# Protocol

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

# Contents

Original Protocol

# Comparison of Clinical Outcomes between Imaging and Physiology-guided Intervention Strategy in Patients with Intermediate Stenosis

## **F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis

## (FLAVOUR)

## Version No: 3.0

**Cardiovascular Center & Clinical Research Center,**

**Seoul National University Hospital**

**Principal investigator: Bon-Kwon Koo**

# Research Summary

| | |
|---|---|
| Trial name and number | **Comparison of Clinical Outcomes between Imaging and Physiology-guided Intervention Strategy in Patients with Intermediate Stenosis**<br>**F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis **(FLAVOUR)** |
| Principal investigator | Bon-Kwon Koo, Seoul National University Hospital, Seoul, Korea |
| Funding agencies | Boston Scientific & St Jude Medical |
| Objectives | To compare the safety and efficacy of physiology (fractional flow reserve [FFR])-guided percutaneous coronary intervention (PCI) strategy with imaging (intravascular ultrasound [IVUS])-guided PCI strategy in patients with intermediate coronary stenosis. |
| Study design | Prospective, open-label, randomized, multicenter trial to test the safety and efficacy of physiology- or imaging-guided PCI in patients with intermediate coronary stenosis. |
| Patient enrollment | 1,300 patients enrolled at 9 centers in Republic of Korea and China |
| Study Period | From the 'IRB approval date of each participating center' to 2021.12.31 |
| Eligible criteria | (1) Inclusion Criteria<br>① Subject must be ≥ 18 years<br>② Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving invasive physiologic or imaging evaluation and PCI with a drug-eluting stent (DES) and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure.<br>③ Patients suspected with ischemic heart disease<br>④ Patients with intermediate degree of stenosis (40-70% stenosis by visual estimation) eligible for stent implantation who need FFR or IVUS clinically for further evaluation<br>⑤ Target vessel size > 2.5mm in visual estimation<br>(2) Exclusion Criteria<br>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.)<br>② Patients with active pathologic bleeding<br>③ Gastrointestinal or genitourinary major bleeding within the prior 3 months.<br>④ History of bleeding diathesis, known coagulopathy (including heparin-induced thrombocytopenia)<br>⑤ Non-cardiac co-morbid conditions are present with life expectancy <1 year or |

| | |
|---|---|
| | that may result in protocol non-compliance (per site investigator's medical judgment).<br>⑥ Target lesion located in coronary arterial bypass graft<br>⑦ Target lesion located in the left-main coronary artery |
| Patient follow-up | Clinical follow-up will occur at 1, 12, 24 months after the procedure. Investigator or designee may conduct follow-up as telephone contacts or office visits. |
| Primary endpoint | Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction (MI) or any repeat revascularization at 24 months after randomization according to the ARC consensus |
| Secondary endpoint | ① POCO at 12months after randomization according to the ARC consensus<br>② Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)<br>③ All-cause and cardiac death<br>④ Target-vessel and all-cause nonfatal MI without peri-procedural MI<br>⑤ Target-vessel and all-cause nonfatal MI with peri-procedural MI<br>⑥ Target vessel/lesion revascularization (ischemia-driven or all)<br>⑦ Non-target vessel/lesion revascularization (ischemia-driven or all)<br>⑧ Any revascularization (ischemia-driven or all)<br>⑨ Stent thrombosis (definite/probable/possible)<br>⑩ Stroke (ischemic and hemorrhagic)<br>⑪ Acute success of procedure (device, lesion and procedure)<br>⑫ Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month |

# Research Proposal

**1. Title of Study**

**Comparison of Clinical Outcomes between Imaging and Physiology-guided Intervention Strategy in Patients with Intermediate Stenosis: F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis **(FLAVOUR)**

