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# Rationale and design of a comparison of angiography-derived fractional flow reserve-guided and intravascular ultrasound-guided intervention strategy for clinical outcomes in patients with coronary artery disease: a randomised controlled trial (FLAVOUR II)

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## ABSTRACT

**Introduction** Percutaneous coronary intervention (PCI) guided by coronary angiography-derived fractional flow reserve (FFR) or intravascular ultrasound (IVUS) has shown improved clinical outcomes compared with angiography-only-guided PCI. In patients with intermediate stenoses, FFR resulted in fewer coronary interventions and was non-inferior to IVUS with respect to clinical outcomes. However, whether this finding can be applied to angiography-derived FFR in significant coronary artery disease (CAD) remains unclear.

**Method and analysis** The comparison of angiography-derived FFR-guided and IVUS-guided intervention strategies for clinical outcomes in patients with coronary artery disease (FLAVOUR II) trial is a multicentre, prospective, randomised controlled trial. A total of 1872 patients with angiographically significant CAD (stenoses of at least 50% as estimated visually through angiography) in a major epicardial coronary artery will be randomised 1:1 to receive either angiography-derived FFR-guided or IVUS-guided PCI. Patients will be treated with second-generation drug-eluting stent according to the predefined criteria for revascularisation: angiography-derived FFR≤0.8 and minimal lumen area (MLA)≤3 $mm^2$ or 3 $mm^2$<MLA≤4 $mm^2$ and plaque burden>70%. The primary endpoint is a composite of all-cause death, myocardial infarction and revascularisation at 12 months after randomisation. We will test the non-inferiority of the angiography-derived FFR-guided strategy compared with the IVUS-guided decision for PCI and the stent optimisation strategy. The FLAVOUR II trial will provide new insights into optimal evaluation and treatment strategies for patients with CAD.

**Ethics and dissemination** FLAVOUR II was approved by the institutional review board at each participating site (The Second Affiliated Hospital of Zhejiang University School of Medicine Approval No: 2020LSYD410) and will be conducted in line with the Declaration of Helsinki. Informed consent would be obtained from each patient before their participation. The study results will be submitted to a scientific journal.

**Trial registration number** NCT04397211.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This trial is the first randomised controlled trial to compare angiography-derived fractional flow reserve (FFR) and intravascular ultrasound (IVUS) as strategies for the management of coronary artery disease (CAD) and, thus, will provide the highest level of evidence.
⇒ This trial is a comparative effectiveness research that compares not only 'physiology' with 'imaging' but also 'non-invasive' with 'invasive' techniques, which could provide new insights into optimal evaluation and treatment strategies for patients with CAD.
⇒ Should the event rate of the primary outcome be unexpectedly low, the non-inferiority margin of 2.5% may be considered to be relatively wide.
⇒ The open-label trial design allows operating physicians to be aware of the allocated group (angiography-derived FFR or IVUS) that may lead to bias.
⇒ Patients of non-Asian races were not included in our trial. Future studies will need to include patients of diverse races and ethnic backgrounds to demonstrate the generalisability of findings.

## INTRODUCTION

Intravascular ultrasound (IVUS) is an adjunctive technique that can improve procedural quality and provide a better percutaneous coronary intervention (PCI) result by optimising revascularisation in the catheter laboratory.[1] Several clinical studies and meta-analyses have shown that an IVUS-guided PCI strategy could reduce the incidence of major clinical events after stent implantation.[2–5] Nevertheless, with a lack of flow-relevant information, IVUS cannot accurately define ischaemia-causing stenoses. In contrast, physiological assessment is more effective in detecting ischaemia and can be used to guide decisions regarding the need for PCI.[6–9] A recent randomised clinical trial demonstrated that the fractional flow reserve (FFR)-guided PCI strategy was non-inferior to IVUS-guided PCI in patients with intermediate stenoses with respect to the composite of all deaths, myocardial infarction (MI) and revascularisation at 2 years with fewer stents.[10 11]

