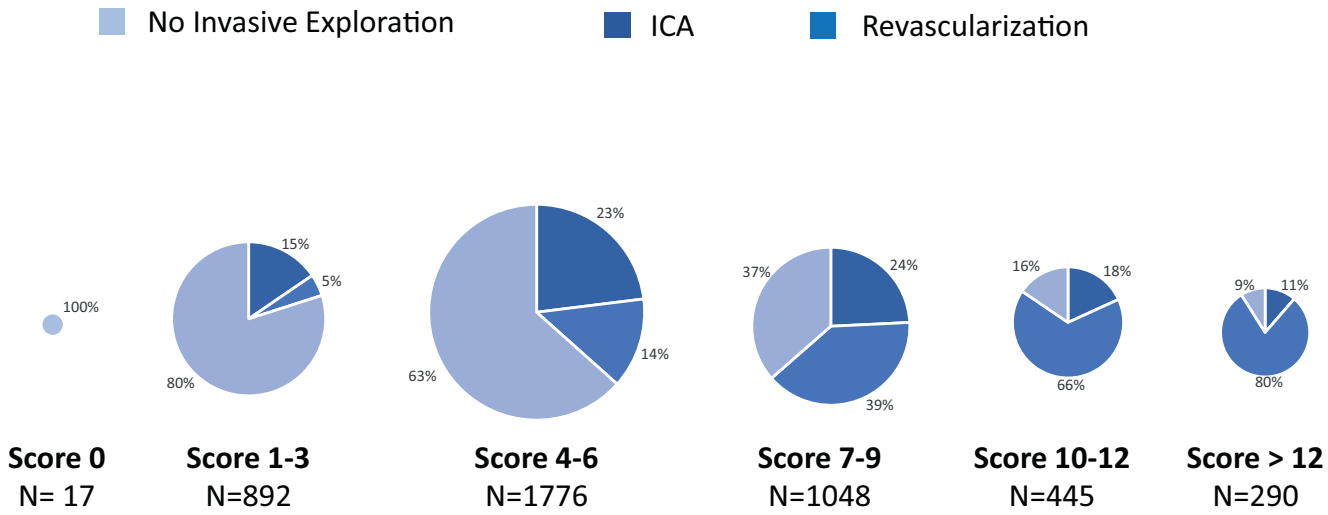


Fig. 2. Revascularization and ICA only distribution by FFS intervals in the ADVANCE validation cohort (n = 4468 patients). The size of the pie chart is proportional to the number of patients in each group. FFS= Functional FFR_{CT} Score; ICA = invasive coronary angiography.

% vs 0.07 %, p = 0.016) compared with the low FFS tertile (Figs. 15 and 16 in the Supplementary Appendix).

3.3. Second validation cohort: FORECAST trial

This analysis includes 212 patients with complete CCTA/FFR_{CT} and 9-month follow-up data (67.9 % male; mean age 65 (±9) years). Other baseline demographics are presented in Table 4 in the Supplementary Appendix. 100/212 (47.1 %) patients had obstructive CAD and 139 (65.6 %) patients had at least one positive FFR_{CT} value (≤0.8). The distribution and severity of coronary artery disease and the FFR_{CT} analysis is detailed in Table 5 in the Supplementary Appendix.

At 9-month follow-up 102 (48.1 %) patients had undergone at least one ICA and 77 (36.3 %) patients were revascularized. 46 patients (21.6 %) experienced at least one MACE, see Table 6 in Supplementary Appendix.

The median FFS was 9 (IQR 4–15) with a median anatomical FFS of 7 (IQR 4–10) and a median physiology FFS of 1 (IQR 0–4). The distribution of FFS and components, and the relationship between the anatomical and physiology components are shown in Figs. 17 and 18 in the Supplementary Appendix.

The FFS demonstrated good discriminatory ability for both (i) revascularization, with AUC of 0.81 (95 % CI 0.75–0.87), and (ii) MACE, with an AUC of 0.76 (95 % CI 0.68–0.84). The previously validated binary cut-off FFS value of 6 demonstrated a 94 % sensitivity for revascularization and 89 % sensitivity for MACE.