**2. Clinical Research Center**

(1) Seoul National University Hospital

101, Daehak-ro, Jongno-gu, Seoul, Korea

(2) Ajou University Hospital

164 World Cup-ro, Yeongtong-gu, Suwon, Korea

(3) Inje University Ilsan Paik Hospital,

170 Juhwa-ro, Ilsanseo-gu,Goyang, Korea

(4) Ulsan University Hospital, University of Ulsan College of Medicine

877 Bangeojinsunhwando-ro, Dong-gu, Ulsan, Korea

(5) Keimyung University Dongsan Medical Center

56 Dalseong-Ro, Jung-Gu, Daegu, Korea

(6) Second Affiliated Hospital of Zhejiang University School of Medicine

88 Jiefang Road, Hangzhou, Zhejiang, China

(7) The General Hospital of Shenyang Military

No.83 Cultural Road Shenhe District Shenyang City

(8) The 2nd Affiliated Hospital of Wenzhou Medical University

109 Xueyuan West Road, Wenzhou, Zhejiang

(9) Ningbo First Hospital

59 Liu ting street, Ningbo, Zhejiang

**3. Principal Investigator, Staff, Co-researchers**

| | Name | Center | Position |
|---|---|---|---|
| Principal investigator | Bon-Kwon Koo | Seoul National University Hospital | Professor |
| Principal investigator | Seung-Jea Tahk | Ajou University Hospital | Professor |
| Principal investigator | JianAn Wang | Second Affiliated Hospital of Zhejiang University School of Medicine | Professor |
| Staff | Joo Myung Lee | Seoul National University Hospital | Clinical Fellow |
| | Jeehoon Kang | Seoul National University Hospital | Clinical Fellow |
| | Jonghanne Park | Seoul National University Hospital | Resident |
| | Doyeon Hwang | Seoul National University Hospital | Resident |
| | Jinlong Zhang | Seoul National University Hospital | Resident |
| | Jeong Hee Jang | Seoul National University Hospital | Clinical Research Associate |
| Co-researchers | Eun-Seok Shin | Ulsan University Hospital | Professor |
| | Chang-Wook Nam | Keimyung university Dongsan medical center | Professor |
| | Joon-Hyung Doh | Inje University Ilsan Paik hospital | Professor |
| | HongSeok Lim | Ajou University Hospital | Professor |
| | Xinyang Hu | Second Affiliated Hospital of Zhejiang University School of Medicine | Professor |
| | Yaling Han | General Hospital of Shenyang Military | Professor |
| | Jifei Tang | 2nd Affiliated Hospital of Wenzhou Medical University | Professor |
| | Xiaomin Chen | Ningbo First Hospital | Professor |
| Administrator of study device (IVUS) | Jung-won Jo | Cardiovascular center, Seoul National University Hospital, Seoul, Korea | Radiographer |

## 4. Funding Agencies

Boston Scientific & St Jude Medical

## 5. Background and Hypothesis

### 1) Background

Percutaneous coronary intervention (PCI) is the current standard treatment for coronary artery diseases.(1) Especially, after the adoption of drug-eluting stents (DES), restenosis and revascularization has significantly decreased. However, due to the increased CAD population and the complexity of lesions treated with PCI, adverse effects after treatment is still a major issue. Therefore, there has been many effort to improve the outcome of PCI, where fractional flow reserve (FFR) and intravascular ultrasound (IVUS) are two strategies that are widely used.

First, FFR-guided PCI is a method to measure the coronary blood flow, and physiologically interpret the stenotic lesion. FFR-guided PCI strategy for coronary artery disease has proved its benefit over angiography-guided PCI or medical treatment by previous randomized clinical trials.(2-5)

Second, IVUS-guided PCI strategy is a method that can provide information about the lesion and PCI appropriateness.(6) Recent clinical studies and meta-analysis also showed that IVUS-guided PCI strategy could also reduce the incidence of major clinical events after drug-eluting stents implantation.(7-9) Also, a recent trial has shown that IVUS-guided PCI strategy can reduce adverse effects up to 50%.(10)

However, there has been no randomized study to compare the outcomes of FFR-guided vs. IVUS-guided PCI in patients of intermediate stenosis. The FFR-guided PCI have been known to reduce the number of treated lesions, used stents, and peri-procedural myocardial infarction (MI) with better stratification of lesions which could be significantly benefit by the revascularization. Although previous study showed that FFR-guided PCI strategy reduced the number of intervention compared with IVUS-guided strategy with comparable rates of major adverse cardiovascular events(11), small number of patients and non-randomized design of the study was the major limitations. In this regards, the randomized comparison between physiology (FFR)-guided strategy and imaging (IVUS)-guided PCI will provide valuable insights to enhance the patient's clinical outcomes with fewer number of intervention. The **F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis **(FLAVOUR) is a** randomized controlled prospective multi-center trial. This study aims to compare safety and efficacy of physiology (FFR)-guided PCI strategy and imaging (IVUS)-guided PCI strategy in patients with intermediate coronary stenosis.

### 2) Hypothesis

The FFR-guided strategy for PCI with a drug-eluting stent (DES) will show significantly lower rates of patients-oriented composite outcomes at 24 months after randomization, compared with IVUS-guided strategy for PCI with a DES in patients with intermediate coronary stenosis.

## 6. Research Materials and Indication for Revascularization

### 1) FFR-guided strategy arm

Pressure-Sensor Wire System

**Criteria for revascularization: The FFR ≤ 0.80 will be targeted for PCI.**

### 2) IVUS-guided strategy arm

iLab$^{TM}$ ultrasound imaging system (Boston Scientific)

**Criteria for revascularization: Minimum lumen area (MLA) ≤ 3mm$^2$ or (MLA ≤ 4mm$^2$ AND Plaque burden >70%)**

### 3) Administrator of study device

Jung-won, Jo (Cardiovascular center, Seoul National University Hospital)

**4) PCI with a DES**

The usage of any specific DES is decided by the operators' discretion

**7. Study Population**

1300 patients derived from Korea and China with angina and intermediate coronary stenosis in coronary angiography who clinically need FFR or IVUS for PCI with a DES will be enrolled in the present trial.

**8. Study Period**

From the 'IRB approval date of each participating center' to 2021.12.31

**9. Eligible criteria, Sample size calculation**

**1) Eligible Criteria**

**(1) Inclusion Criteria**

① Subject must be ≥ 18 years

② Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving invasive physiologic or imaging evaluation and PCI 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 intermediate degree of stenosis (40-70% stenosis by visual estimation) eligible for stent implantation who need FFR or IVUS clinically for further evaluation

⑤ Target vessel size ≥ 2.5mm in visual estimation

**(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 are present with life expectancy <1 year or that may result in protocol non-compliance (per site investigator's medical judgment).

⑥ Target lesion located in coronary arterial bypass graft

⑦ Target lesion located in the left-main coronary artery

**2) Definition of FFR or IVUS guided strategy groups**

The FFR or IVUS guided strategy groups are defined as the patients who will be evaluated by FFR or IVUS to decide the revascularization with a DES for the intermediate coronary stenosis in major coronary artery. The patients who will be deferred by FFR-guided or IVUS guided strategy will be also included as each assigned group as with the patients who will be treated by PCI according to the pre-defined criteria of revascularization.