Currently, advances in computer science have enabled the estimation of coronary physiologic status through the use of computational fluid dynamics, which is based on three-dimensional angiographic reconstruction.[12–17] Angiography-derived FFR is a non-invasive method to calculate a physiologic index from angiogram without the use of pressure wire and hyperaemic medications. Quantitative flow ratio (QFR), an angiography-derived FFR, has an excellent diagnostic performance compared with invasive FFR[13–17] and a superiority in clinical outcomes compared with angiography-guided PCI at 1 year, as shown in a randomised clinical trial.[9]

Both IVUS and angiography-derived FFR have been shown to result in fewer adverse clinical outcomes compared with angiography-guided PCI.[3 9] An outcome-based clinical trial has not been performed to establish whether the non-inferior result of physiology-guided PCI strategy could be maintained in cases of more severe stenoses and when using a non-invasive computational physiologic index instead. Therefore, the aim of our trial is to compare the angiography-derived FFR-guided PCI strategy with the IVUS-guided PCI strategy in terms of adverse clinical outcomes among patients with angiographically significant stenoses.

## METHODS AND ANALYSIS

### Study objectives and hypothesis

The primary objective of this study is to compare the clinical outcomes, safety and efficacy of angiography-derived FFR-guided PCI with IVUS-guided PCI in patients with coronary artery disease (CAD). The working hypothesis of this study is that the angiography-derived FFR-guided PCI strategy will show a non-inferior rate of patient-oriented composite outcome (POCO) at 12 months compared with IVUS-guided PCI in patients with angiographically significant stenoses. POCO is defined as a composite of death from any cause, MI and revascularisation at 12 months.[18]

### Study organisations

In total, 23 centres from China and Korea will participate in this trial including The Second Affiliated Hospital of Zhejiang University School of Medicine (China), Seoul National University Hospital (Korea), Affiliated Hangzhou First People's Hospital (China), Zhongnan Hospital of Wuhan University (China), Peking University Third Hospital (China), The Affiliated Hospital of Hangzhou Normal University (China), Renji Hospital Shanghai Jiaotong University School of Medicine (China), Second Hospital of Shanxi Medical University (China), The First Affiliated Hospital of Wenzhou Medical University (China), The Second Affiliated Hospital of Wenzhou Medical University (China), Changxing People's Hospital (China), The Affiliated Hospital of Medical School of Ningbo University (China), Huzhou Central Hospital (China), Jinhua Central Hospital (China), The Affiliated Hospital of Shandong University of TCM (China), The Fourth People's Hospital of Jinan (China), Dongyang People's Hospital (China), The First Affiliated Hospital of Nanchang University (China), Zhejiang Greentown Cardiovascular Hospital (China), Jining No.1 People's Hospital (China), The Second Affiliated Hospital of Shantou University Medical College (China), First Affiliated Hospital of Kunming Medical University (China), Zhejiang Hospital (China) and Ulsan University Hospital (Korea). The FLAVOUR II trial protocol has been registered at http://clinicaltrals.gov (NCT04397211).

### Study design

The FLAVOUR II trial is a prospective, open-label, multicentre, randomised controlled trial investigating the clinical outcomes, safety and efficacy of an angiography-derived FFR-guided PCI strategy in patients with significant CAD (figure 1). Patients with stenoses in the major epicardial coronary artery with a diameter≥50%, as estimated visually through angiography and without any exclusion criteria, will be randomised 1:1 to receive either angiography-derived FFR-guided or IVUS-guided PCI. Target lesion PCI will be performed using second-generation drug eluting stent according to predefined criteria (angiography-derived FFR≤0.8; IVUS minimal lumen area (MLA)≤3 $mm^2$ or 3 $mm^2$<MLA≤4 $mm^2$ and plaque burden>70%).

For patients with multivessel disease, revascularisation of non-study target lesions can be performed at the discretion of the operator. In addition, the use of IVUS or angiography-derived FFR as per the assigned group will be allowed as a means of PCI optimisation. The treatment strategy may be altered in case of unsuccessful device passage or inadequate data retrieval for any reason.

