Supplementary Appendix

Supplement to: Koo B-K, Hu X, Kang J, et al. Fractional flow reserve or intravascular ultrasonography to guide PCI. N Engl J Med 2022;387:779-89. DOI: 10.1056/NEJMoa2201546

This appendix has been provided by the authors to give readers additional information about the work.

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2. Major Protocol Revision

When this study was started in May 2016, the original hypothesis was that the FFR-guided strategy would show significantly lower rates of patient-oriented composite outcomes at 24 months after the index procedure than the IVUS-guided strategy in patients with intermediate coronary stenosis. The event rates of the FFR-guided PCI strategy and IVUS-guided PCI strategy were estimated based on previous trials (FAME I 2 year results[1]), and a meta-analysis comparing IVUS-guided PCI versus angiography-guided PCI strategies,[2] leading to estimated event rates of 15% and 20%, respectively.

The power calculation was as follows:

- Primary end point: patient-oriented composite outcome (a composite of all-cause death, MI, any repeat revascularization) at 24 months after PCI
- Design: Equality (two-sided test)
- Sampling ratio: FFR-guided strategy : IVUS-guided strategy = 1:1
- Type I error (α): two-sided 2.5%
- Accrual time : 2 years
- Total time : 4 years (accrual 2 year + follow-up 2 years)
- Assumption: POCO 15.0% vs. 20.0% in FFR or IVUS-guided strategy, respectively
- Statistical power (1- β): 80%
- Primary statistical method : Kaplan-Meier survival analysis with log-rank test
- Potential withdrawal rates : total 2%
- Based on the above assumption, expected number of events are 318. We would need total 1,860 patients (930 patients in each group) with consideration of withdrawal rates.

However, in June 2017, there was a major protocol revision in June 2017. The estimated event rate was modified, along with the hypothesis of the trial. For the following reasons, we decided to make a major modification to the trial design.

First, we modified the estimated event rate based on new data. In the 2017 ACC's 66th annual

scientific session, the results of the DEFINE-FLAIR and iFR-SWEDEHEART trials were presented with simultaneous publication in N Eng J Med and those two studies had similar patient populations and primary outcomes as our study. Considering the event rate of the FFR arm in these two studies (which was 7.0% in the DEFINE-FLAIR study[3] and 6.1% in the iFR-SWEDEHEART study[4] 1 year after the index procedure), we extrapolated the event rate and estimated an event rate of 10% at the 24-month follow-up in the FFR group. For the IVUS group, the original estimated event rate was 20% based on a meta-analysis that evaluated IVUS guided PCI[2]. However, subsequent studies reported larger risk reduction with IVUS usage, while a meta-analysis which analyzed seven trials with 3192 patients and reported a 40% reduction in the risk of major adverse cardiac events[5]. In addition, despite the concerns of higher peri-procedural MI associated with IVUS usage, a meta-analysis showed no increase in the associated risk of peri-procedural MI.[6] Therefore, there was a consensus that the event rate in the IVUS group should be adjusted to reflect the new data such as in a substudy of the ADAPT-DES trial.[7] While adjusting for the differences in the PCI rate, definition of peri-procedural MI, and primary outcomes, the estimated event rate in the IVUS arm was adjusted to 12%.

The second major modification was to change the superiority design to a noninferiority design. The database was locked on January 28, 2022 and the investigators did not perform any interim analysis or look at any data prior to this date. Therefore, the decision to change the trial design to a noninferiority design was based solely on new concepts and data. Numerous articles have reported the prognostic importance of plaque burden and plaque vulnerability, even in those with high FFR or without evidence of myocardial ischemia. In addition, in terms of hard end points, IVUS-guided PCI consistently showed a benefit over angiography-guided PCI. As the outcome of our study population was determined by the events in deferred lesions and PCI segments, there is a possibility that more PCI with new generation stents and more successful PCI can result in better clinical outcomes than before according to new data. Therefore, we believed that the working hypothesis should be “the FFR-guided PCI strategy will be noninferior to the IVUS-guided PCI strategy with regard to clinical outcomes” as the PCI rate would be higher in the IVUS group.

3. Data Sharing Statement

The FLAVOUR trial is planning to continue analysis, including post-hoc subgroup analysis. Until then, no individual participant data will be available. Any relevant inquiry should be emailed to Dr. Bon-Kwon Koo (Email: bkkoo@snu.ac.kr)

4. Inclusion and Exclusion Criteria

(1) Inclusion Criteria

① Subject must be ≥ 19 years.

② Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving invasive physiologic or imaging evaluation and percutaneous coronary intervention (PCI) with a drug-eluting stent and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure.

③ Patients suspected with ischemic heart disease.

④ Patients with *de novo* intermediate degree of stenosis (40-70% stenosis by visual estimation) eligible for stent implantation who need fractional flow reserve (FFR) or intravascular ultrasound (IVUS) clinically for further evaluation.

⑤ Target vessel size≥2.5mm in visual estimation.

⑥ Target vessels are limited to proximal to mid LAD, proximal to distal LCX, and RCA proximal to the PL-PDA bifurcation (LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; PL, postero-lateral; PDA, posterior descending artery).

(2) Exclusion Criteria

① The patient has a known hypersensitivity or contraindication to any of the following medications: Heparin, Aspirin, Clopidogrel, Prasugrel, Ticagrelor, Contrast media (Patients with documented sensitivity to contrast media which can be effectively premedicated with steroids and diphenhydramine. [e.g. rash] may be enrolled.)

② Patients with active pathologic bleeding.

③ Gastrointestinal or genitourinary major bleeding within the prior 3 months.

④ History of bleeding diathesis, known coagulopathy (including heparin-induced thrombocytopenia).

⑤ Non-cardiac co-morbid conditions with life expectancy<2 years.

⑥ Target lesion located in coronary arterial bypass graft.

⑦ Target lesion located in the left main coronary artery.

⑧ Target lesion located in previous PCI segment with in-stent restenosis.