The corresponding discriminatory ability for MACE was lower for the CAD-RADS with AUC of 0.73 (95 % CI: 0.65–0.81), although with significant overlap in the confidence intervals when compared with the FFS (Fig. 3).

The study cohort was divided into the previously defined tertiles of FFS as follows: low FFS (≤4)- 58 patients (27.4 %), intermediate FFS[5–7]- 37 patients (17.5 %) and high FFS (≥8)- 117 patients (55.1 %). The baseline characteristics were similar except for sex distribution and Diamond-Forrester risk classification, as shown in Table 6 in the Supplementary Appendix.

There was a significant increase in invasive angiography usage from 10.3 % in the low FFS tertile to 74.3 % of patients with high FFS ($p < 0.001$). Similarly, the rates of revascularization were significantly higher in the high FFS tertile (58.1 %) compared with the intermediate and low tertiles (18.9 % and 3.4 %, respectively; $p < 0.001$). MACE, driven by hospitalization for cardiac events, occurred in 6.8 % of patients in the low FFS tertile compared to 32.4 % of patients in the high FFS tertile ($p < 0.001$). There were 2 myocardial infarction events, both occurring in patients within the high FFS tertile. Fig. 4 depicts the Kaplan-Meier curves for revascularization and MACE stratified by FFS tertiles.

Male sex, Diamond-Forrester score, obstructive CAD and FFS were all significant predictors of MACE in univariable Cox regression analysis. 4 additive multivariable Cox regression models were constructed and the FFS remained a significant predictor of MACE in all 3 models in which it was included (Table 2). Furthermore, the ROC analysis showed the highest AUC for MACE of 0.79 (95 % CI 0.72–0.86) for a model including sex, Diamond-Forrester score, obstructive CAD, any positive FFR_{CT} and FFS (Fig. 5).

4. Discussion

This study describes the validation of a novel scoring tool, the Functional FFR_{CT} Score (FFS), which combines the total burden of coronary stenosis and flow impairment. The main findings are that (a) the