### Study population and entry criteria

Patients with suspected CAD and stenoses with a diameter of at least 50% as estimated through angiography will be screened for enrolment in this study. After an independent research team reviews the patients'

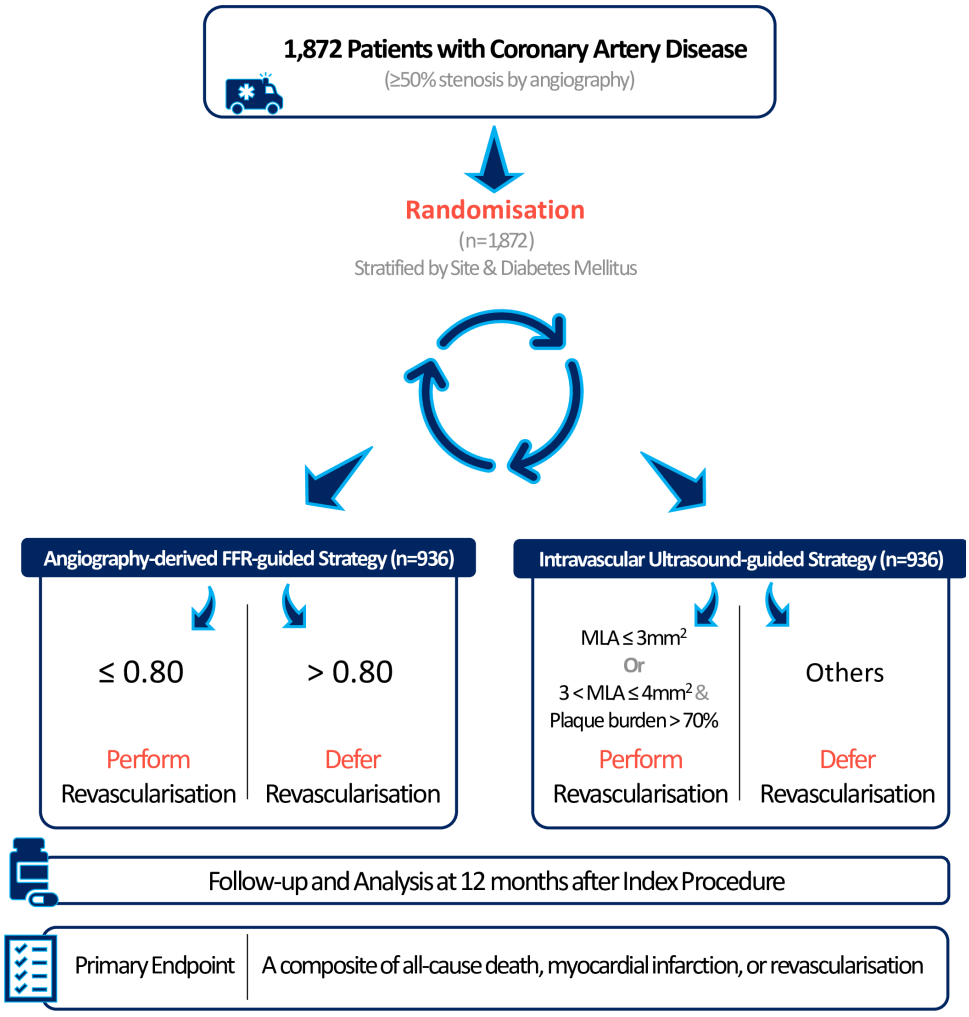


**Figure 1** Study diagram of FLAVOUR II trial. FFR, fractional flow reserve; MLA, minimal lumen area.

medical history to determine eligibility, patients who meet all inclusion criteria without exclusion criteria will provide written informed consent. The study details shall be explained before collecting the patients' data, including (1) FLAVOUR II represents a phase IV clinical trial; (2) participation is voluntary, and there is no penalty for withdrawal; and (3) the potential risks, benefits and other information. Box 1 presents the inclusion and exclusion criteria for this study. Randomisation will be performed using a web-based randomisation programme by an independent organisation (S-Soft), and stratified by participating centres and diabetes mellitus. Study participants will have the right to withdraw from the study at any time and for any reason.

## Research materials, PCI and its optimisation

For the angiography-derived FFR-guided strategy arm, an imaging-based FFR (QFR or Murray law-based QFR (μQFR)) will be used, and the criterion for PCI is QFR or μQFR≤0.8.[9 19 20] Briefly, μQFR, an upgraded technique, is able to compute FFR from a single angiographic view with incorporating Murray bifurcation fractal law. Its diagnostic performance and clinical implications were demonstrated previously.[19–22] In the catheterisation laboratory, one single operator will perform angiography-derived FFR measurement.