**3) Sample Size Calculation**

Hypothesis: The FFR-guided strategy will show significantly lower rates of patients-oriented composite outcomes at 24 months after randomization, compared with IVUS-guided strategy in patients with intermediate coronary stenosis.

Based on the event rates of a previous trials evaluated FFR-guided PCI strategy (FAME I 2 year results)(3) or meta-analysis compared IVUS-guided PCI versus angiography-guided PCI strategy(8), we predicted the rates of patient-oriented composite outcomes (POCO) at 24 months after PCI to be 15% and 20%, respectively.

- Primary endpoint: 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 ($\alpha$): 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- $\beta$): 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.

**4) Recruitment**

All consecutive patients with diameter stenosis > 40-70% of coronary artery by visual estimation will be screened for enrollment in this study and if PCI with a DES is planned, should be invited to participate in the study. A member of each research team should review the patients' medical history for eligibility. If all eligibility criteria are met and written informed consent is provided, the patient may be enrolled in the study. Prior to collecting study data, the details of the study will be explained to the participant including: (1) that the study represents a phase IV clinical trial, (2) that participation is voluntary, and there is no penalty for withdrawal, (3) potential risks and benefits for participation, and (4) contact information for additional concerns. Vulnerable subjects are excluded according to the eligible criteria.

**10. Methods**

**1) Study designs**

Following angiography, patients with intermediate diameter stenosis >40-70% of coronary artery by visual estimation and have lesions that are eligible for coronary intervention without any exclusion criteria, will be randomized 1:1 to receive either FFR-guided strategy or IVUS-guided strategy for evaluation of the lesions.

**According to the pre-defined criteria for revascularization (FFR ≤ 0.80 in FFR-guided strategy group; MLA < 3mm$^2$ or MLA < 4mm$^2$ and plaque burden > 70% in IVUS-guided strategy group), the patient's**

**will be treated with PCI or not.**

If any violation of the protocols (for example, PCI was performed despite of FFR > 0.80, PCI was performed despite of MLA > 3mm$^2$, PCI was deferred despite of FFR ≤ 0.80, or PCI was deferred despite of MLA < 3mm$^2$) are presented according to the operator's discretion, the specific reasons will be mandatorily described in electronic case report form.

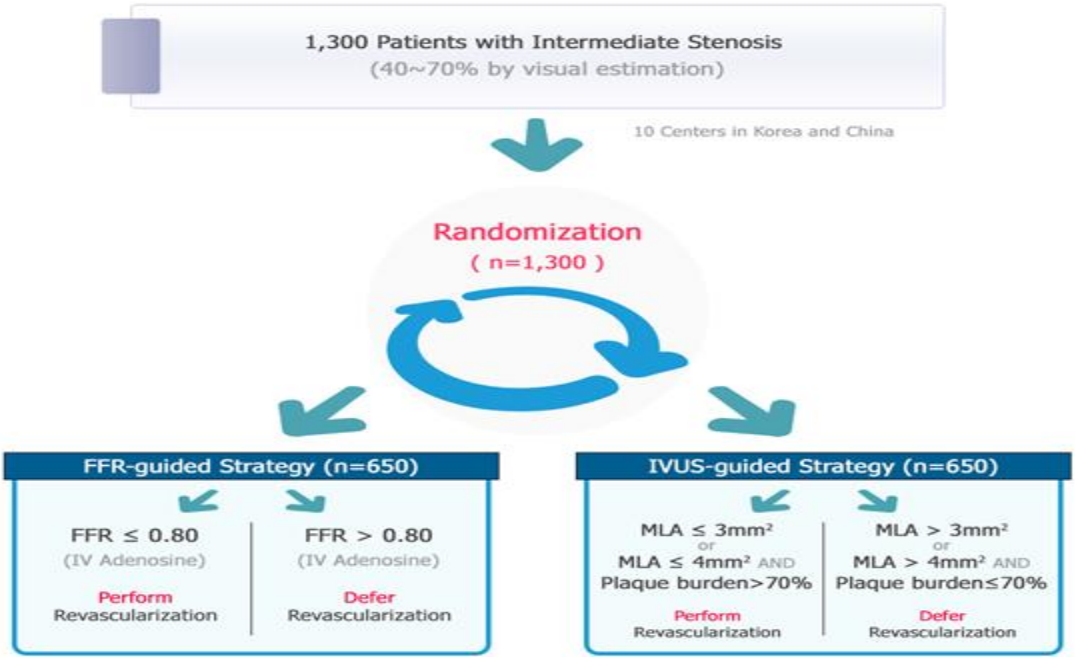
**In FFR-guided strategy group, the method of hyperemia induction and hyperemic agents will be restricted with intravenous adenosine infusion.**

**In case of multivessel disease, PCI to the non-intermediate stenosis (more than 70% stenosis by visual estimation) will be permitted and left to the operator's discretion, however, this vessel will not be eligible as a target vessel for this study. In addition, the use of IVUS or FFR according to the assigned group will be permitted as tools for the optimizing PCI in stent type, PCI procedures and any adjunctive pharmacologic treatment will be left to the operator's discretion.**

There will be **NO** regulation for any specific usage of the DES. The usage of any specific DES is decided by the operators' discretion. If the operator does not perform PCI with a DES (for example, PCI with plain old balloon angioplasty or PCI with a bare metal stent), this will be a protocol violation, and the specific reasons will be mandatorily described in electronic case report form.

If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available.