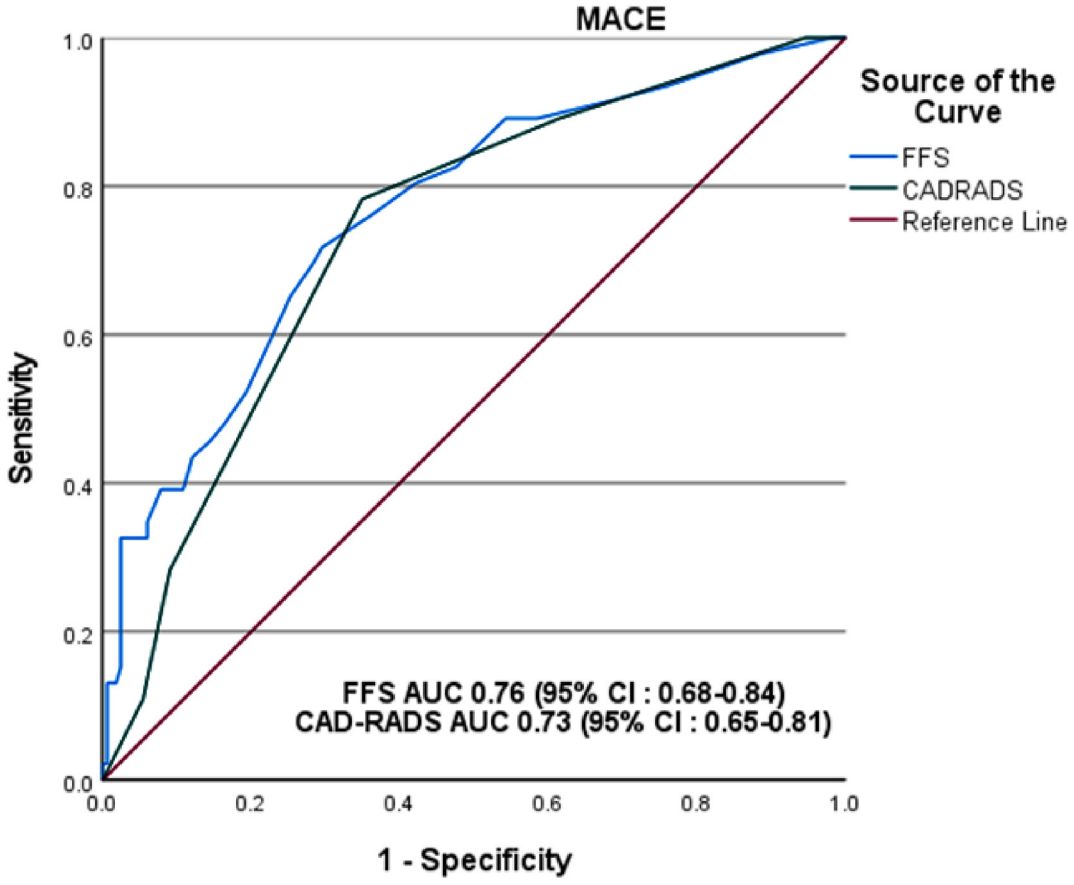
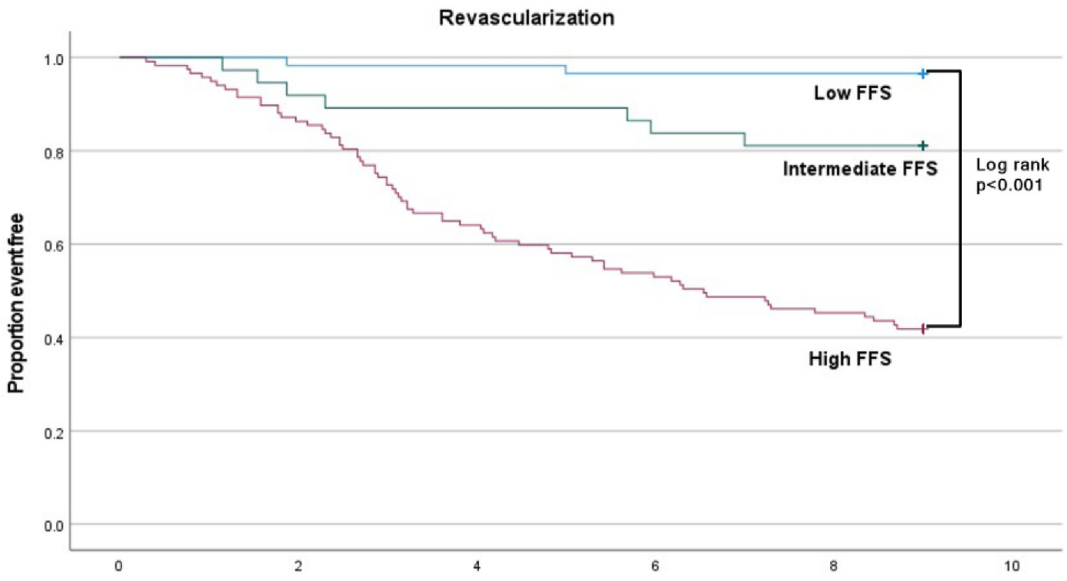
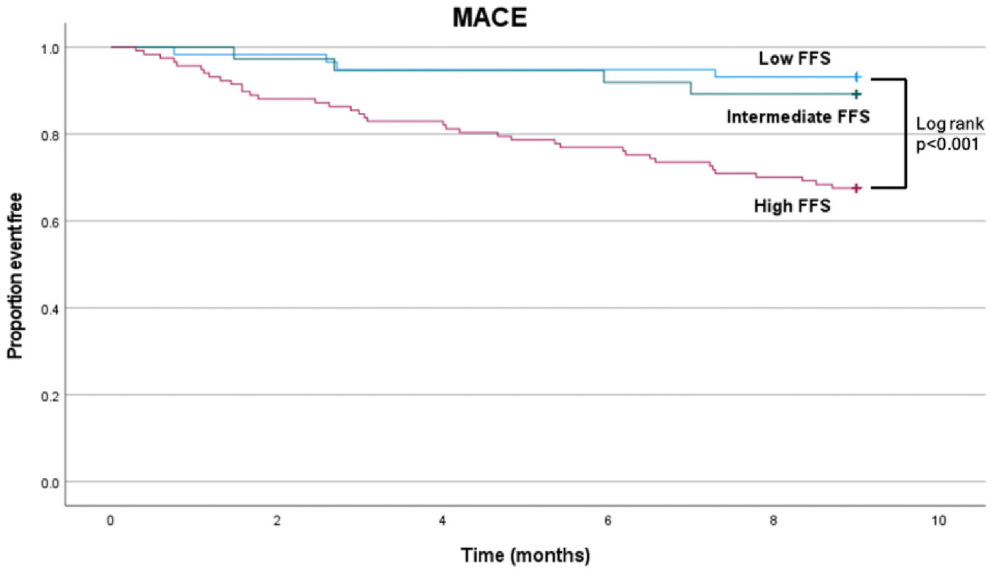