For the IVUS-guided strategy arm, the criterion for PCI is an MLA≤3 $mm^2$ or 3 $mm^2$<MLA≤4 $mm^2$ and plaque burden>70%. These criteria are based on previous studies.[10 11 23–25] Optimisation goals for each group are presented in table 1.[10 11 26–30] The IVUS images will also be analysed by one onsite operator.

An independent core laboratory analysis will be performed for each part of the raw data. Quantitative coronary angiography (QCA) will be analysed in a blinded fashion at the QCA core laboratory of Seoul National University Hospital Cardiovascular Centre, the IVUS raw data will be analysed in a blinded fashion at the imaging core laboratory of Ulsan University Hospital and the angiography-derived FFR or three-dimensional angiography analysis will be performed at CardHemo core lab, Med-X Research Institute, Shanghai Jiao Tong University.

## Study endpoints and their analysis

The analysis of the primary endpoint will be performed on an intention-to-treat (ITT) basis first and then on a per-protocol

**Box 1 Inclusion and exclusion criteria**

Inclusion criteria
1. Subject must be ≥18 years of age.
2. Subject is able to verbally confirm understanding of risks, benefits and treatment alternatives of receiving invasive physiologic or imaging evaluation and PCI with a DES and he/she or his/her legally authorised representative provides written informed consent prior to any study-related procedure.
3. Patients suspected of having ischaemic heart disease.
4. Patients with ≥50% stenoses by angiography-based visual estimation eligible for stent implantation.
5. Target vessel size≥2.5 mm in visual estimation.
6. Target vessels are limited to major epicardial coronary arteries (LAD, LCX, RCA).

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 (eg, 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 thrombocytopaenia).
5. Non-cardiac comorbid conditions with life expectancy<1 year.
6. Total occlusion of the target vessel.
7. Target lesion located in coronary arterial bypass graft.
8. Left main coronary artery stenoses≥50% (when the target lesion located in the left coronary artery).
9. Not eligible for angiography-derived FFR (ostial RCA>50% stenoses, myocardial bridging, severe tortuosity, severe overlap, poor image quality etc).

DES, drug-eluting stent; FFR, fractional flow reserve; LAD, left anterior descending artery; LCX, left circumflex artery; PCI, percutaneous coronary intervention; RCA, right coronary artery.

**Box 2 Endpoints**

Primary endpoint
POCO, defined as a composite of all death, MI (including periprocedural MI) or any revascularisation at 12 months after randomisation.

Secondary endpoints
1. POCO at 24 and 60 months after randomisation.
2. Target vessel failure (a composite of cardiac death, target vessel MI or target vessel revascularisation).
3. Cost-effectiveness analysis.
4. All-cause and cardiac death.
5. Any non-fatal MI without periprocedural MI.
6. Any non-fatal MI with periprocedural MI.
7. Any target vessel/lesion revascularisation.
8. Any non-target vessel/lesion revascularisation.
9. Any revascularisation (ischaemia driven or all).
10. Stent thrombosis (definite/probable/possible).
11. Stroke.
12. Acute success of procedure and rate of PCI optimisation.

ARC, Academic Research Consortium; MI, myocardial infarction; PCI, percutaneous coronary intervention; POCO, patient-oriented composite outcome;

basis. The secondary endpoints will be analysed for both groups. The end points are presented in box 2.

## Follow-up

Clinical follow-up will occur at 1, 12, 24 and 60 months during clinical visits or via telephone. The data collection schedule is presented in table 2. The physicians responsible for clinical follow-up will be blinded to the allocated strategy.

## Ethics and dissemination

The trial was conducted according to the standards specified in the International Council for Harmonisation of Technical Requirements for Good Clinical Practice and the principles of the Declaration of Helsinki. Ethical approval for this study was obtained from the institutional review board at each participating site (The Second Affiliated Hospital of Zhejiang University School of Medicine Approval No: 2020LSYD410). This study will be conducted in compliance with applicable local and country regulatory requirements. All the patients provided informed consent before randomisation.

