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Clinical implications of three-vessel fractional flow reserve measurement in patients with coronary artery disease

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Aims There are limited data on the clinical implications of total physiologic atherosclerotic burden assessed by invasive physiologic studies in patients with coronary artery disease. We investigated the prognostic implications of total physiologic atherosclerotic burden assessed by total sum of fractional flow reserve (FFR) in three vessels (3V-FFR).

Methods and results A total of 1136 patients underwent FFR measurement in three vessels (3V FFR-FRIENDS study, NCT01621438). The patients were classified into high and low 3V-FFR groups according to the median value of 3V-FFR (2.72). The primary endpoint was major adverse cardiac events (MACE, a composite of cardiac death, myocardial infarction and ischaemia-driven revascularization) at 2 years. Mean angiographic percent diameter stenosis and FFR were 43.7 ± 19.3% and 0.90 ± 0.08, respectively. There was a negative correlation between 3V-FFR and estimated 2-year MACE rate ($P < 0.001$). The patients in low 3V-FFR group showed a higher risk of 2-year MACE than those in the high 3V-FFR group [(7.1% vs. 3.8%, hazard ratio (HR) 2.205, 95% confidence interval (CI) 1.201–4.048, $P = 0.011$]. The higher 2-year MACE rate was mainly driven by the higher rate of ischaemia-driven revascularization in the low 3V-FFR group (6.2% vs. 2.7%, HR 2.568, 95% CI 1.283–5.140, $P = 0.008$). In a multivariable adjusted model, low 3V-FFR was an independent predictor of MACE (HR 2.031, 95% CI 1.078–3.830, $P = 0.029$).

Conclusion Patients with high total physiologic atherosclerotic burden assessed by 3V-FFR showed higher risk of 2-year clinical events than those with low total physiologic atherosclerotic burden. The difference was mainly driven by ischaemia-driven revascularization for both functionally significant and insignificant lesions at baseline. Three-vessel FFR might be used as a prognostic indicator in patients with coronary artery disease.

Clinical trial registration 3V FFR-FRIENDS study (https://clinicaltrials.gov/ct2/show/NCT01621438, NCT01621438).

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

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Introduction

Invasive treatment for ischaemic heart disease has been focused on the identification and revascularization of obstructive coronary artery disease (CAD). However, it is well known that a discrepancy exists between angiographic stenosis severity and the presence of myocardial ischaemia.[1] As the presence of ischaemia is a prerequisite for the improvement of clinical outcomes with percutaneous coronary intervention (PCI),[2] the decision to perform revascularization should be guided by evidence of myocardial ischaemia. A pressure-derived physiologic index, fractional flow reserve (FFR), is regarded as a standard invasive method to evaluate the functional significance of epicardial coronary artery stenosis.[3] The clinical outcomes of FFR-guided PCI were reported to be better than those of angiography-guided PCI or medical treatment.[2,4,5] However, clinical events still occur in patients with high FFR.[4,6]

The PROSPECT trial was performed to investigate the prognostic implications of invasive imaging study for non-culprit lesions and found that imaging studies of three vessels for plaque composition and burden can be helpful in the prediction of future cardiovascular events.[7–9] The RIPCORD study evaluated the clinical implications of routine FFR measurement in all coronary arteries and demonstrated its influence on the decision of treatment strategy.[10] However, the prognostic implications of total sum of FFR in three vessels as total physiologic atherosclerotic burden has not been evaluated yet.

The 3V FFR-FRIENDS trial (three-vessel fractional flow reserve for the assessment of total physiologic atherosclerotic burden and its clinical impact in patients with coronary artery disease, NCT01621438) was performed to investigate the clinical relevance of total physiologic atherosclerotic burden assessed by total sum of FFR in three-vessels (3V-FFR).

Methods

Study design and patient population

The 3V FFR-FRIENDS trial was a prospective, multinational, and multicentre study and the primary purpose was to compare 2-year clinical outcomes between patients classified according to the median value of 3V-FFR. Patients were consecutively screened and enrolled from 12 centres in 3 countries (Korea, China, and Japan) between November 2011 and March 2014 (participating centres are listed in the Supplementary material online, *Appendix S1*) (*Figure 1*). This study included patients who were at least 18 years old and had >30% stenosis by visual estimation in major epicardial coronary arteries and underwent successful FFR measurement in three major coronary arteries. In cases of PCI, FFR was measured after stent implantation. Patients with depressed left ventricular systolic function (ejection fraction <35%), acute ST-elevation myocardial infarction (MI) within 72 h, previous coronary artery bypass graft surgery (CABG), chronic renal disease, abnormal epicardial coronary flow (TIMI flow <3), or planned CABG after diagnostic angiography were excluded. The study protocol was approved by the institutional review board or ethics committee at each participating centre and all patients provided written informed consent.