5. Sample Size Calculation

Sample size estimation was based on the results of previous trials. For the FFR group, the estimated event rate of 10% at 24-month follow-up was assumed from the results of the 1-year event rates of the DEFINE-FLAIR[3] and iFR-SWEDEHEART trials.[4] For the IVUS group, an estimated event rate of 12% was assumed from the event rates of previous studies including the substudy of the ADAPT-DES trial[5-7], while adjusting the differences in baseline characteristics and event definitions. According to these estimations, the power calculation was performed as follows:

- Primary end point: patient-oriented composite outcome (POCO, a composite of death from any cause, MI, any revascularization) at 24 months after PCI
- Design: noninferiority, delta = 2.5%
- Sampling ratio: FFR-guided PCI strategy: IVUS-guided PCI strategy = 1:1
- Type I error (α): 5%
- Accrual time: 2 years
- Total time: 4 years (accrual 2 year + follow-up 2 years)
- Assumption: POCO 10.0% vs. 12.0% in FFR vs. IVUS-guided strategy, respectively
- Statistical power (1- β): 90%
- Primary statistical method: Kaplan-Meier survival analysis with log-rank test
- Potential attrition rate: total 2%
- Stratification in randomization: Presence of diabetes mellitus

Based on the above assumption, we would need total 1,700 patients (850 patients in each group) with consideration of attrition rate.

6. Randomization and Follow-up

Randomization

In the FLAVOUR study, verbal consent was obtained before procedure and written informed consent was obtained after the procedure. This was because eligibility for this study could not be fully assessed before diagnostic angiography.

Before the procedure, the primary physician provided adequate information about the trial and guaranteed an appropriate amount of time to ask questions, discuss the research protocol, and determine whether the patient should participate. The following points were explained to the participant: (1) this study is a phase IV clinical trial; (2) participation is voluntary, there is no penalty for withdrawal, and withdrawal is possible at any time; (3) potential risks and benefits for participation; and (4) contact information for additional concerns. Subsequently, verbal consent was obtained from all participants. During the procedure, randomization was performed after eligibility was fully evaluated and it was confirmed that the patient was adequate for study enrollment. Randomization was performed before any coronary intervention or IVUS/FFR was carried out for a lesion, including the non-study target lesion. Sedative medications are not routinely used in Korea and China. After the procedure, a written informed consent was obtained and any additional information was provided to the patients if required/requested.

Follow-up

During the follow-up period, clinical follow-up was mandatory. At routine follow-up, the vital status was monitored, along with surveillance of any clinical events. In any case the patient missed scheduled follow-up visits, other efforts, including telephone contact, were used. For clinical event recording, complete monitoring of the eCRF and electronic health records was performed, along with on-site source-document verification. An additional interviewer who was responsible for the patient-reported outcomes double-checked for any clinical events that might have been overlooked in the outpatient clinic. An independent clinical event adjudication committee, blinded to the treatment group assignment performed adjudication for all primary and secondary clinical events.

The date of the end of trial follow-up was December 1st, 2021 and the date of database lock was

January 28th, 2022.

7. Criteria of Revascularization and Successful PCI

(1) Revascularization Criteria

Group	Criteria for revascularization
IVUS-guided PCI group	Minimal lumen area (MLA) $\leq 3mm^2$ or $3\ mm^2 < MLA \leq 4mm^2$ and plaque burden > 70%
FFR-guided PCI group	FFR ≤ 0.80

Indications for revascularization in the IVUS group were defined based on the association of IVUS parameters with functional significance and clinical outcomes. Previous studies on Asian and Western populations suggested that an MLA <3.0 mm^2 is the best cut-off value to predict FFR <0.80 in lesions with intermediate stenosis[8,9]. However, it is well known that one MLA value cannot fully represent the functional significance,[10] a and as shown in the PROSPECT [11] and VIVA studies,[12] plaque burden is also an important prognostic indicator. Based on these previous study results, we pre-specified the indications for revascularization in the IVUS group as "an MLA ≤ 3 mm^2 or 3 to ≤ 4 mm^2 with a plaque burden > 70%".

(2) Criteria of Successful PCI

Group	Criteria for Successful PCI
IVUS-guided PCI group	Plaque burden at stent edge $\leq 55\%$ and minimal stent area $\geq$ $5.5mm^2$ or Plaque burden at stent edge $\leq 55\%$ and minimal stent area $\geq$ distal reference lumen area
FFR-guided PCI group	Post PCI FFR ≥ 0.88 or Post PCI delta FFR ([FFR at stent distal edge] – [FFR at stent

	proximal edge]) < 0.05

Regarding the criteria in the IVUS group, Kang et al. previously reported that plaque burden at the stent edge>55% was one of the predictors for edge restenosis after DES implantation[13]. In other studies, Song et al. reported that a minimal stent area of less than 5.3-5.5mm^2 was the best cut-off value for the prediction of stent restenosis[14], while Lee et al. reported that the minimal stent area and the ratio of the minimal stent area to the distal reference area were the best predictors for future events.[15] Our criteria of successful PCI in the IVUS-guided PCI group combined these results to define the successful results.

For the criteria of successful PCI in the FFR group, there has been no single post-stent FFR best cutoff value despite the consistent results on the association between post-stent FFR and clinical outcome. It may be due to the differences in baseline patient and lesion characteristics, procedures, and devices used in previous studies which determine the rate and best cutoff value of post-stent FFR. The initially suggested optimal cutoff value of 0.90 was derived from the patients mainly treated with bare metal stents[16] and it has become lower along with the use of drug-eluting stents form complex lesions.[17] In a study by Argarwal, et al, best cutoff value of post-stent FFR was suggested as 0.86.[18] Considering the differences in baseline characteristics between those studies and ours, we defined the post-stent FFR 0.88 as one of the criteria of successful PCI in our study. In addition, we added the additional criterion of trans-stent pressure gradient to define the successful PCI to compensate the inevitable limitation of post-stent FFR which is influenced by not only the degree of stent optimization, but also the disease in non-stented segments. Tanaka, et al investigated the clinical relevance of the pressure drop within the stented segment, and the ratio of coronary pressure at the stent distal edge to the proximal edge lower than 0.95 was associated with the stent under- expansion, edge dissection, or residual plaque at the stent edge.[19] Considering the limited data on the association between pressure gradient across the lesion and the complexity of applying the ratio of coronary pressure at the stent distal edge to the proximal edge, we defined delta FFR across the stent of <0.05 as one of criteria for successful PCI in the FFR group.