The study results will be submitted to an international scientific journal. The findings will also be disseminated through relevant international conferences and will be used for further research and technology development.

**Table 1** Percutaneous coronary intervention optimisation criteria

| Group | Criteria for PCI optimisation |
|---|---|
| IVUS-guided PCI group | Plaque burden at stent edge≤55% and minimal stent area≥5.5 $mm^2$<br>Or<br>Plaque burden at stent edge≤55% and minimal stent area≥distal reference lumen area |
| Angiography-derived FFR-guided PCI group | Post-PCI angiography-derived FFR≥0.88<br>Or<br>Post-PCI delta angiography-derived FFR ((angiography-derived FFR at stent distal edge)–(angiography-derived FFR at stent proximal edge))<0.05 |

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

**Table 2** Data collection

| | Baseline | | Follow-up | | | | |
|---|---|---|---|---|---|---|---|
| | Pre-PCI | Post-PCI | 3 months ± 30 days | 6 months ± 30 days | 12 months ± 90 days | 24 months ± 90 days | 60 months ± 90 days |
| Medical/clinical/ history (age, sex, risk factors, clinical dx, angina status, cardiac history) | O | | | | | | |
| Informed consent | O | | | | | | |
| Inclusion/exclusion criteria | O | | | | | | |
| Brief physical examination | O | | | | | | |
| Vital status | O | | § | § | § | § | § |
| Weight, height | O | | | | | | |
| 12 lead ECG* | O | O | | | | | |
| Angiogram* | O | O | | | | | |
| Angiography-derived FFR raw data† | O | O | | | | | |
| IVUS-imaging raw data† | O | O | | | | | |
| Invasive FFR-tracing raw data† | § | § | | | | | |
| Procedure time | | O | | | | | |
| CBC | O | | | | | | |
| Electrolytes, LFT | O | | | | | | |
| Creatinine, BUN | O | | § | § | § | § | § |
| Fasting plasma TG, HDL, total cholesterol, LDL | O | | § | § | § | § | § |
| Fasting glucose level | O | | § | § | § | § | § |
| HbA1C (only in diabetic patients) | O | | § | § | § | § | § |
| Medications‡ | O | O | O | O | O | O | O |
| CK, CK-MB, Troponin I or Troponin T¶ | O | O | | | | | |

*There will be no mandatory angiographic follow-up. There will be no mandatory laboratory follow-ups.
†QCA will be analysed in the core laboratory of Seoul National University Hospital. Raw IVUS imaging data will be analysed in the core laboratory of Ulsan University Hospital. Angiography-derived FFR or three-dimensional angiography analysis will be performed at the core laboratory of Pulse Medical Imaging Technology. Postprocedural data will be collected if PCI is performed.
‡Medication data included medication at baseline (before admission) and after discharge.
§Not mandatory but recommended tests.
¶Postprocedural cardiac enzyme (CK, CK-MB or Troponin I (or Troponin T)) measurement is mandatory to assess periprocedural myocardial infarction in patients undergoing PCI.
BUN, blood urea nitrogen; CBC, complete blood count; CK, creatine kinase; CK-MB, creatine kinase MB; FFR, fractional flow reserve; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; IVUS, intravascular ultrasound; LDL, low-density lipoprotein; LFT, liver function test; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; TG, triglyceride.

## Data confidentiality

All parties will maintain the confidentiality of protected health information throughout the clinical trial. All data will be secured against unauthorised access. Study participants shall be assigned a unique coded identifier on the electronic case report forms, and the data will be protected in locked cabinets at the clinical centres with the use of passwords, encryption and secure storage. Specific issues of confidentiality and privacy are outlined in the informed consent form.

## Data safety and monitoring board (DSMB)

The accumulated data safety and coordinating manager visits will be monitored by the DSMB. A designated trial monitor could review data for both safety purposes and compliance with hospital records. The DSMB will also

monitor protocol compliance, adverse events and all documents and records maintained by each investigator or site, including the participants' medical records. To ensure participant safety, all cumulative safety data will be reported to the DSMB on an ongoing basis throughout enrolment and follow-up periods. In the case of any safety issues, the DSMB might recommend that the steering committee modify or stop the study. Nevertheless, all final decisions will be made by the steering committee. The DSMB reports will remain strictly confidential and available to the regulatory body on request.