Angiographic analysis and quantitative coronary angiography

Coronary angiography was performed using standard techniques. Angiographic views were obtained after administration of intracoronary nitrate (100 or 200 μg). All angiograms were analysed at a core laboratory (Seoul National University Hospital) in a blinded fashion. Quantitative coronary angiography was performed in optimal projections with validated software (CAAS II, Pie Medical System, Maastricht, The Netherlands). Minimum lumen diameter, reference vessel size, and lesion length were measured and percent diameter stenosis (%DS) was calculated.

Coronary physiologic measurements

All coronary physiologic measurements were performed after diagnostic angiography. A 5 - 7 Fr guide catheter without side holes was used to engage the coronary artery, and a pressure-temperature sensor guide wire (St. Jude Medical, St. Paul, MN, USA) was used for FFR measurement. FFR measurement protocol was standardized among the participating centres before the beginning of the study. The pressure sensor was positioned at the distal segment of a target vessel, and intracoronary nitrate (100 or 200 μg) was administered before each FFR measurement. Continuous intravenous infusion of adenosine or ATP was used to induce hyperaemia. Hyperaemic proximal aortic pressure (Pa) and distal coronary arterial pressure (Pd) were obtained during sustained hyperaemia and FFR was calculated by the mean of Pd/Pa during hyperaemia. FFR was not measured in diminutive right coronary artery or left circumflex artery. In those 100 cases, 3V-FFR was calculated as a mean value of FFR in two vessels multiplied by 3. When PCI was indicated, coronary intervention was performed, using current standard techniques with 2nd generation drug-eluting stents. The decision for PCI was at the discretion of the operators. For lesions with significant per-vessel FFR (≤0.80), PCI was recommended as the current guideline. In cases of PCI, post-PCI FFR measurement was mandatory and that value was used for the calculation of 3V-FFR.

Patient follow up, outcome measurements, and adjudication of clinical events

Clinical data were obtained at outpatient clinic visits or by telephone contact when needed. An independent clinical event committee whose members were unaware of clinical, angiographic, and physiologic data adjudicated all events. The primary outcome was major adverse cardiac events (MACE) at 2 years, including cardiac death, any myocardial infarction and any ischaemia-driven revascularization. All clinical outcomes were defined according to the Academic Research Consortium, including the addendum to the definition of MI. All deaths were considered cardiac unless an undisputable non-cardiac cause was present. Ischaemia-driven revascularization was defined as a revascularization procedure with at least one of the following: (i) recurrence of angina, (ii) positive non-invasive test, and (iii) positive invasive physiologic test.

Statistical analysis

The primary hypothesis of the current study was that patients with low 3V-FFR would show significantly higher 2-year MACE rate than those with high 3V-FFR. The estimated sample size of 1136 patients was based on a two-sided χ^2 test with an α level of 0.05, a statistical power of 0.80, and drop-out rates of 5%, assuming 2-year rates of MACE of 12% in the low 3V-FFR group and 7% in the high 3V-FFR group based on a previous study.[5]

Categorical variables were presented as numbers and relative frequencies (percentages), and continuous variables as means and standard deviations or median with interquartile range (IQR) (Q1–Q3) according to their distribution which was checked by the Kolmogorov–Smirnov test. Linear regression analysis was used to estimate the correlation coefficient between quantitative variables. Event rates were calculated based on Kaplan–Meier censoring estimates and presented with the cumulative