Fig. 3. Receiver Operating Characteristic Curve (ROC) of the FFS and CAD-RADS for MACE in the FORECAST validation cohort (n = 212 patients). FFS= Functional FFRCT Score; CAD-RADS = Coronary Artery Disease - Reporting and Data System; AUC=Area under ROC; CI = confidence interval.



No at risk

Low FFS	58	57	57	56	56
Intermediate FFS	37	34	33	31	30
High FFS	117	101	75	62	53



No at risk

Low FFS	58	57	55	55	54
Intermediate FFS	37	36	35	34	33
High FFS	117	103	97	90	82

Fig. 4. Kaplan–Meier estimates of the cumulative probability of revascularization and MACE as stratified by FFS tertiles. MACE = major adverse cardiac events; FFS=Functional FFR_{CT} Score.

Table 2
Cox regression analysis - predictors of MACE by 9-month follow-up in the FORECAST validation cohort (n = 212 patients).

Variable	HR	95 % CI	p value
Univariate Cox regression			
Sex			
• Male	1	0.44–0.94	Reference 0.02
• Female	0.64		
Diamond-Forester	1.01	1.00–1.01	0.03
Obstructive CAD	5.44	2.62–11.29	<0.001
Any positive FFR_{CT} (≤0.8)	8.76	2.71–28.24	<0.001
FFS (continuous variable)	1.08	1.05–1.10	<0.001
Multivariable Cox regression- Model 1			
Sex			
• Male	1	0.23–1.08	Reference 0.50
• Female	0.50		
Diamond-Forrester	1.00	0.99–1.01	0.51
Obstructive CAD	4.89	2.32–10.31	<0.001
Multivariable Cox regression- Model 2			
Sex			
• Male	1	0.25–1.20	Reference 0.13
• Female	0.55		
Diamond-Forrester	1.00	0.99–1.01	0.57
Obstructive CAD	2.91	1.30–6.51	0.009
Any positive FFR_{CT}	4.11	1.15–14.69	0.029
Multivariable Cox regression- Model 3			
Sex			
• Male	1	0.28–1.36	Reference 0.28
• Female	0.62		
Diamond-Forester	1.00	0.99–1.01	0.60
Obstructive CAD	2.73	1.15	0.02
FFS (continuous variable)	1.05	1.01–1.08	0.002
Multivariable Cox regression- Model 4			
Sex			
• Male	1	0.30–1.43	Reference 0.29
• Female	0.65		
Diamond-Forester	1.00	0.99–1.01	0.64
Obstructive CAD	1.88	0.76–4.61	0.16
Any positive FFR_{CT} (≤0.8)	3.34	0.91–12.27	0.06
FFS (continuous variable)	1.04	1.01–1.08	<0.01

Obstructive CAD = coronary artery disease with luminal diameter stenosis ≥70 % and/or left main stem diameter stenosis ≥; FFS=Functional FFRCT Score; FFS= Functional FFR_{CT} Score.

FFS is quick to calculate manually, highly reproducible and correlates closely to other validated scoring models and (b) the FFS is closely associated with revascularization and MACE in two populations with chronic coronary syndrome. However, in one of these populations, the FFS does not outperform CAD-RADS in predicting events.