### Clinical event adjudication committee (CEAC)

The CEAC is made up of cardiologists and epidemiologists who are not involved in the study and are blinded to the allocation group of the participants. CEAC adjudicates all clinical events and is responsible for the judgement and categorisation of clinical events.

## STATISTICAL CONSIDERATIONS

### Sample size calculations

Based on previous trials, we expect the rate of POCO at 12 months after randomisation to be 7.0% in the angiography-derived FFR-guided arm[31 32] and 8.0% in the IVUS-guided arm.[3 33 34] We calculated that a sample size of 1872 patients would provide 80% power to test the hypothesis that angiography-derived FFR-guided PCI is non-inferior to IVUS-guided PCI with respect to the primary endpoint. The non-inferiority margin of the event rate is 2.5%[10 11] at a one-sided type I error rate of 2.5%.

### Analysis

All endpoints will be analysed on an ITT and per-protocol basis. The per-protocol analysis will be performed as an exploratory and sensitivity analysis of the ITT. ITT analysis will be performed with all patients who signed the written informed consent form and randomised in the study, regardless of the actual assessment and treatment. The per-protocol is defined as the analysis performed with those who do not violate the protocol. Table 3 presents the statistical methods that we intend to employ for the analysis of both primary and secondary outcomes.

The R programming V.4.1.2 (R Foundation, Vienna, Austria) and the IBM SPSS V.23.0 statistics programme will be used for all analysis.

## DISCUSSION

PCI is currently the standard treatment for CAD. However, owing to the increased population of CAD and the complexity of lesions treated with PCI, adverse effects after treatment remain a major issue. IVUS-guided PCI strategy is a method that can provide additional information about PCI appropriateness including detailed three-dimensional geometry, plaque characteristics and their distributions.[1 23 35] Moreover, it could optimise revascularisation by providing information for sizing the appropriate stent and minimising stent-related problems, especially in complex PCI.[1] Hong *et al* reported that IVUS guidance has been proven to improve clinical outcomes in comparison with angiography-guided PCI.[3] Moreover, one meta-analysis study conducted by Jang *et al* in over 25 000 patients reported that IVUS-guided PCI is associated with lower rates of clinical events compared with angiography-guided PCI (OR: 0.79; 95% CI: 0.69 to 091; p=0.001).[26] In another recent meta-analysis, Buccheri *et al* have included over 15 000 patients, and consistently demonstrated that IVUS can reduce the risk of death (OR: 0.74; 95% credible interval (CrI): 0.58 to 0.98), MI (OR: 0.72; 95% CrI: 0.52 to 0.93), target lesion revascularisation (OR: 0.74; 95% CrI: 0.58 to 0.90) and stent thrombosis (OR: 0.42; 95% CrI 0.20 to 0.72).[2] These studies have demonstrated the benefits of an IVUS-guided revascularisation strategy.

Coronary physiological assessment has been regarded as the gold standard for detecting ischaemia-causing stenoses in catheterisation laboratories. Several randomised controlled trials have demonstrated improved clinical outcomes when using physiologic assessment to guide PCI.[6 8 9 36–39] Recently, coronary angiography-derived FFR, which relies on creating a three-dimensional reconstruction and computational fluid dynamics, has become a new method for measuring FFR without a pressure wire or hyperaemic agent. Several studies have shown its excellence in diagnostic performance using FFR as a reference standard, with a classification agreement of up to 90%.[12–17] Moreover, a recent clinical trial, which enrolled more than 3800 patients, reported that the angiography-derived FFR-guided strategy improved 1-year outcomes compared with the standard angiography guidance.[9]