**2) Flow chart**



Analysis at 24months after Index Procedure

| | |
|---|---|
| Primary Endpoint | Patient-oriented composite outcome<br>(A composite of All death, Any Myocardial Infarction, Any Revascularization) |
| Major Secondary Endpoint s | ① Angina severity measured with Seattle Angina Questionnaires<br>② Target-vessel and all-cause nonfatal MI excluding per-procedural MI |

**3) Randomization**

Patients will be randomized to either the FFR-guided strategy or IVUS-guided strategy at the time of enrollment with 1:1 ratio. Stratified randomization by participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

**4) Follow-up data**

| | Baseline | Post-Procedure | Follow Up | | |
|---|---|---|---|---|---|
| | | | 1 month ± 14days | 1 year ± 90days | 2 years ± 90days |
| Medical/Clinical/ History (age, sex, risk factors, clinical dx, angina status, cardiac hx) | × | | | | |
| Informed Consent | × | | | | |
| Inclusion/Exclusion Criteria | × | | | | |
| **Seattle Angina Questionnaires** | × | | | × | × |
| Brief Physical Examination | × | | | | |
| Vital status | × | | × | × | × |
| Weight, height | × | | | | |
| 12 lead ECG[#] | × | × | | | |
| Angiogram[#] | × | | | | |
| **FFR-tracing raw data*** | × | × | | | |
| **IVUS-imaging raw data*** | × | × | | | |
| CBC | × | | | | |
| Electrolytes, LFT | × | | | | |
| Creatinine, BUN | × | | **x** | × | × |
| hs-CRP | × | | × | × | × |
| Fasting plasma TG, HDL, total cholesterol | × | | × | × | × |
| Fasting glucose level | × | | × | × | × |
| HgbA1C | × | | × | × | × |
| Medications[†] | × | | × | × | × |
| **CK, CK-MB, Troponin I or Troponin T** | × | × | | | |
| proBNP | × | | × | × | × |

**[#] There will be no mandatory angiographic follow-up. There will be no mandatory laboratory follow up. ECG and coronary angiographic data (baseline and follow-up) will be collected only if endpoints occur.**

*** The raw data of FFR measurement or IVUS imaging data will be analyzed in the Core-Laboratory in Seoul National University Hospital. The Post-procedural data will be collected in case the PCI is performed.**

**§ The baseline and post-procedural cardiac enzyme (CK, CK-MB, Troponin I (or Troponin T)) measurement is mandatory to assess the peri-procedural myocardial infarction**

**† Medication data included medication at baseline (before admission) and post-discharge**

**5) Primary and Secondary Endpoints**

(1) Primary endpoint

Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction (MI, including peri-procedural MI) or any repeat revascularization at 24 months after randomization according to the ARC consensus

(2) Secondary endpoint

① (POCO at 12months after randomization according to the ARC consensus

② Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)

③ All-cause and cardiac death

④ Target-vessel and all-cause nonfatal MI without peri-procedural MI

⑤ Target-vessel and all-cause nonfatal MI with peri-procedural MI

⑥ Target vessel/lesion revascularization (ischemia-driven or all)

⑦ Non-target vessel/lesion revascularization (ischemia-driven or all)

⑧ Any revascularization (ischemia-driven or all)

⑨ Stent thrombosis (definite/probable/possible)

⑩ Stroke (ischemic and hemorrhagic)

⑪ Acute success of procedure (device, lesion and procedure)

⑫ Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month

**6) Potential risk and adequacy of protection against risks**

Complications of FFR measurements include coronary dissection, thrombus formation, side branch occlusion, arterial rupture/perforation, and embolization. IVUS-evaluation will be shared similar complications. However, the evaluation of presence of myocardial ischemia in supplying territory of intermediate coronary stenosis with FFR or IVUS evaluation is standard procedure in real-world practice, and there will be no additional hazard from FFR-measurement conducting in this study

**7) Patient withdrawal**

Once enrolled, each patient should remain in the study until the required follow-up period is completed. However, all patients have the right to withdraw at any point during the study without penalty or loss of benefit. The investigator may discontinue any patient at any time if medically necessary.

The following events will result in terminating the patient's follow-up:

① Patient voluntary withdrawal

② Patient withdrawn by investigator as clinically indicated

③ Patient lost to follow-up (unofficial withdrawal)

If the study treatment(s) or observations are discontinued in any patient, the reason will be recorded and the data coordinating center must be notified promptly.

**8) Compensation or treatment protocol when trial-related indemnity is needed**

Any side effect or adverse effect that should occur within the trial will be thoroughly observed. All effects will be notified to investigators, and the best treatment strategy will be performed. Therefore, the patient should inform the investigator for any adverse effect that happens within, or after the trial. For adverse effects that are clearly related to the trial, the investigators will have obligation on compensation for indemnity for all costs.