8. Definition of Clinical Outcomes

Primary outcome: patient-oriented composite outcome (POCO), defined as a composite of death from any cause, myocardial infarction (including peri-procedural MI) or any revascularization at 24 months after randomization according to the ARC consensus.[20]

Death

Death from any cause: considered cardiac unless an unequivocal noncardiac cause can be established. Specifically, any unexpected death even in patients with coexisting potentially fatal non-cardiac disease (eg, cancer, infection) should be classified as cardiac.

Death from cardiac cause: Any death due to proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment, will be classified as cardiac death.

Death from non-cardiac cause: Any death not covered by the above definitions and clearly documented non-cardiovascular cause, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

Myocardial infarction

Spontaneous Myocardial infarction

Considered an event after the first 24 hours after randomization which is unrelated to the procedure defined as,

EITHER

#. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

① Ischemic symptoms;

AND/OR

② Development of new pathologic Q-waves on the ECG;

AND/OR

③ ECG changes indicative of ischemia (ST segment elevation or depression);

OR

#. Development of new pathologic Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event.

OR

#. Pathological findings of an acute MI.

Peri-procedural Myocardial infarction: Definition of Peri-procedural MI in the FLAVOUR trial

#. Stable Angina: Peri-procedural MI in the setting of elective PCI is defined by a confirming cardiac specific biomarker (a positive value of CK-MB or Troponin I/T) on any one sample obtained after the procedure. "CKMB elevation >3 times upper limit of normal" Or "Troponin elevation that is >5 times the 99th percentile of diagnostic value for the specific institution" AND the presence of, new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB, symptoms of ischemia with ECG changes indicative of new ischemia (new ST-T changes), angiographic documentation of new coronary artery occlusion or dissection.

#. ACS: Peri-procedural MI in the setting of ACS PCI for evolving MI is defined as follows: When peak CK-MB or Troponin from the index infarction HAS been reached: EITHER "If the biomarkers have returned to below the upper limit of normal. A new elevation in CK-MB > 3 times upper limit of normal or Troponin >5 times the 99 percentile" OR "If the biomarkers have not returned to below the upper limit of normal A rise of >50% in CK-MB or Troponin above the previous nadir level AND the presence of, new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB, symptoms of ischemia with ECG changes indicative of new ischemia (new ST-T changes), angiographic documentation of new coronary artery occlusion

or dissection.

Target vessel Myocardial infarction:

Target vessel MI is defined as the MI located in entire major intervened coronary vessel with clearly documented evidence, such as ECG, echocardiography, CT angiography or invasive angiography.

Revascularization

Any revascularization is considered clinically indicated if angiography at follow-up shows a percent diameter stenosis ≥50% and if one of the following occurs:

① A positive history of recurrent angina pectoris, presumably related to the target vessel;
② Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel;
③ Abnormal results of any invasive functional diagnostic test (eg, Doppler flow velocity reserve, fractional flow reserve);
④ A TLR or TVR with a diameter stenosis ≥70% even in the absence of the above-mentioned ischemic signs or symptoms.

Ischemia driven revascularization is defined as a revascularization procedure with one of the followings,

① A positive history of recurrent angina pectoris, presumably related to the target vessel
② Objective signs of ischemia at rest (EKG changes) or during exercise test (or equivalent), presumably related to the target vessel
③ Abnormal results of any invasive functional diagnostic test (eg, fractional flow reserve)

Target vessel revascularization is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself.

Stent thrombosis

Definite stent thrombosis: Angiographic confirmation OR Pathological confirmation of stent thrombosis

Angiographic confirmation of stent thrombosis: The presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least one of the following criteria within a 48-hour time window:

① Acute onset of ischemic symptoms at rest
② New ischemic ECG changes that suggest acute ischemia
③ Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
④ Nonocclusive thrombus: An intracoronary thrombus is defined as a noncalcified filling defect or lucency surrounded by contrast material seen in multiple projections, persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream
⑤ Occlusive thrombus: TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if it originates from the side branch).

Pathological confirmation of stent thrombosis: Evidence of a recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

Probable stent thrombosis: According to the clinical definition, probable stent thrombosis was

considered to have occurred after intracoronary stenting in the following cases:

① Any unexplained death within the first 30 days

② Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause

Possible stent thrombosis: According to the clinical definition, possible stent thrombosis was considered to have occurred in any case of unexplained death from 30 days after intracoronary stenting until the end of the trial follow-up.

Stroke

Rapid onset of focal or global neurological deficits. If the duration is <24 hours, the event is deemed a transient ischemic attack (TIA), except if an intervention is performed as defined below. If the duration is ≥24 hours, it is deemed a stroke.

Stroke is subdivided into ischemic, hemorrhagic, and undetermined types. Ischemic stroke refers to an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue. Hemorrhagic stroke is an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Stroke is diagnosed when the following criteria are met:

1. Rapid onset of a focal/global neurological deficit with at least one of the following:

- Change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphagia/aphasia, hemianopia, amaurosis fugax, or other new neurological signs or symptoms consistent with stroke.

2. Confirmation of the diagnosis by at least one of the following:

① Neurology or neurosurgical specialist

② Brain imaging (CT, MRI, or cerebral vessel angiography)

③ Lumbar puncture diagnostic of intracranial hemorrhage

9. Seattle Angina Questionnaire Analysis

The Seattle Angina Questionnaire (SAQ), composed of 19 questionnaires, was assessed to quantify patient-reported outcomes regarding the symptoms of angina and the extent to which angina affects daily life. Clinical significance in this score was defined according to previous literature, as a difference of 8 points or more on the physical-limitation scale, 25 or more on the angina-stability scale, 20 or more on the angina-frequency scale, 12 or more on the treatment-satisfaction scale, and 16 or more on the quality-of-life scale.