Previous data have demonstrated that the burden of atheroma and coronary flow impairment, as discrete entities, are associated with clinical outcome in patients with chronic coronary syndromes. Specifically, evidence from randomised trials and observational studies demonstrate the association between atheroma (and its overall burden) and a variety of adverse ischaemic events.[17–19] Furthermore, there is evidence of an inverse association between the level of invasive fractional flow reserve (FFR) and the rate of MACE.[20] Despite these data, no existing predictive scoring tool combines information about atheroma and flow impairment in a quick-to-calculate, yet clinically valuable, manner.

Moreover, the relative importance of atheroma versus ischaemia in terms of prediction of events has not been clear. Recent data suggest that overall atheroma burden may be dominant in the prediction of risk of events. Specifically, substudies of both PROMISE and ISCHAEMIA have reported that the incremental burden of atheroma in these populations is superior to the incremental burden of ischaemia in predicting future major adverse cardiac events.[18,21] However, given that both the burden of atheroma and the impairment in coronary flow have clearly been shown to be associated with the risk of major adverse cardiac events, it is both logical and plausible that a scoring model that describes both of these characteristics will offer considerable clinical potential as a prognostic tool.

Whilst the role of FFR_{CT} as a gatekeeper to invasive angiography is well established from previous observational studies[10,12,22] and the recently published randomized FORECAST trial,[11] the real-world experience from the ADVANCE registry highlights certain limitations for the single 0.8 cut off value. Although a positive FFR_{CT} occurred in 61.9 % of the patients, only 34.4 % of patients were referred for ICA, despite most of them also having significant coronary stenosis(es) on CCTA (69 %). Furthermore, there was a particularly low rate of revascularization for patients with positive FFR_{CT} readings which were close to the cut-off point (0.8): only 12.6 % of patients within the 0.76–0.80 % FFR_{CT} strata compared to 53.7 % of patients within the FFR_{CT} ≤0.7 strata.[10] These data suggest that there is potential value in using the FFR_{CT} data as a spectrum, rather than with a binary cut off, with which to assess risk and choose management.

To justify the concept of a clinically relevant scoring tool that combines both coronary stenosis severity burden and flow impairment burden, such a model would need to perform better than currently available alternatives. CAD-RADs[15] is a simple scoring model and, as such, is the most widely used by frontline clinical reporters. However, CAD-RADS is based solely on the most severe lesion and, hence, does not provide a comprehensive estimation of plaque burden. An analysis based on the CONFIRM registry using a test sample of 17,793 patients, and a validation sample of 2506 patients, found that both plaque burden and stenosis severity, particularly in the proximal coronary segments, carry significant additional risk prediction value.[23] To overcome this issue, several more comprehensive risk scoring tools have been validated, such as the Comprehensive CCTA risk score, which have proved to be superior to CAD-RADs in predicting events.[24] Furthermore, for multivessel CAD, the CT-SYNTAX(13) has demonstrated good correlation to the extensively validated invasive SYNTAX score.[25] However, as demonstrated in this analysis, such models are complicated and time consuming and, consequently, of limited use in busy clinical practice, despite their research value. Importantly, the newly developed Functional FFR_{CT} Score correlates well with the CT-SYNTAX score whilst being 10 times quicker to calculate.

Moreover, all the existing scores are based exclusively on anatomy and therefore do not include the additional potential prognostic value of ischaemia. The SYNTAX III study suggested that there is indeed an additional clinical impact when FFR_{CT} data is considered alongside the anatomical scoring, with a 7 % change in clinical management and a 12 % change in per-vessel revascularization decision.[26] However, although the Functional CT-SYNTAX score incorporates physiology, its calculation is similarly laborious to its anatomical counterpart. Furthermore, Functional CT-SYNTAX disregards coronary atheroma that is not flow limiting[26] which is particularly important given that 54 % of events in the PROMISE trial occurred in patients with non-obstructive CAD (1–69 % DS).[18] The recently published CAD-RADS 2.0 reporting system expanded on the original score by including plaque burden alongside six other modifiers.[27] However, the new model lacks prospective validation as a risk prediction tool and is significantly more complex than the original score. Our aim was to devise a score that was sufficiently simple for busy clinicians to incorporate it in their clinical practice, whilst also combining the coronary stenosis and FFR_{CT} burden.