**9) Violence of study protocol**

Although the evaluation strategy of intermediate coronary stenosis will be decided by randomization process to either FFR-guided strategy or IVUS-guided strategy, whether revascularized the target lesion or not will be decided by operator according to the clinical decision. **However, the followings will be recorded as protocol violation and the reason will be recorded and the data coordinating center must be notified promptly.**

**① Revascularization is not performed despite of FFR ≤ 0.80 (FFR-guided group)**

**② Revascularization is performed despite of FFR > 0.80 (FFR-guided group)**

**③ Revascularization is not performed despite of MLA ≤ 3mm$^2$ or (MLA ≤ 4mm$^2$ AND Plaque burden >70%) (IVUS-guided group)**

**④ Revascularization is performed despite of MLA > 3mm$^2$ or (MLA > 4mm$^2$ AND Plaque burden ≤ 70%) (IVUS-guided group)**

**⑤ Both FFR-guided strategy and IVUS-guided strategy are used for one or more coronary artery in one subject.**

**⑥ PCI is performed without a DES (for example, PCI with plain old balloon angioplasty or PCI with a Bare-metal stent)**

**10) Event adjudication and reporting, Data safety and monitoring plan (DSMP)**

**(1) Data safety and monitoring plan**

| Type of Report | Prepared by Staffs for: | Time limit of notification |
|---|---|---|
| Serious adverse event | IRB | Submitted per 6 months |
| | DCC/EC/Principal investigator | Within 48 hours |

| | | |
|---|---|---|
| | DSMB | |
| Annual progress report | EC/Principal investigator | Submitted per 1 year |
| Deviations from investigational plan | IRB | Submitted per 6 months |
| | EC/Principal investigator | Notify within 7 days. |
| Final summary report | EC/Principal investigator | Within 1 month |

*DCC: Data Coordinating Center, EC: Executive Committee (Co-researchers)

**(2) Executive Committee**

| | Name | Center | Position |
|---|---|---|---|
| Chairman | Bon-Kwon Koo | Seoul National University Hospital | Professor |
| Committee members | Seung-Jea Tahk | Ajou University Hospital | Professor |
| | Eun-Seok Shin | Ulsan university hospital | Professor |
| | Changwook Nam | Keimyung university Dongsan medical center | Professor |
| | Joonhyung Doh | Inje university Ilsan Paik hospital | Professor |

**(3) Serious Adverse Events**

The definition of serious adverse events is in the following paragraph. **It must be reported to the principal investigator within 48hours after recognition of the event and to the IRB every 6 months.**

① Results in persistent or significant disability or incapacity (significant, persistent or permanent change or disruption in patient's body function/structure, physical activity or quality of life

② Requires in-patient hospitalization or prolongs hospitalization

③ Results in a congenital anomaly/birth defect or,

④ Life-threatening events or death

Clinical events include not only POCO, all death, stent thrombosis, stroke, but also other endpoint events. Clinical events and safety data will be reported to principal investigator regularly, and examined by staffs for patient's safety throughout the study.

The coordinating center needs to report progress to Executive committee and principal investigator annually. This study will not be stopped early based on efficacy results.

**(4) Event adjudication Committee**

All primary and secondary events will be independently adjudicated by Event Adjudication Committee.

| | Name | Center | Position |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Chairman | Jang-Whan Bae | Chungbuk National University Hospital, Cheongju, Korea | Professor |
| Committee members | Sang Hyun Park | Eulji University Hospital, Daejeon, Korea | Assistant Professor |
| | Jin-Sin Koh | Gyeongsang National University Hospital, Jinju, Korea | Assistant Professor |

**(5) Data Safety and Monitoring Board**

All serious adverse events will be reviewed by independent DSMB.

| | Name | Center | Position |
|---|---|---|---|
| Chairman | Jung-Sun Kim | Yonsei University College of Medicine, Seoul, Korea | Professor |
| Committee members | Cheol Woong Yu | Korea University Anam Hospital, Seoul, Republic of Korea | Professor |
| | Soo-Jung Kim | Kyung-Hee University Hospital, Seoul, Republic of Korea | Professor |
| | | | |

**11) Data safety monitoring plan**

The principal investigator will make the monitoring manager to visit and examine coordinating centers regularly, every 3 months. A designated trial monitor will review data not only for completeness, but also for accordance of the hospital data and eCRF data. Compliance with the protocol and adverse events will be also examined. This trial monitor may inspect all documents and required records that are maintained by the Investigator/site, including medical records (office, clinic, or hospital) for the subjects in this trial. The coordinating centers will permit access to such records.

**The monitoring manager: Jeong Hee Jang (The cardiovascular center of Seoul National University Hospital), Jinlong Zhang with MRCC**

**12) Statistical Consideration and Analysis**

**(1) Analysis Population**

All patients are to be randomized in a 1:1 fashion to either FFR-guided strategy or IVUS-guided strategy group. All primary and secondary endpoints will be analyzed both on an intention-to-treat basis (all patients a nalyzed as part of their assigned treatment group). Patients receiving multi-lesion evaluation by FFR or IVUS, the target lesion/vessel will be declared by the operator prior to the interventional procedure.

For intention-to-treat analysis, all patients who signed the written informed consent form and are ran domized in the study will be included in the analysis sample, regardless of whether or not the correct treatment was administered, or whether crossover occurred.

Per-protocol population will be defined as population who did not violate the study pro tocol. The definition of protocol following is as follows;

I. Revascularization is performed when FFR ≤ 0.80 and revascularization is not performed when FFR > 0.80 (FFR-guided group)

II. Revascularization is performed when MLA ≤ 3mm2 or (MLA ≤ 4mm2 AND Plaque burden >70%) (IVUS-guided group) and revascularization is not performed when of MLA > 3mm2 or (MLA > 4mm2 AND Plaque burden ≤ 70%) (IVUS-guided group)

The definition of protocol violation is as follows;

① **Revascularization is not performed despite of FFR ≤ 0.80 (FFR-guided group)**

② **Revascularization is performed despite of FFR > 0.80 (FFR-guided group)**

③ **Revascularization is not performed despite of MLA ≤ 3mm$^2$ or (MLA ≤ 4mm$^2$ AND Plaque burden >70%) (IVUS-guided group)**

④ **Revascularization is performed despite of MLA > 3mm$^2$ or (MLA > 4mm$^2$ AND Plaque burden ≤ 70%) (IVUS-guided group)**

⑤ **Both FFR-guided strategy and IVUS-guided strategy are used for one or more coronary artery in one subject.**

⑥ **PCI is performed without a DES (PCI with Plain Old balloon Angioplasty or PCI with a Bare-metal stent)**

Analysis with Per-protocol population will be performed as exploratory and sensitivity analysis for that of intention-to-treat population.