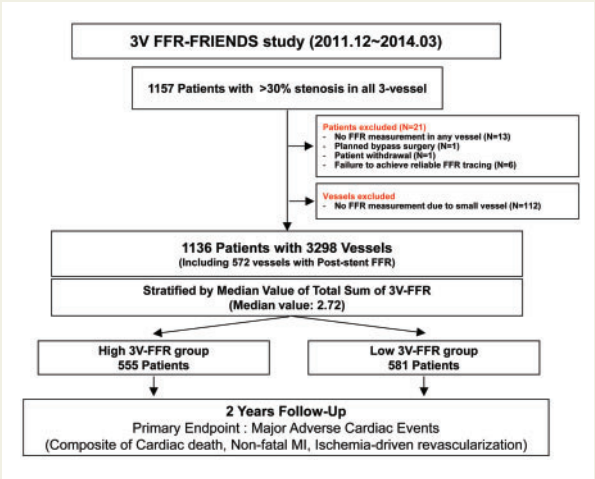


Figure 1 Study flow. The 3V FFR-FRIENDS study (three-vessel fractional flow reserve for the assessment of total stenosis burden and its clinical impact in patients with coronary artery disease, NCT01621438) evaluated the clinical relevance of 3V-FFR measurement and compared clinical outcomes between patients with high and low 3V-FFR, classified according to the median value of 3V-FFR (2.72). FFR, fractional flow reserve; MI, myocardial infarction; 3V-FFR, FFR in three vessels.

incidence, and the log-rank test was used to compare survival curves between groups. Cox proportional hazard regression was used to calculate hazard ratio (HR) and 95% confidence interval (CI) to compare between-group differences.

A multivariable Cox model was used to identify independent predictors of MACE. The covariates that were considered clinically relevant or that showed a univariate relationship with outcome ($P < 0.1$) were entered into multivariable Cox models. Variables selected for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final models. C-statistics with 95% CI were calculated to validate the discriminant function of the model. In order to select the best cut-off value (BCV) of 3V-FFR, a method using maximally selected log-rank statistics was used as previously described.[11]

In order to evaluate the association between 3V-FFR and estimated MACE risk according to treatment strategy, probability of risk was estimated using the Cox proportional hazards model and was plotted using the LOWESS (locally weighted scatterplot smoothing) regression line. In addition, the prognostic impact of per-vessel FFR was also evaluated using the same method. The difference in clinical outcomes according to native vessel FFR values between medically treated vessels and stented vessels was also plotted using the LOWESS regression line.

All probability values were two-sided and *P*-values < 0.05 were considered statistically significant. The SPSS version 18.0 (SPSS Inc., Chicago, IL, USA), SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA) and R 3.2.3 (R Corporation, USA) statistical packages were used for statistical analyses.

Results

Characteristics of patients and lesions

Figure 1 shows the flow of this study and *Table 1* summarizes the baseline characteristics of 1136 patients. Mean angiographic %DS and FFR of 3298 vessels were 43.7 ± 19.3% (median: 36.0%, IQR: 25.2–47.8%) and 0.90 ± 0.08 (median: 0.91, IQR: 0.85–0.96), respectively. PCI was performed in 572 vessels (17.3%) and post-stent FFR and %DS were used for those vessels. In 314 vessels (11.5%) with FFR ≤ 0.80, PCI was deferred due to insignificant angiographic stenosis (185 vessels, 58.9%), diffuse disease (48 vessels, 15.3%), no angiographic progression since previous angiography (31 vessels, 9.9%), negative results of non-invasive tests (17 vessels, 5.4%), small myocardial territory (15 vessels, 4.8%), and other reasons (17 vessels, 5.4%). Per-vessel FFR and %DS showed significant negative correlation ($r = -0.350$, $P < 0.001$). *Figure 2* presents the distribution of per-vessel FFR, %DS, and 3V-FFR. Among the 3298 vessels, 2891 vessels (87.7%) had FFR > 0.80, and 2600 vessels (79.8%) had %DS < 50%. Significant complications related with FFR measurements occurred in three patients (coronary spasm, thrombus formation, and coronary dissection).

Comparison between high and low fractional flow reserve in three vessels groups

The median value of 3V-FFR was 2.72 (IQR: 2.57–2.79). According to this median value, 555 patients (48.9%) were classified into the high 3V-FFR group and 581 patients (51.1%) into the low 3V-FFR group. *Table 1* demonstrates the comparison of patient and lesion characteristics between high and low 3V-FFR groups. Patients in the low 3V-FFR group showed higher proportion of hypertension, diabetes mellitus and history of previous PCI. In addition, those in the low 3V-FFR group showed more extensive involvement of CAD suggested by higher %DS, longer lesion length and lower per-vessel FFR (*Table 1*).