10. Quantitative Flow Ratio Analysis

The quantitative flow ratio (QFR) was analyzed by an independent core laboratory using the software package QAngio XA 3D (Medis Medical Imaging Systems, Leiden, the Netherlands). The end diastolic frames of two matched images, separated by >25° and with an acquisition time difference of less than 120 minutes were selected and used for reconstruction of 3-dimensional (3D) model. The arterial contour was automatically detected, and manual correction was performed, if necessary. The software reconstructed the 3D vessel model for QFR computation. QFR was calculated using a modelled hyperemic flow velocity based on TIMI frame count analysis without drug-induced hyperemia.

11. Supplementary Figures

Figure S1. Schematic Study Design

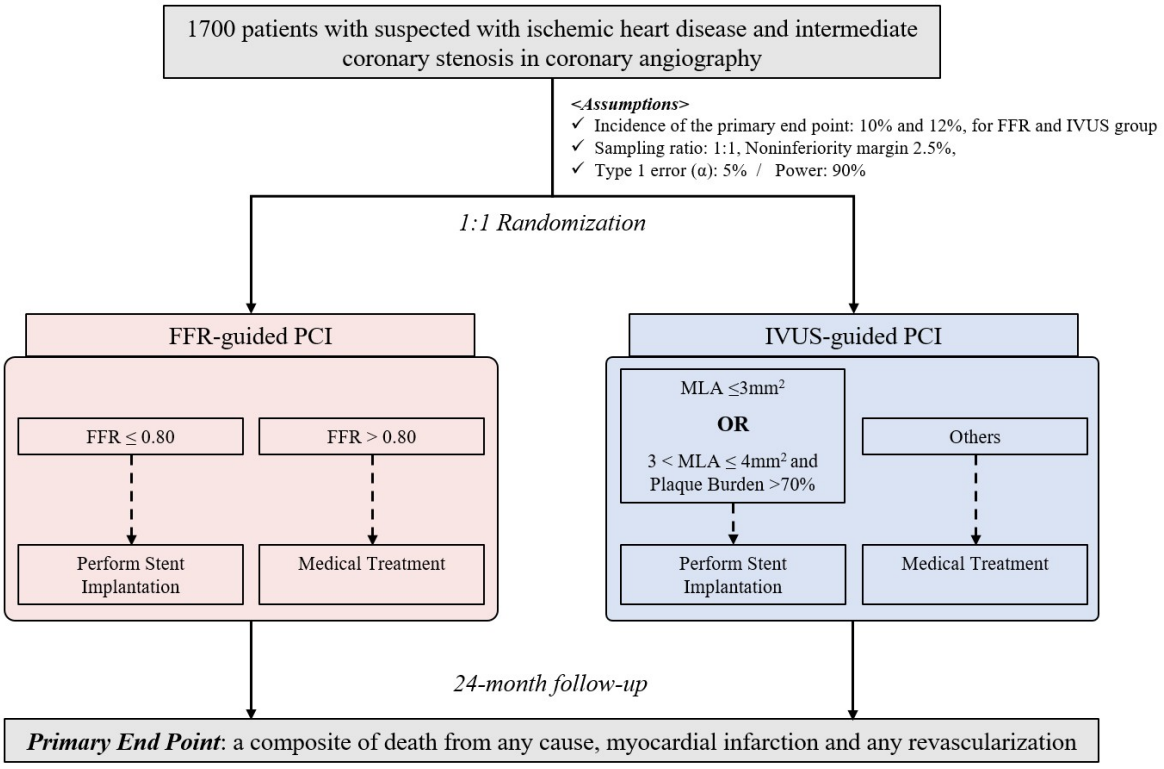
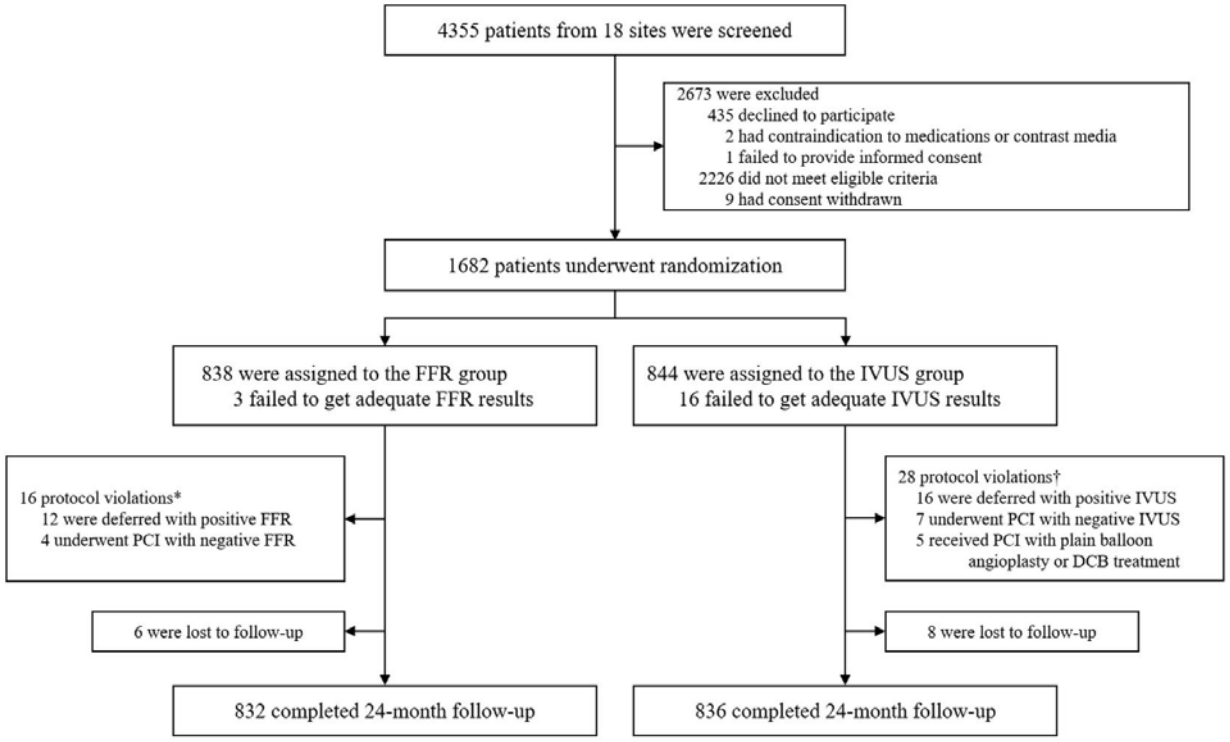