**(2) Primary Endpoint Analysis**

Primary endpoints (the rates of POCO at 2 years) will be analyzed firstly on an intention-to-treat basis (all

patients analyzed as part of their assigned treatment group), and then, per-protocol basis at 12 months and 24 months after randomization. The null hypothesis will be evaluated with Kaplan-Meier survival with log rank test. All primary and secondary endpoints will be analyzed on per-patient basis.

**(3) Secondary Endpoint Analysis**

The individual components of primary composite outcome (POCO) will be analyzed on an intention-to-treat basis and peri-protocol basis at 24 months after randomization.

Stent-oriented composite endpoint (Target lesion failure: a composite of cardiac death, target-vessel MI, or target lesion revascularization) will be analyzed using $\chi^2$-test and Kaplan-Meier survival with log rank test. Other secondary endpoints including all-cause and cardiac death, target vessel/lesion revascularization, non-target vessel/lesion revascularization, any revascularization, target-vessel and all-cause (including non-target vessel) nonfatal MI, stent thrombosis, stroke (ischemic or hemorrhagic), will be analyzed using $\chi^2$-test and Kaplan-Meier survival with log rank test. Acute success of procedure (device, lesion, and procedure) and adherence to study dose of drug (prasugrel) will be analyzed using $\chi^2$-test.

The Angina severity measured with Seattle Angina Questionnaires (Appendix #1) will be compared between the two groups with independent sample t-test.

The baseline coronary angiographic characteristics will be analyzed on per-lesion.

| Primary Endpoint | Statistical methods | Time point of analysis |
|---|---|---|
| Patient-oriented composite outcome (POCO) | Kaplan-Meier survival estimates and log-rank tests,<br>Chi-square test | 2 years after randomization |
| **Secondary Endpoint** | **Statistical methods** | **Time point of analysis** |
| Patient-oriented composite outcome (POCO) | Kaplan-Meier survival estimates and log-rank tests | 1 years after randomization |
| Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| All-cause and cardiac death | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Target-vessel and all-cause nonfatal MI | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Target vessel/lesion revascularization (ischemia-driven or all) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Non-target vessel/lesion revascularization (ischemia-driven or all) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Any revascularization (ischemia-driven or all) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Stent thrombosis (definite/probable/possible) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Stroke (ischemic and hemorrhagic) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Acute success of procedure (device, lesion and procedure) | $\chi^2$-test | 1 and 2 years after randomization |
| Angina severity measured with Seattle Angina Questionnaires | Independent sample t-test | Baseline, 1 and 2 years after randomization |

**(4) Treatment of Missing Values**

The primary analysis of the study endpoints will not be covariate adjusted. No imputation methods will be used to infer missing values of baseline variables. For the study endpoints, patients lost to follow-up and subsequently lost to assessment of primary endpoint, will be considered to be censored in the estimation of Kaplan-Meier event rates. As a secondary analysis, we will also examine the patients who have been lost to follow-up. We will perform a comparison of baseline characteristics in patients with vs.

without 2-year follow up. The baseline characteristics will include as followed Table 1. In addition, a s ensitivity analysis will be performed to assess the impact of these patients on the study outcomes. For patients lost to follow-up, multiple imputation techniques will be used to calculate pooled estimates of the treatment effect and confidence intervals which will then be compared to the primary statistical ana lysis.

**Table 1**.

| ***Demographics*** | ***Cardiac Risk Factors*** | ***Clinical Indication of PCI*** |
|---|---|---|
| Age, years | Current smoker | Stable angina |
| Gender | Previous PCI | Unstable angina |
| Diabetes mellitus | Previous CABG | Acute myocardial infarction |
| Hypertension | Previous MI | NSTEMI |
| Dyslipidemia | Previous CHF | STEMI |
| Peripheral artery disease | Previous CVA | |
| Chronic renal failure | Family history of CAD | |
| | LV ejection fraction | |
| | LV dysfunction (LVEF<30%) | |
| ***Complexity of CAD*** | ***Medication at discharge*** | |
| Angiographic disease extent | Aspirin | |
| 1VD | Prasugrel | |
| 2VD | Clopidogrel | |
| 3VD | Statin | |
| No. of treated lesion/patients | ACE inhibitor/ Angiotensin-II receptor blocker | |
| Type B2 or C lesions† | | |
| At least 1 ISR | Beta-blocker | |
| At least thrombus present | Calcium-channel blocker | |
| At least 1 Bifurcation | | |
| At least 1 Small vessel* | | |
| At least 1 Long lesion** | | |
| Severe calcification | | |
| Multivessel PCI | | |

† Type B2 or C lesions according to ACC/AHA classification.

*small vessel denotes lesion with reference diameter ≤2.75mm

**long lesion denotes lesion with length ≥20mm

**(5) Multivariate Analyses**

Multivariate predictors of all primary and secondary endpoints will be determined using multivariate regression models, using either binary or Cox's proportional hazard method. Forward orbackward stepwise selection algorithms will be used to select predictors as needed. Baseline demographic and clinical variables that are predictive at the 0.1 level will be included in the models. The purpose of this is twofold: to do a covariate adjusted analysis of treatment for all primary and secondary endpoints and to identify the risk factors which are associated with the study endpoints. The included covariates in univariate analysis will be as with Table 1.