Clinical outcomes according to three-vessel fractional flow reserve

Figure 3 shows the association between 3V-FFR and 2-year MACE rate. Regardless of treatment strategy, there was a negative correlation between the MACE rate and 3V-FFR (HR per 0.1 increase 0.736, 95% CI 0.627–0.864, $P < 0.001$). *Figure 4* presents the comparison of 2-year MACE rates between high and low 3V-FFR groups. Patients in low 3V-FFR group showed a higher MACE rate than those in high 3V-FFR group (7.1% vs. 3.8%, HR 2.205, 95% CI 1.201–4.048, $P = 0.011$). The higher 2-year MACE rate was mainly driven by the higher rate of ischaemia-driven revascularization in the low 3V-FFR group (6.2% vs. 2.7%, HR 2.568, 95% CI 1.283–5.140, $P = 0.008$) (*Table 2*). A multivariable adjusted Cox regression model showed that low 3V-FFR was an independent predictor of 2-year MACE (HR 2.031, 95% CI 1.078–3.830, $P = 0.029$) (*Table 3*). The BCV of 3V-FFR to predict 2-year MACE was 2.59 based on the maximum log-rank statistics. When the patients were divided into 2 groups using this BCV, the low 3V-FFR group showed higher MACE rate than the high 3V-FFR group (10.7% vs. 4.2%, HR 3.171, 95% CI 1.800–5.584, $P < 0.001$) (see Supplementary material online, *Figure S1A*). This difference was maintained among 789 patients with per-vessel FFR > 0.8 in all 3 vessels (12.6% vs. 3.7%, HR 3.920, 95% CI 1.161–12.231, $P < 0.001$) (see Supplementary material online, *Figure S1B*). In patients with ischaemia-driven revascularization, 25 patients (62.5%) presented with acute coronary syndrome, 9 patients had aggravated

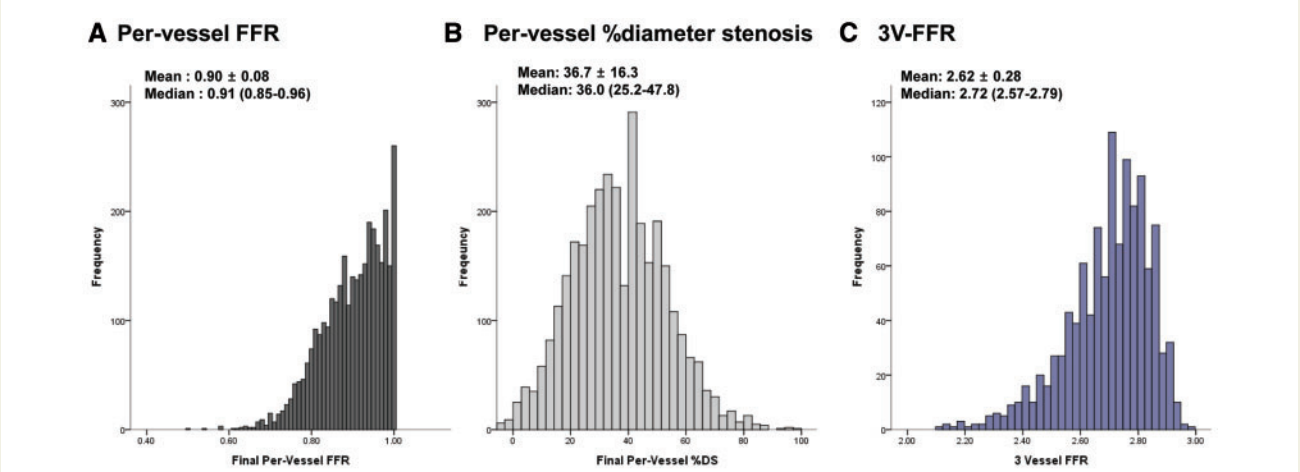


Figure 2 Distribution of per-vessel FFR, angiographic percent diameter stenosis, and three-vessel FFR. Distribution of per-vessel FFR, angiographic percent diameter stenosis and 3V-FFR were presented. By per-vessel analysis, 79.8% and 87.7% of vessels were angiographically insignificant (percent diameter stenosis < 50%), and functionally insignificant (FFR > 0.8), respectively. FFR, fractional flow reserve; 3V-FFR, FFR in three vessels.

angina with progression of the coronary stenosis and the others showed positive non-invasive tests during follow-up and underwent revascularization. Among the 314 deferred lesions with low FFR (≤0.8), MACE occurred in 12 vessels due to acute coronary syndrome (9 vessels) and objective signs of disease progression with positive results of non-invasive tests (3 vessels).