Figure Legend: The FLAVOUR was planned to enroll 1700 patients who were 19 years or older, suspected to have ischemic heart disease and showed de novo intermediate degree of stenosis (40-70% stenosis by visual estimation) at a target vessel size ≥ 2.5 mm by visual estimation on coronary angiography. Eligible patients were randomly assigned in a 1:1 ratio to receive FFR-guided PCI or IVUS-guided PCI. Clinical follow-up was performed up to 24 months after the randomization.

Abbreviations: FFR, fractional flow reserve; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention

Figure S2. Enrollment, Randomization, and Follow-up



Patients with an intermediate coronary stenosis identified by coronary angiography were eligible for enrollment. Patients were randomly assigned in a 1:1 ratio to receive FFR-guided PCI or IVUS-guided PCI. The primary end point was analyzed at the 24-month follow-up, in the intention-to-treat population which included all patients who underwent randomization.

* Protocol violation in the FFR group is defined as PCI performed in lesions with a FFR > 0.80, PCI deferred in lesions with FFR ≤ 0.80, or PCI performed without a drug-eluting stent (i.e. plain balloon angioplasty or DCB treatment).

† Protocol violation in the IVUS group is defined as PCI performed in lesions with MLA > 4mm^2

or [3 mm^2 < MLA ≤ 4mm^2 and plaque burden ≤ 70%], PCI deferred in lesions with MLA ≤ 3mm^2 or [3 mm^2 < MLA ≤ 4mm^2 and plaque burden > 70%], or PCI performed without a drug-eluting stent (i.e. plain balloon angioplasty or DCB treatment).

Abbreviations: DCB, drug coated balloon; FFR, fractional flow reserve; IVUS, intravascular ultrasound; MLA, minimal lumen area; PCI, percutaneous coronary intervention.

Figure S3. Subgroup analysis stratified by the presence of diabetes

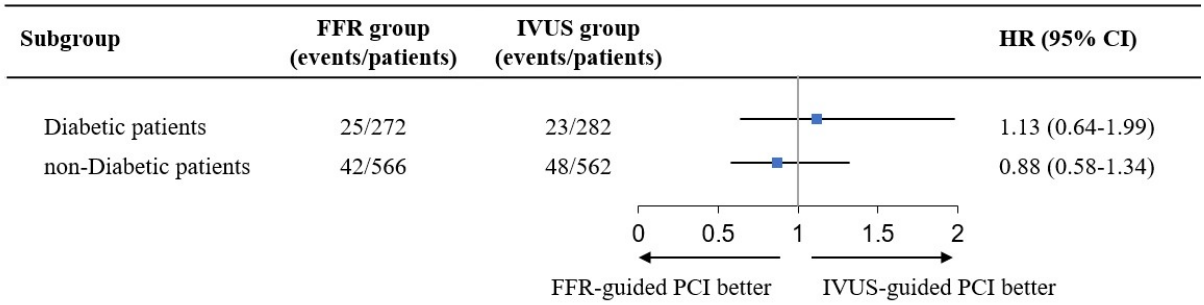
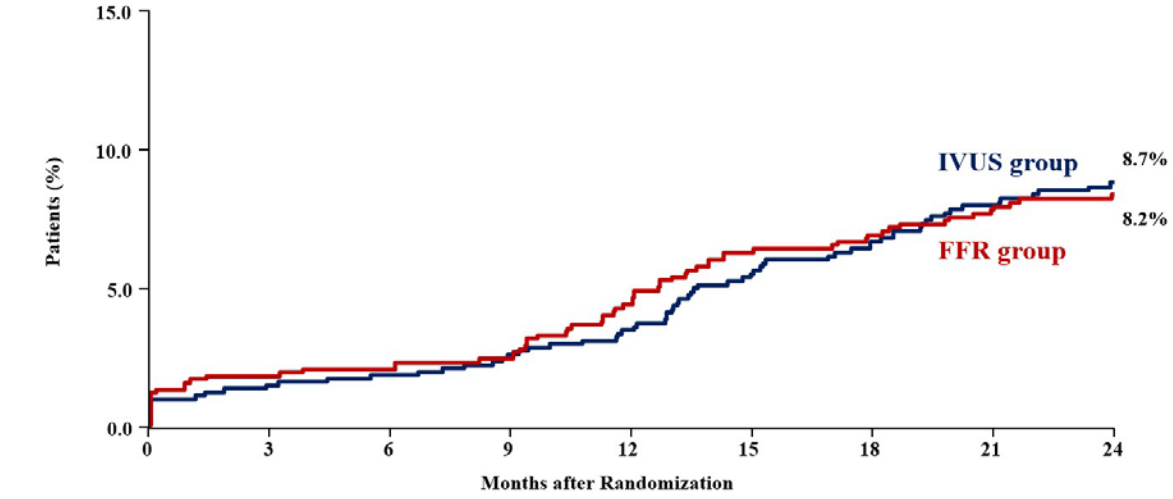


Figure Legend: The incidence of the primary end point (a composite of death from any cause, myocardial infarction, and any revascularization at 24 months after randomization) was compared in the subgroup stratified by the presence of diabetes. Results were similar in analyses stratified by the presence of diabetes.