In the FORECAST cohort the ROC analysis demonstrated no significant difference in AUC for MACE for the FFS compared with the CAD-RADS, with the confidence intervals being substantially overlapped. In the COX regression analysis, both the presence of obstructive CAD and the detection of any positive FFR_{CT} were independent predictors of MACE at 9-month follow-up in an univariable model. However, the FFS was the only significant predictor of MACE in Model 4 (including sex, DF, obstructive CAD, any positive FFR_{CT} and FFS). Moreover, the ROC analysis for MACE demonstrated the largest AUC for Model 4, although with significant overlap in the confidence intervals of all 4 models. Therefore, the FFS has the potential to offer incremental discriminatory value for MACE compared with the tools we currently use in clinical practice.

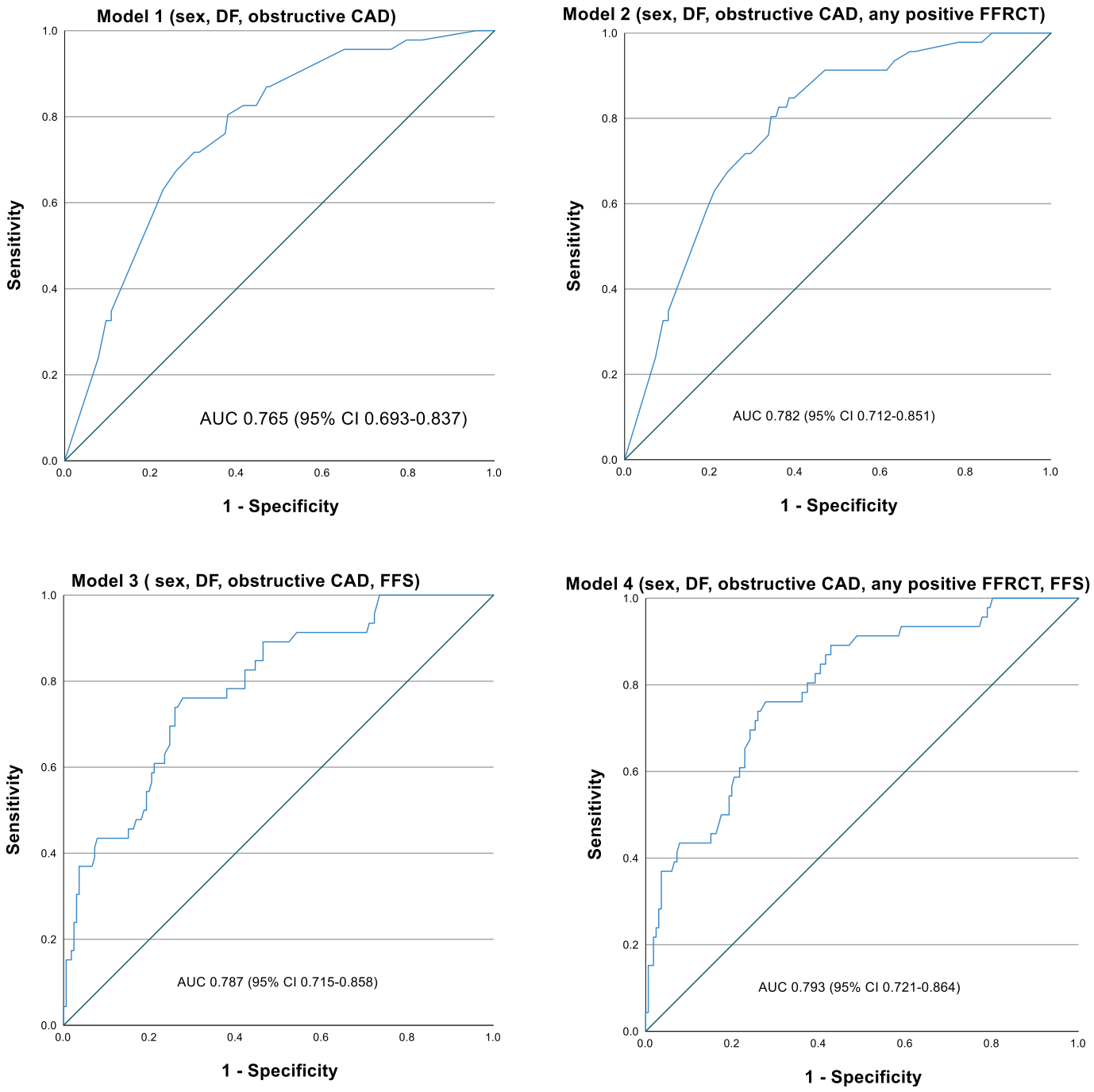


Fig. 5. Receiver Operating Characteristic Curve (ROC) of Models 1–4 for MACE in the FORECAST validation cohort (n = 212 patients). Model 1 includes sex, Diamond-Forrester (DF) classification and any obstructive CAD; Model 2 includes Model 1 variables and any positive FFRCT (binary cut-off, ≤0.80); Model 3 includes Model 1 variables and FFS; Model 4 includes Model 1 variables, any positive FFRCT (binary cut-off, ≤0.80) and FFS. CAD = coronary artery disease, defined as any luminal diameter stenosis≥70 % and/or left main stem stenosis≥50 %. FFS= Functional FFRCT Score; AUC=Area under ROC; CI = confidence interval.

Particularly important is that the FFS is now tested upon populations in which the result will not inevitably drive coronary revascularization, as was the case in ADVANCE and FORECAST, because it is feasible that the discriminatory power of the test may be at it greatest in a primary prevention population to predict events including MI, death and revascularization in the future. It will be vital, given the lack of superiority of FFS versus CAD-RADS in the FORECAST population in this work, to compare the combined burden of atheroma and ischaemia with atheroma burden alone.

Further evidence for the potential clinical utility of the FFS is demonstrated in the tertile analysis, in which significant increments are seen in the rates of invasive angiography, revascularization and MACE at 9-month follow-up between the high and low FFS tertiles. Particularly interesting is the fact that only patients in the high FFS group underwent CABG, suggesting that the FFS shows potential in not only selecting patients who would benefit from revascularization, but also aiding the likely choice between PCI and CABG in a similar fashion to the previously validated CT-SYNTAX and Functional CT-SYNTAX scores.[13,14] Nevertheless, by including estimates of both atheroma burden and flow impairment the FFS utility extends beyond considering patients for ICA and revascularization, as a simple tool for communicating overall risk and tailoring therapy.