Per-vessel fractional flow reserve, treatment strategy, and clinical outcomes

The lower per-vessel FFR was significantly associated with higher MACE rate even after the adjustment with %DS (see Supplementary material online, *Figure S2*). Among 572 stented vessels, pre-intervention native vessel FFR was available in 371 vessels. Among these vessels, the different pattern of clinical outcomes according to native vessel FFR values in medically treated vessels and stented vessels with available pre-intervention FFR was presented (see Supplementary material online, *Figure S3*). In medically treated vessels with FFR < 0.75, the risk of 2-year MACE was exponentially increased. In stented vessels with pre-intervention FFR > 0.75, the risk of MACE was higher than medically treated vessels.

Discussion

This study evaluated the clinical relevance of 3V-FFR as a marker of total physiologic atherosclerotic burden and the main findings were as follows. First, in 1136 patients with median angiographic %DS of 36% and FFR of 0.91, there was a negative correlation between 3V-FFR and 2-year MACE rate. Second, when the patients were divided into two groups by the median value of 3V-FFR (2.72), the low 3V-FFR group showed higher event rate than the high 3V-FFR group. In addition, the low 3V-FFR was an independent predictor of MACE. Third, along with 3V-FFR, per-vessel FFR also had prognostic implication in our study cohort. These results imply that 3V-FFR which represents total physiologic atherosclerotic burden has prognostic implication. The clinical indication of FFR measurement may need to be expanded beyond the decision making for revascularization.

Clinical implications of three-vessel fractional flow reserve as a marker of total physiologic atherosclerotic burden

Previous studies showed that the total plaque burden assessed by intravascular ultrasound (IVUS) or coronary CT angiography could be helpful in the prediction of future cardiovascular events.[8,12,13] Shan *et al.*[8] analysed the IVUS data of patients enrolled in the PROSPECT study and reported that high overall percent atheroma volume was associated with a higher chance of vulnerable plaque and future cardiovascular events. Lin *et al.*[12] investigated the clinical relevance of the non-obstructive stenosis (<50% stenosis) in coronary CT angiography and found that the presence and extent of those stenoses was associated with higher risk of 3-year mortality.

FFR is an invasive physiologic index that represents the degree of flow reduction due to an epicardial stenosis.[14] Therefore, the sum of FFR values of three major epicardial vessels can be considered as a patient-level surrogate marker of total physiologic atherosclerotic burden. Previously, the concept of functional SYNTAX score was proposed to represent the total atherosclerotic burden in vessels with functional significance.[15] Conversely, the 3V-FFR represents the total physiologic atherosclerotic burden as the 3V-FFR value was derived from the summation of per-vessel FFR of all three vessels values regardless of functional significance. However, the prognostic implication of total physiologic atherosclerotic burden has not yet been investigated. In the current study, we evaluated the prognostic implication of 3V-FFR values. As we did not directly measure the anatomical plaque burden, we used the term 'physiologic atherosclerotic burden' rather than 'plaque burden'. It is interesting to note a recent study by Jin *et al.*,[16] which revealed that the correlation with FFR was

Table 1 Clinical and lesion characteristics

	Total	High 3V-FFR (≥2.72)	Low 3V-FFR (<2.72)	*P*-value
Patients	1136	555 (48.9%)	581 (51.1%)	
General characteristics				
Age (years)	61.9 ± 9.8	61.9 ± 10.2	61.9 ± 9.4	0.950
Male	835 (73.5%)	388 (69.9%)	447 (76.9%)	0.007
Ejection fraction (%)	62.4 ± 7.4	62.8 ± 7.0	62.0 ± 7.6	0.086
Cardiovascular risk factors				
Hypertension	689 (60.7%)	316 (56.9%)	373 (64.2%)	0.012
Diabetes mellitus	363 (32.0%)	161 (29.0%)	202 (34.8%)	0.037
Hypercholesterolaemia	597 (52.6%)	285 (51.4%)	312 (53.7%)	0.428
Previous MI	100 (8.8%)	48 (8.6%)	52 (9.0%)	0.858
Previous PCI	360 (31.7%)	147 (26.5%)	213 (36.7%)	<0.001
Clinical presentations				0.008
Stable angina	684 (60.2%)	312 (56.2%)	372 (64.0%)	
Unstable angina	186 (16.4%)	91 (16.4%)	95 (16.4%)	
Myocardial infarction	68 (6.0%)	35 (6.3%)	33 (5.7%)	
Others	198 (17.4%)	117 (21.1%)	81 (13.9%)	
Discharge medications				
Aspirin	891 (79.3%)	419 (75.5%)	481 (82.8%)	0.005
P2Y12 inhibitor	709 (62.4%)	323 (58.2%)	386 (66.4%)	0.002
ACEI/ARB	416 (36.6%)	184 (33.2%)	232 (39.9%)	0.001
Beta-blocker	423 (37.2%)	201 (36.2%)	232 (39.9%)	0.319
Statin	998 (87.9%)	477 (85.9%)	521 (89.7%)	0.133
Lesions				
Quantitative coronary angiography				
Reference diameter (mm)	3.0 ± 0.6	3.1 ± 0.6	2.9 ± 0.6	<0.001
Minimum lumen diameter (mm)	1.7 ± 0.7	1.9 ± 0.7	1.5 ± 0.6	<0.001
Diameter stenosis (%)	43.7 ± 19.3	38.7 ± 18.1	48.9 ± 19.0	<0.001
Lesion length (mm)	11.1 ± 8.9	9.9 ± 7.4	12.3 ± 10.1	<0.001
Per-vessel FFR[a]				
Mean	0.90 ± 0.08	0.93 ± 0.06	0.86 ± 0.08	<0.001
Median	0.91 (0.85–0.96)	0.95 (0.90–0.98)	0.87 (0.81–0.93)	<0.001