Abbreviations: FFR, fractional flow reserve; IVUS, intravascular ultrasound

Figure S4. Per-protocol Analysis for 24-month Cumulative Incidence of the Primary End Point



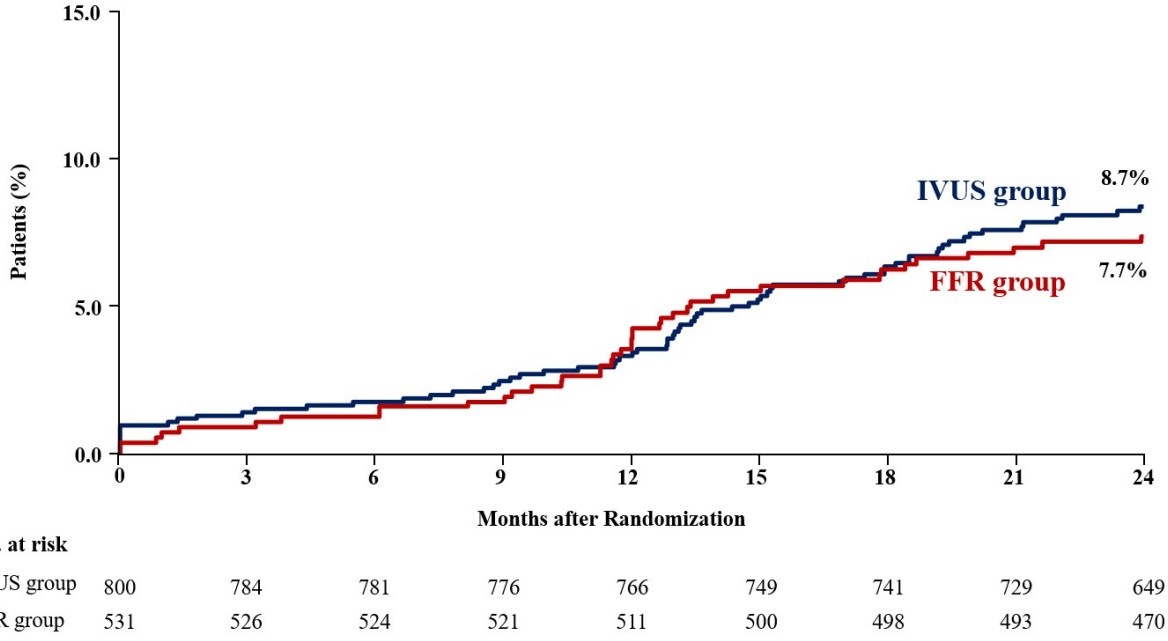
No. at risk									
IVUS group	800	784	781	776	766	749	741	729	649
FFR group	819	799	797	793	777	762	759	751	685

Figure Legend: The per-protocol analyses yielded similar results to the intention-to-treat a nalyses for the primary study end point.

Abbreviations: FFR, fractional flow reserve; IVUS, intravascular ultrasound

* The primary end point was a composite of death from any cause, myocardial infarction, and any revascularization at 24 months after randomization.

Figure S5. Post-hoc Analysis Excluding 288 Patients in Whom Nicorandil Was Used as the Hyperemic Agent for 24-month Cumulative Incidence of the Primary End Point



No. at risk									
IVUS group	800	784	781	776	766	749	741	729	649
FFR group	531	526	524	521	511	500	498	493	470

Figure Legend: The post-hoc analysis also yielded similar results to the intention-to-treat analyses for the primary study end point.

Abbreviations: FFR, fractional flow reserve; IVUS, intravascular ultrasound

* The primary end point was a composite of death from any cause, myocardial infarction, and any revascularization at 24 months after randomization.

12. Supplementary Tables

Table S1. List of the primary and all secondary outcomes

Outcomes	Included in the current study
Patient-oriented composite outcome (POCO, a composite of all death, myocardial infarction or any revascularization at 24 months)	Yes
POCO at 12months after randomization	Yes
Stent-oriented composite end point (a composite of cardiac death, target-vessel MI, or target lesion revascularization)	Yes
Cost-effectiveness	No
All-cause and cardiac death	Yes
Target-vessel and all-cause nonfatal MI without peri-procedural MI	Yes
Target-vessel and all-cause nonfatal MI with peri-procedural MI *	Yes
Periprocedural MI	Yes
Target vessel revascularization	Yes
Target lesion revascularization	Yes
Non-target vessel revascularization	Yes
Non-target lesion revascularization	Yes
Any revascularization	Yes
Stent thrombosis (definite/probable/possible)	Yes
Stroke (ischemic and hemorrhagic)	Yes
Acute device success of the procedure	Yes
Acute lesion success of the procedure	Yes
Acute procedural success of the procedure	Yes
Angina severity measured with Seattle Angina Questionnaires at 12-month	No
Angina severity measured with Seattle Angina Questionnaires at 24-month	Yes
Plaque characteristics by IVUS	No
QFR analysis	Yes

Table S2. Discharge medications

	Total	FFR-guided PCI	IVUS-guided PCI
All patients	N=1682	N=838	N=844
Aspirin, n (%)	1323 (78.7)	630 (75.2)	693 (82.1)
P2Y$_{12}$ inhibitor, n (%)	1383 (82.2)	653 (77.9)	730 (86.5)
DAPT, n (%)	1093 (65.0)	487 (58.1)	606 (71.8)
Statin, n (%)	1612 (95.8)	800 (95.5)	812 (96.2)
Beta blocker, n (%)	733 (43.6)	355 (42.4)	378 (44.8)
ACE inhibitor or ARB, n (%)	843 (50.1)	421 (50.2)	422 (50.0)
Calcium channel blocker, n (%)	563 (33.5)	278 (33.2)	285 (33.8)
Patients who received PCI	N=923	N=372	N=551
Aspirin, n (%)	903 (97.8)	361 (97.0)	542 (98.4)
P2Y$_{12}$ inhibitor, n (%)	915 (99.1)	367 (98.7)	548 (99.5)
DAPT, n (%)	898 (97.3)	358 (96.2)	540 (98.0)
Statin, n (%)	889 (96.3)	361 (97.0)	528 (95.8)
Beta blocker, n (%)	408 (44.2)	158 (42.5)	250 (45.4)
ACE inhibitor or ARB, n (%)	477 (51.7)	187 (50.3)	290 (52.6)
Calcium channel blocker, n (%)	287 (31.1)	111 (29.8)	176 (31.9)
Patients who received medical treatment	N=759	N=466	N=293
Aspirin, n (%)	420 (55.3)	269 (57.7)	151 (51.5)
P2Y$_{12}$ inhibitor, n (%)	468 (61.7)	286 (61.4)	182 (62.1)
DAPT, n (%)	195 (25.7)	129 (27.7)	66 (22.5)
Statin, n (%)	723 (95.3)	439 (94.2)	284 (96.9)
Beta blocker, n (%)	325 (42.8)	197 (42.3)	128 (43.7)
ACE inhibitor or ARB, n (%)	366 (48.2)	234 (50.2)	132 (45.1)
Calcium channel blocker, n (%)	276 (36.4)	167 (35.8)	109 (37.2)