**(6) Survival Analyses**

All time-to-event outcomes will be summarized using Kaplan-Meier survival estimates and compared between treatment groups using log-rank tests.

**13) Study Schedule**

Patient enrollment: IRB approval date ~ 2018.04 (roughly 24 months of enrollment)

End of follow-up period: 2020. 04 (2 years of follow-up)

Analysis and report: ~2021.12.31

**11. Care for the safety of the subjects**

**1) Institutional Review Board (IRB) / Ethical Committee Approval**

Institutional Review Board / Ethical Committee approval for the protocol and informed consent form will be obtained by the investigator prior to study participation. The approval letter must be signed by the IRB Chairperson or authorized representative prior to beginning the present study. No changes will be made to the protocol or informed consent form without appropriate approval from the IRB. According to IRB requirements, the investigator will report study progress until it is completed. Further, any protocol amendments as well as associated informed consent changes will be submitted to the IRB and written approval must be obtained prior to implementation.

**2) Elements of Informed Consent**

This trial will involve patients with CHD, who have been deemed eligible for coronary revascularization. We anticipate enrolling 1300 patients with a mean age in the 60s. Pregnant women and patients under the age of 18 will be excluded from the trial for ethical and safety concerns.

Prior to collecting study data, the details of the study will be explained to the potential participant in an independent area, including: (1) that the study represents a phase IV clinical trial, (2) that participation is voluntary, and there is no penalty for withdrawal, (3) Withdrawal from this study is possible at any time (4) potential risks and benefits for participation, and (5) contact information for additional concerns.

Potential participants should have sufficient time to overview the study and make inquiries. Patients are informed of the purpose of the study, the treatment alternative, the random manner of assignment to treatment, the need to be available for telephone follow-up and return clinic visits at regular intervals for questionnaires and/or medical tests, and of their options to accept or refuse entry into the study without affecting their clinical care.

All patients or legally authorized patient representatives must sign the current IRB approved informed consent form prior to any study-related activities and the index procedure. After sufficient comprehension of the study, the patient or legally authorized patient representative should sign the consent form along with the present date. Failure to obtain signed informed consent will render the patient ineligible for the study. The signed informed consent will be kept in the patient's medical records and a copy given to the patient or legally authorized patient representative. All sources of research materials will be in the form of medical records, coronary angiograms, electrocardiograms and routine blood work. This material will obtained both for routine medical care as well as

for research purposes.

**3) Confidentiality**

The confidentiality of protected health information shall be maintained by all parties involved at all times throughout the clinical trial. All data should be secured against unauthorized access. Study patients will be assigned a unique coded identifier on eCRFs. Patient data will be protected by the use of locked cabinets at the Clinical Centers and use of passwords, data encryption and secure, limited access storage of electronic data. The explicit issue of privacy and confidentiality is outlined in the Informed Consent Form. Under the limits of protected health information and prescribed regulations, personnel form regional health authorities may access study data.

**4) Storage and Disposal of Data**

Research records will be maintained for at least three years after the last expenditure report (including articles, research papers etc.) For the recorded data, unauthorized access or disposing data should be forbidden, without permission from the research organization. If the data are recorded electronically, the data should be regularly backed up on disc; a hard copy should be made of particularly important data; relevant software must be retained to ensure future access, and special attention should be given to guaranteeing the security of electronic data.

A regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good ClinicalPractice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements

## 12. References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Final Protocol

# Comparison of Clinical Outcomes between Imaging and Physiology-guided Intervention Strategy in Patients with Intermediate Stenosis

## **F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis

## (FLAVOUR)

## Version No: 11.5


**Co-Principal investigators:**

**Seoul National University Hospital, Korea, Bon-Kwon Koo**

**Ajou University Hospital, Korea, Seung-Jae Tahk**

**Send affiliated hospital of Zhejiang Univ School of Medicine, Jianan Wang**

# Research Summary

| | |
|---|---|
| Trial name | **Comparison of Clinical Outcomes between Imaging and Physiology-guided Intervention Strategy in Patients with Intermediate Stenosis**<br><br>**F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis **(FLAVOUR)** |
| Principal investigator | Bon-Kwon Koo, Seoul National University Hospital, Korea |
| Funding agencies | Boston Scientific |
| Objectives | To compare the safety and efficacy of physiology (fractional flow reserve [FFR])-guided percutaneous coronary intervention (PCI) strategy with imaging (intravascular ultrasound [IVUS])-guided PCI strategy in patients with de novo intermediate coronary stenosis. |
| Study design | Prospective, open-label, randomized, multicenter trial to test the safety and efficacy of physiology- or imaging-guided PCI in patients with intermediate coronary stenosis. |
| Patient enrollment | 1,700 patients enrolled at 18centers in Republic of Korea and China |
| Study Period | From the 'IRB approval date of each participating center' to 2022.12.31 |
| Eligible criteria | (1) Inclusion Criteria<br><br>⑥ Subject must be ≥ 19 years<br><br>⑦ Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving invasive physiologic or imaging evaluation and PCI with a drug-eluting stent (DES) and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure.<br><br>⑧ Patients suspected with ischemic heart disease<br><br>⑨ Patients with de novo intermediate degree of stenosis (40-70% stenosis by visual estimation) eligible for stent implantation who need FFR or IVUS clinically for further evaluation<br><br>⑩ Target vessel size > 2.5mm in visual estimation<br><br>⑪ Target vessels are limited to proximal to mid LAD, proximal to distal LCX, and RCA proximal to the PL-PDA bifurcation<br><br>**(2) Exclusion Criteria**<br><br>⑧ 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.)<br><br>⑨ Patients with active pathologic bleeding<br><br>⑩ Gastrointestinal or genitourinary major bleeding within the prior 3 months. |