Values are mean ± SD, median (interquartile ranges, 25th–75th), or *n* (%).
FFR, fractional flow reserve; MI, myocardial infarction; PCI, percutaneous coronary intervention; 3V-FFR, FFR in three vessels; SD, standard deviation; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker.
[a]The per-vessel FFR value referred to post-PCI FFR value in case of stent implantation.

better with percent total atheroma volume ($r = -0.71$, $P < 0.001$) than with minimal lumen area ($r = 0.54$, $P < 0.001$).

Prognostic implications of three-vessel fractional flow reserve

Although the RIPCORD study evaluated the clinical relevance of routine FFR measurement in all coronary arteries and demonstrated its influence on planning the treatment strategy,[10] this study did not investigate the prognostic implications of total sum of FFR in 3 vessels. Our study investigated the influence of 3V-FFR on 2-year clinical outcomes. Despite relatively lower angiographic and physiologic lesion severity compared with previous studies, there was a negative association between 3V-FFR and 2-year MACE rate. When the patients were divided into high and low 3V-FFR groups according to a median 3V-FFR value of 2.72, the low 3V-FFR group showed about two-fold higher risk of MACE than the high 3V-FFR group. Furthermore, low 3V-FFR was an independent predictor of MACE, even after multivariable adjustment. These results consistently demonstrated the clinical relevance of 3V-FFR.

It is noteworthy that there were different patient subsets according to PCI. For example, in a patient with multivessel disease and insignificant per-vessel FFR value could have a similar 3V-FFR value to a patient who was revascularized for functionally significant lesions and have a high final per-vessel FFR value after PCI. In our study, medically treated patients and those with PCI showed similar 2-year MACE rate according to 3V-FFR value. This observation was in line with the FAME 2 trial, in which revascularized patients for functionally significant lesions (FFR-guided PCI plus medical therapy group) showed similar 2-year event rates with patients without any functionally significant stenosis (registry group).[4]

Our study results are an extension of previous studies which showed the relationship between FFR and clinical outcomes, even in

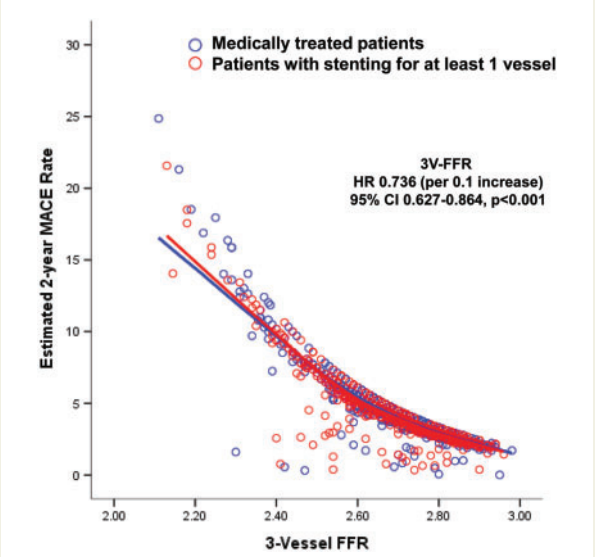


Figure 3 Estimated 2-year MACE rate according to 3V-FFR. The probability of 2-year MACE was estimated using a Cox proportional hazard regression model in patients who were medically treated (blue circle) or treated by revascularization at least for one vessel (red circle). There was a negative correlation between MACE rate and 3V-FFR (hazard ratio per 0.1 increase 0.736, 95% CI 0.627–0.864, $P < 0.001$). The blue line indicates a regression line of medically treated patients and the red line for that of revascularized patients. FFR, fractional flow reserve; MACE, major adverse cardiac events; 3V-FFR, FFR in three vessels.