Abbreviations: ACE, Angiotensin-converting enzyme; ARB, Angiotensin receptor blocker; DAPT, dual antiplatelet therapy

Table S3. Per-vessel Analysis of Target Vessel and Non-Target Vessel PCI During Index Procedure

	Total	FFR-guided PCI	IVUS-guided PCI
Target vessel	*n=1820*	*n=919*	*n=901*
Location			
- LAD, n (%)	1127 (61.9)	573 (62.4)	554 (61.5)
- LCX, n (%)	229 (12.6)	119 (12.9)	110 (12.2)
- RCA, n (%)	464 (25.5)	227 (24.7)	237 (26.3)
Lesion length, mm	20.3±10.6	20.1±10.3	20.5±11.0
Reference vessel diameter, mm	3.0±0.5	3.0±0.5	3.0±0.5
Minimum lumen diameter, mm	1.3±0.4	1.3±0.4	1.3±0.4
Target vessel PCI, n (%)	831 (45.7)	305 (33.2)	526 (58.4)
Non-target vessel	*n=583*	*n=291*	*n=292*
Location			
- LM, n (%)	21 (3.6)	8 (2.7)	13 (4.5)
- LAD, n (%)	186 (31.9)	94 (32.3)	92 (31.5)
- LCX, n (%)	207 (35.5)	107 (36.8)	100 (34.2)
- RCA, n (%)	169 (29.0)	82 (28.2)	87 (29.8)
Non-target vessel PCI, n (%)	319 (54.7)	144 (49.5)	175 (59.9)

Abbreviations: LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; PCI, percutaneous coronary intervention; RCA, right coronary artery

* Data presented as mean ± standard deviation or as n (%).

Table S4. Clinical Outcomes by Per-protocol Analysis

	Total (n=1619)	FFR-guided PCI (n=819)	IVUS-guided PCI (n=800)	Event-rate difference	95% Confidence Interval†
Primary end point					
Death from any cause, myocardial infarction, and any revascularization at 24 months	136 (8.5)	67 (8.2)	69 (8.7)	-0.5	-3.2 – 2.3
Secondary end point					
Death from any cause, myocardial infarction, and any revascularization at 12 months	62 (4.1)	38 (4.7)	28 (3.5)	1.2	-0.8 – 3.1
Death from cardiac cause, target vessel MI, or target lesion revascularization at 12 months	52 (3.2)	27 (3.3)	25 (3.2)	0.2	-1.6 – 1.9
Death from any cause	30 (1.9)	11 (1.4)	19 (2.4)	-1.0	-2.4 – 0.3
- Death from cardiac cause	18 (1.1)	7 (0.9)	11 (1.4)	-0.5	-1.6 – 0.5
- Death from non-cardiac cause	12 (0.8)	4 (0.5)	8 (1.0)	-0.5	-1.4 – 0.3
Myocardial infarction	29 (1.8)	16 (2.0)	13 (1.7)	0.3	-1.0 – 1.6
- Peri-procedural myocardial infarction‡	18 (1.1)	10 (1.2)	8 (1.0)	0.2	-0.8 – 1.2
- Spontaneous myocardial infarction	11 (0.7)	6 (0.7)	5 (0.7)	0.1	-0.7 – 0.9
- Target vessel myocardial infarction	5 (0.3)	3 (0.4)	2 (0.3)	0.1	-0.4 – 0.7
Stent thrombosis	2 (0.1)	1 (0.1)	1 (0.1)	0.0	-0.4 – 0.3
Revascularization	90 (5.7)	47 (5.8)	43 (5.5)	0.3	-1.9 – 2.6
- Ischemia driven revascularization	70 (4.4)	38 (4.7)	32 (4.1)	0.6	-1.4 – 2.7
- Target vessel revascularization	46 (2.9)	27 (3.3)	19 (2.4)	0.9	-0.7 – 2.6
- Target lesion revascularization	35 (2.2)	21 (2.6)	14 (1.8)	0.8	-0.6 – 2.3

- Non-target vessel revascularization	51 (3.2)	23 (2.9)	28 (3.6)	-0.7	-2.5 – 1.0
- Non-target lesion revascularization	64 (4.0)	31 (3.9)	33 (4.2)	-0.4	-2.3 – 1.6
Stroke	16 (1.0)	6 (0.7)	10 (1.3)	-0.5	-1.5 – 0.4

Abbreviations: FFR, fractional flow reserve; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention

* Data presented as n (%). Clinical end points were evaluated in the intention-to-treat population at 24 months after randomization. The percentages shown are Kaplan–Meier estimates.

† Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

‡ Peri-procedural myocardial infarction was defined as follows. Patients diagnosed as stable angina: CK-MB elevation >3 times upper limit of normal OR Troponin elevation that is >5 times the 99th percentile of diagnostic value for the specific institution AND the presence of, new pathological Q waves or new persistent non-rate related LBBB, symptoms of ischemia with ECG changes indicative of new ischemia, angiographic documentation of new coronary artery occlusion or dissection. Patients diagnosed as acute coronary syndrome: Peak CK-MB or Troponin has been reached OR a new elevation in CK-MB > 3 times upper limit of normal OR Troponin >5 times the 99 percentile AND the presence of, new pathological Q waves or new persistent non-rate related LBBB, symptoms of ischemia with ECG changes indicative of new ischemia, angiographic documentation of new coronary artery occlusion or dissection.