Despite the proven advantages of IVUS and angiography-derived FFR, there has been no randomised study to compare the outcomes of IVUS-guided strategies, incorporating precise guidance and optimisation, versus angiography-derived FFR-guided strategies, incorporating non-invasive virtual computation and coronary physiology, for angiographically significant stenoses. A randomised clinical trial, FFR-guided and IVUS-guided intervention strategy for clinical outcomes in patients with intermediate stenosis (FLAVOUR), which compared IVUS-guided and FFR-guided PCI strategies in 1682 patients, showed that the FFR-guided PCI strategy was non-inferior compared with the IVUS-guided PCI strategy, and the FFR group received remarkably fewer stents than the IVUS group.[11] This study compared two invasive tools in patients with intermediate stenoses in which the physiologic assessment is more effective based on the ability to detect ischaemia-causing stenoses as a PCI candidate. Meanwhile, the comparison showed a significantly different PCI rate and number of stents between the two groups. Nevertheless, the impact of physiological assessment and imaging could differ in patients with significant stenoses, where imaging guidance tends to be more effective as the decision-making for PCI becomes

Table 3 Statistical methods

| Primary endpoint | Statistical methods | Time points of analysis |
|---|---|---|
| Patient-oriented composite outcome | Kaplan-Meier survival estimates and log-rank tests<br>$\chi^2$ test | 12 months after randomisation |
| **Secondary endpoint** | **Statistical methods** | **Time points of analysis** |
| Patient-oriented composite outcome | Kaplan-Meier survival estimates and log-rank tests | 24 and 60 months after randomisation |
| Cost-effectiveness | T-test | 12, 24 and 60 months after randomisation |
| Target vessel failure (a composite of cardiac death, target vessel MI or target vessel revascularisation) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 12, 24 and 60 months after randomisation |
| All-cause and cardiac death | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 12, 24 and 60 months after randomisation |
| Any non-fatal MI without periprocedural MI | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 12, 24 and 60 months after randomisation |
| Any non-fatal MI with periprocedural MI | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 12, 24 and 60 months after randomisation |
| Any target vessel/lesion revascularisation | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 12, 24 and 60 months after randomisation |
| Any non-target vessel/lesion revascularisation | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 12, 24 and 60 months after randomisation |
| Any revascularisation (ischaemia-driven or all) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 12, 24 and 60 months after randomisation |
| Stent thrombosis (definite/probable/possible) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 12, 24 and 60 months after randomisation |
| Stroke (ischaemic and haemorrhagic) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 12, 24 and 60 months after randomisation |
| Acute success of procedure and rate of PCI optimisation | $\chi^2$-test | At discharge (1 week after index procedure) |

MI, myocardial infarction; PCI, percutaneous coronary intervention.

less crucial, but the guidance of the procedure and optimisation becomes a more critical concern.

Thus, we planned a non-inferiority design based on the following rationale. Both IVUS-guided and angiography-derived FFR-guided PCI strategies have shown benefits over angiography-guided PCI in terms of clinical events.[3 9] Although physiological assessment showed non-inferiority in the intermediate lesions,[11] IVUS could be relatively more effective based on the guidance of the procedure and optimisation in angiographically significant lesions. Additionally, after non-inferiority is proven by rejecting the null hypothesis, the secondary endpoint, including stent number per patient (per vessel) and cost-effectiveness, will be analysed. Angiography-derived FFR, a non-invasive computational technology without any additional procedure, will prove to be non-inferior in terms of clinical outcomes at 1 year with fewer medical resources.

This is the first randomised controlled trial to compare angiography-derived FFR and IVUS as strategies for the management of patients with angiographically significant stenoses. In FLAVOUR II, we will be able to assess the safety and efficacy of a new imaging-derived coronary physiology and a standard imaging technique. It is a comparative effectiveness research that compares not only 'physiology' with 'imaging', but also 'non-invasive' with 'invasive' techniques.

## Trial status

FLAVOUR II is currently ongoing, and patient recruitment was completed on 20 September 2023.

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**Contributors** JZ and XH contributed to the conception and design of the work and drafting the work; and provided final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JJ, DL, LG, XP, YP, WH, JL, HZ, JH, FJ, JP, ZC, BY, JM, PC, QL, DS, LL, SL, YF, ZM, LT, E-SS and ST contributed to the acquisition of data for the work and revising it critically for important intellectual content; and provided final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. B-KK and JW contributed to the conception and design of the work and revising it critically for important intellectual content; and provided final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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