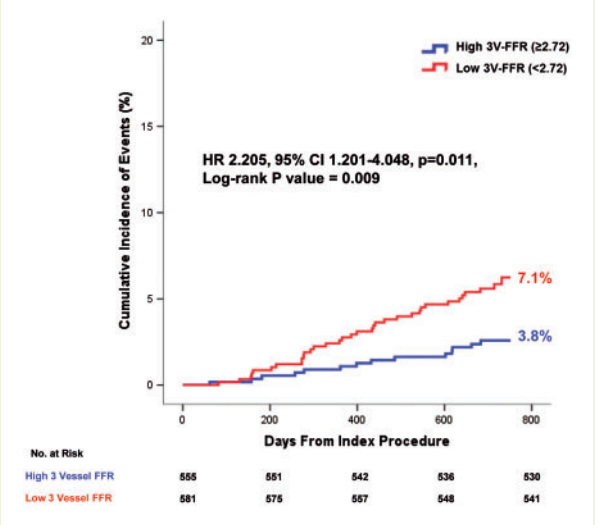
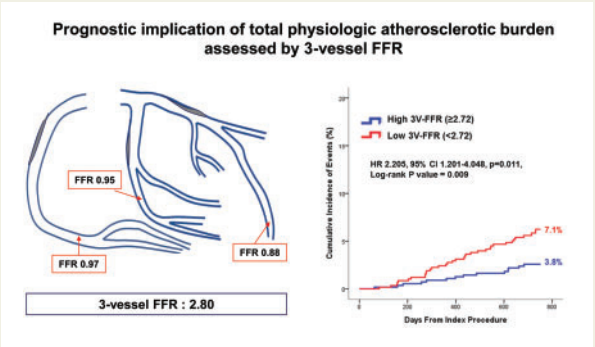


Figure 4 Comparison of 2-year clinical event rate between high and low 3V-FFR groups, classified according to the median value of 3V-FFR (2.72). Comparison of 2-year MACE rates between patients with high and low 3V-FFR groups, classified according to the median value of 3V-FFR (2.72) is presented. Patients in the low three-vessel FFR group (<2.72) showed a higher MACE rate than those in high 3V-FFR group (≥2.72). FFR, fractional flow reserve; MACE, major adverse cardiac events; 3V-FFR, FFR in three vessels.



Take home figure Prognostic implication of total physiologic atherosclerotic burden (3V-FFR). FFR, fractional flow reserve; 3V-FFR, FFR in three vessels.

non-ischaemic range.[17,18] The FFR value needs to be interpreted as a continuous value and be considered as a tool for risk assessment as well as a decision making tool for revascularization. In addition, our results support the results of previous studies which showed the influence of diffuse atherosclerosis on FFR value.[19,20] It is interesting to note that the mean angiographic %DS was 43.7 ± 19.3% and 79.8% of vessels had <50% stenosis in our study. This represents that most of the vessels included in our study were not within the range of current indication for FFR measurement. Therefore, recent studies, as well as ours, suggest that the clinical indication for FFR measurement needs to be expanded beyond the scope of ischaemia detection.

Implications of per-vessel fractional flow reserve and treatment strategy on clinical outcomes

In our study cohort, per-vessel FFR was associated with the risk of MACE, although its mean value was 0.90 ± 0.08. Johnson *et al.*[17] demonstrated continuous and independent association between pre-interventional FFR and subsequent clinical outcomes by patient and study level meta-analysis. However, most data in that meta-analysis were collected from FFR measurement under current clinical indications. Our study also showed a similar trend as Johnson *et al.*'s study, despite the difference in angiographic and physiologic lesion characteristics. The estimated 2-year MACE risk was different between medically treated vessels and stented vessels in our study (see Supplementary material online, *Figure S3*). This result is in line with the DEFER trial, which showed the long-term safety of medically treated lesions with FFR > 0.75.[21] In a recent *post hoc* analysis of the FAME study, residual angiographic stenoses without functional significance did not have prognostic implications.[22] These results consistently show the importance of FFR-guided revascularization strategy.