Table S5. Post-hoc Analysis of Clinical Outcomes Excluding 288 Patients in Whom Nicorandil Was Used as the Hyperemic Agent

	Total (n=1331)	FFR-guided PCI (n=531)	IVUS-guided PCI (n=800)	Event-rate difference	95% Confidence Interval†
Primary end point					
Death from any cause, myocardial infarction, and any revascularization at 24 months	110 (8.3)	41 (7.7)	69 (8.7)	-1.0	-4.0 – 2.0
Secondary end point					
Death from any cause, myocardial infarction, and any revascularization at 12 months	50 (3.8)	22 (4.1)	28 (3.5)	0.6	-1.5 – 2.8
Death from cardiac cause, target vessel MI, or target lesion revascularization at 12 months	36 (2.7)	11 (2.1)	25 (3.2)	-1.1	-2.8 – 0.6
Death from any cause	24 (1.8)	5 (0.9)	19 (2.4)	-1.5	-2.8 – -0.1
- Death from cardiac cause	14 (1.1)	3 (0.6)	11 (1.4)	-0.8	-1.9 – 0.2
- Death from non-cardiac cause	10 (0.8)	2 (0.4)	8 (1.0)	-0.6	-1.5 – 0.2
Myocardial infarction	19 (1.4)	6 (1.1)	13 (1.7)	-0.5	-1.8 – 0.7
- Peri-procedural myocardial infarction‡	10 (0.8)	2 (0.4)	8 (1.0)	-0.6	-1.5 – 0.2
- Spontaneous myocardial infarction	9 (0.7)	4 (0.8)	5 (0.7)	0.1	-0.8 – 1.0
- Target vessel myocardial infarction	5 (0.4)	3 (0.6)	2 (0.3)	0.3	-0.4 – 1.0
Stent thrombosis	2 (0.2)	1 (0.2)	1 (0.1)	0.1	-0.4 – 0.5
Revascularization	77 (5.9)	34 (6.4)	43 (5.5)	0.9	-1.7 – 3.6
- Ischemia driven revascularization	60 (4.5)	28 (5.3)	32 (4.1)	1.2	-1.1 – 3.6
- Target vessel revascularization	39 (3.0)	20 (3.8)	19 (2.4)	1.4	-0.6 – 3.3
- Target lesion revascularization	29 (2.2)	15 (2.8)	14 (1.8)	1.1	-0.6 – 2.7

- Non-target vessel revascularization	43 (3.3)	15 (2.9)	28 (3.6)	-0.7	-2.7 – 1.2
- Non-target lesion revascularization	53 (4.0)	20 (3.8)	33 (4.2)	-0.4	-2.6 – 1.7
Stroke	14 (1.1)	4 (0.8)	10 (1.3)	-0.5	-1.6 – 0.6

Abbreviations: FFR, fractional flow reserve; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention

* Data presented as n (%). Clinical end points were evaluated in the intention-to-treat population at 24 months after randomization. The percentages shown are Kaplan–Meier estimates.

† Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for secondary or other outcomes, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes.

‡ Peri-procedural myocardial infarction was defined as follows. Patients diagnosed as stable angina: CK-MB elevation >3 times upper limit of normal OR Troponin elevation that is >5 times the 99th percentile of diagnostic value for the specific institution AND the presence of, new pathological Q waves or new persistent non-rate related LBBB, symptoms of ischemia with ECG changes indicative of new ischemia, angiographic documentation of new coronary artery occlusion or dissection. Patients diagnosed as acute coronary syndrome: Peak CK-MB or Troponin has been reached OR a new elevation in CK-MB > 3 times upper limit of normal OR Troponin >5 times the 99 percentile AND the presence of, new pathological Q waves or new persistent non-rate related LBBB, symptoms of ischemia with ECG changes indicative of new ischemia, angiographic documentation of new coronary artery occlusion or dissection.

Table S6. Seattle Angina Questionnaire Analysis

	FFR-guided PCI	IVUS-guided PCI
Physical Limitation Domain		
Baseline	65±15	64±16
Final	67±14	66±14
Angina Stability Domain		
Baseline	52±21	51±22
Final	74±18	74±18
Angina Frequency Domain		
Baseline	80±16	80±16
Final	84±13	84±13
Treatment Satisfaction Domain		
Baseline	73±15	73±15
Final	72±11	73±11
Quality of Life Domain		
Baseline	58±17	57±17
Final	66±11	66±13
Total sum of the Seattle Angina Questionnaire		
Baseline	95±11	95±11
Final	100±9	100±10

Abbreviations: FFR, fractional flow reserve; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention

Table S7. Representativeness of Study Participants

Disease, problem, or condition under investigation	Participants who were suspected to have ischemic heart disease and showed de novo intermediate degree of stenosis (40-70% stenosis) at a target vessel size ≥ 2.5 mm by visual estimation on invasive coronary angiography
Special consideration related to	
Sex	The sex difference for the prevalence of coronary artery disease varies across age groups, while women less likely receive cardiovascular screening tests or optimal treatment for coronary artery disease[21]. In our study 70.6% of participants were male.
Age	Prevalence increases substantially with age; older patients often have more risk factors of cardiovascular disease[22,23]. Patients who were 19 years or older, with no upper limit of age were screened for our study.
Ethnicity	The study population was an East-Asian patient cohort. Asian patients have lower coronary artery disease prevalence than other racial and ethnic groups (non-Hispanic White, African American, Hispanic populations)[24].
Geography	Participants were from two countries: China and Korea.
Other considerations	Socioeconomic status influences the access to cardiac evaluation and treatment.

Overall representativeness of this trial	The participants in the FLAVOUR trial were predominantly male patients, which was collected from self-report. Only biologic sex was reported. Other baseline demographic characteristics, such as age, underlying diabetes, hypertension, chronic renal failure, prior myocardial infarction and prior myocardial infarction were similar with previous studies. The FLAVOUR enrolled patients from 18 sites in two countries in Asia: China and Korea. We did not include centers from other countries.

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