This study has a number of important limitations. Firstly, as this is a secondary analysis of prospectively collected data, all findings are exploratory and need to be interpreted in light of the ADVANCE Registry and FORECAST study inclusion/exclusion criteria.[11,12] In the first validation cohort we have observed a very low rate of MACE, undoubtedly related to the ADVANCE Registry inclusion criteria and management.[10,12] Conversely, in the FORECAST validation cohort, although the rate of clinical events was relatively high, with 46 out of 212 patients experiencing a MACE at 9-month follow-up, this consisted mostly of hospitalization for cardiac events, rather than "harder" end-points. Secondly, within the FFS, the chosen thresholds for stenosis severity and FFR_{CT}, although based on previous published data, are essentially empirical, as it is the decision to add 1 point for LMS involvement. Future sensitivity analyses from our group are currently underway, aiming to refine the FFS. Thirdly, the FFS in its current form does not take account of the novel advanced CCTA analyses describing adverse plaque characteristics, atheroma patterns and adverse haemodynamic characteristics, nor does it include different measurements of FFR_{CT} such as lesion-specific FFR_{CT} and delta FFR_{CT}, which are of considerable future interest. The decision not to include these parameters in the FFS in its current form is motivated by our aim to keep the score simple and easy to calculate manually by busy clinicians. However, future iterations of the FFS could benefit from adding these parameters, ideally via an automatised calculation algorithm.

5. Conclusions

This study provides proof of concept for the novel Functional FFR_{CT} Score (FFS) as a predictor of clinical events. The FFS is feasible, highly reproducible and shows very strong correlation with more complex scores. In conclusion, by combining the burden of coronary stenosis and flow impairment, the FFS demonstrates good discriminatory abilities for revascularization and is an independent predictor of MACE at 9-month follow-up in multivariable Cox proportional model. Further investigation into the potential role of FFS and components to predict future clinical events is now warranted.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2023.10.005.

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