Limitations

This study has some limitations. First, the event rates were generally lower than those of previous studies. This difference seems to be due to the unique design of this study and lower angiographic lesion

Table 2 Comparison of clinical outcomes between the high and low three-vessel fractional flow reserve groups, classified according to the median value of fractional flow reserve in three vessels (2.72)

	High 3V-FFR ≥ 2.72 (*n* = 555)	Low 3V-FFR < 2.72 (*n* = 581)	HR (95% CI)	*P*-value
Major adverse cardiac events[a]	15 (3.8%)	34 (7.1%)	2.205 (1.201–4.048)	0.009
Cardiac death	5 (1.3%)	5 (0.9%)	0.967 (0.280–3.341)	0.958
Myocardial infarction	5 (1.3%)	7 (1.8%)	1.371 (0.435–4.319)	0.590
Ischaemia-driven revascularization	11 (2.7%)	29 (6.2%)	2.568 (1.283–5.140)	0.008

Values are *n* (%). Cumulative incidence of events was presented as Kaplan–Meier estimates.
3V-FFR, fractional flow reserve in three vessels; CI, confidence interval.
[a]Major adverse cardiac events were defined as a composite of cardiac death, myocardial infarction, and ischaemia-driven revascularization.

Table 3 Independent predictors of 2-year major adverse cardiac events[a]

Variable	Adjusted HR (95% CI)	*P*-value
Previous myocardial infarction	**3.138 (1.073–9.174)**	**0.037**
Multi-vessel disease	**2.278 (1.142–4.544)**	**0.019**
Low 3V-FFR (<2.72)	**2.031 (1.078–3.830)**	**0.029**
Acute coronary syndrome	**1.931 (1.024–3.639)**	**0.042**
Age (10 years)	**1.438 (1.036–1.994)**	**0.030**
Hypertension	0.807 (0.439–1.484)	0.490
Diabetes mellitus	1.124 (0.608–2.075)	0.710
Hyperlipidaemia	1.172 (0.633–2.169)	0.613
Left ventricular dysfunction (EF ≤ 50%)	1.089 (0.336–3.527)	0.887
Left main disease	1.273 (0.609–2.665)	0.521

FFR, fractional flow reserve; HR, hazard ratio; CI, confidence interval; 3V-FFR, fractional flow reserve in three vessels; EF, ejection fraction.
[a]C-index of the multivariable Cox regression model was 0.738 (0.666–0.810).

severity than that of previous studies. In addition, even though 97.4% patients completed 2-year follow-up, there was still a possibility of under-reporting of non-fatal clinical events like in all registries. Second, the actual event rates in the low 3V-FFR group were lower than the assumed value in sample size calculation. However, the observed difference in MACE rate between the high and low 3V-FFR groups reached a statistical power of 77% with the current sample size. Third, invasive imaging studies were not performed. Therefore, the relationship between total anatomical atherosclerotic burden or plaque characteristics and clinical outcomes could not be investigated. Fourth, the clinical outcome in this study was actually not the natural history but the clinical outcome mainly modulated by revascularization of significant lesions. Fifth, the difference of 2-year MACE rates between high and low 3V-FFR groups was mainly driven by ischaemia-driven revascularization. As the current study included lesions with relatively low grade stenosis, the rate of death or MI was relatively low, like previous studies with deferred lesions.[4] Lastly, investigators were not blinded to initial per-vessel FFR values. Although all events were adjudicated by an independent event adjudication committee and most events were associated with objective evidence of disease progression, the influence of bias due to lack of blinding cannot be completely excluded.

Conclusion

Patients with high total physiologic atherosclerotic burden assessed by 3V-FFR showed higher risk of 2-year clinical events than those with low total physiologic atherosclerotic burden. The difference was mainly driven by ischaemia-driven revascularization for both functionally significant and insignificant lesions at baseline. Three-vessel FFR might be used as a marker of total physiologic atherosclerotic burden and a prognostic indicator in patients with CAD.

Summarizing illustration

This study evaluated the clinical relevance of 3V-FFR as a marker of total physiologic atherosclerotic burden. Patients with high total physiologic atherosclerotic burden assessed by 3V-FFR (low 3V-FFR) showed higher risk of 2-year clinical events than those with low total physiologic atherosclerotic burden (high 3V-FFR). Three-vessel FFR might be used as a marker of total physiologic atherosclerotic burden and a prognostic indicator in patients with coronary artery disease.

Supplementary material

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

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