| | |
|---|---|
| | ⑪ History of bleeding diathesis, known coagulopathy (including heparin-induced thrombocytopenia)<br>⑫ Non-cardiac co-morbid conditions with life expectancy < 2 years<br>⑬ Target lesion located in coronary arterial bypass graft<br>⑭ Target lesion located in the left main coronary artery<br>⑮ Target lesion located in previous PCI segment with in-stent restenosis. |
| Patient follow-up | Clinical follow-up will occur at 1, 12, 24 months after the procedure. Investigator or designee may conduct follow-up as telephone contacts or office visits. |
| Primary endpoint | Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction [MI, including peri-procedural MI (12,13)] or any revascularization at 24 months after randomization according to the ARC consensus(16) |
| Secondary endpoint | 1. POCO at 12months after randomization according to the ARC consensus<br>2. Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)<br>3. Cost-effectiveness analysis<br>4. All-cause and cardiac death<br>5. Target-vessel and all-cause nonfatal MI without peri-procedural MI<br>6. Target-vessel and all-cause nonfatal MI with peri-procedural MI (12,13)<br>7. Peri-procedural MI using referred definitions (17-19)<br>8. Target vessel/lesion revascularization (ischemia-driven or all)<br>9. Non-target vessel/lesion revascularization (ischemia-driven or all)<br>10. Any revascularization (ischemia-driven or all)<br>11. Stent thrombosis (definite/probable/possible)<br>12. Stroke (ischemic and hemorrhagic)<br>13. Acute success of procedure (device, lesion and procedure)<br>14. Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month<br>15. Plaque characteristics by IVUS (including plaque burden, eccentricity, posterior attenuation, positive remodeling, calcification, etc.)<br>16. QFR analysis (fixed QFR, contrast QFR, delta QFR, and post PCI QFR) |

# Research Proposal

## 1. Title of Study

**Comparison of Clinical Outcomes between Imaging and Physiology-guided Intervention Strategy in Patients with Intermediate Stenosis**

**: F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis **(FLAVOUR)**

## 2. Clinical Research Center

(1) Seoul National University Hospital

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(4) Keimyung University Dongsan Medical Center

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(5) Samsung Medical Center

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(14) Hangzhou Normal University's affiliated Hospital

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(15) Zhejiang Hospital

12 Lingyin Road , Hangzhou

(16) Yeungnam University Medical Center

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(17) Wenzhou People's Hospital

Wenzhou People's Hospital: 57 Canghou Street, Wenzhou, Zhejiang, China

(18) Ningbo University

The Affiliated Hospital of Medical School of Ningbo University: 247 Renmin Road, Ningbo, Zhejiang, China

## 3. Co-Principal Investigator, Co-researchers, Staff

| | Name | Center | Position |
|---|---|---|---|
| **Co-Principal investigator** | Bon-Kwon Koo | Seoul National University Hospital | Professor |
| | Seung-Jea Tahk | Ajou University Hospital | Professor |
| | JianAn Wang | 2nd Affiliated Hospital of Zhejiang University | Professor |
| **Co-researchers** | Jeehoon Kang | Seoul National University Hospital | Professor |
| | Won Kim | KyungHee University Medical Center | Professor |
| | Chang-Wook Nam | Keimyung University Dongsan Medical Center | Professor |
| | Seungho Heo | Keimyung University Dongsan Medical Center | Professor |
| | Yun-Kyeong-Cho | Keimyung University Dongsan Medical Center | Professor |
| | **Incheol Kim** | Keimyung University Dongsan Medical Center | Professor |
| | **Cheolhyeon Lee** | Keimyung University Dongsan Medical Center | Professor |
| | Joo-Yong Hahn | Samsung Medical Center | Professor |
| | Joon-Hyung Doh | Inje University Ilsan Paik Hospital | Professor |
| | Sung Gyun Ahn | Yonsei University Wonju Severance Hospital | Professor |
| | Myeong-Ho Yoon | Ajou University Hospital | Professor |
| | Hyung Mo Yang | Ajou University Hospital | Professor |
| | Soyoun Choi | Ajou University Hospital | Professor |

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|---|---|---|---|
| | Byung-Joo Choi | Ajou University Hospital | Professor |
| | Hong Seok Lim | Ajou University Hospital | Professor |
| | Kyung Woo Suh | Ajou University Hospital | Professor |
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| | Fan Jiang | The Affiliated Hospital Of Hangzhou Normal University | Professor |
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| | Wenming He | The Affiliated Hospital of Medical School of Ningbo University | Professor |
| **Staff** | Jinlong Zhang | Second affiliated hospital of Zhejiang university school of medicine | Resident |
| | Jeong Hee Jang | Seoul National University Hospital | Clinical Research Associate |
| | Lee Sun Hwa | Seoul National University Hospital | Clinical Research Associate |
| **Administrator of study device(IVUS)** | Jung-won Jo | Seoul National University Hospital | Radiographer |

## 4. Funding Agencies

Boston Scientific

This study is a research project independently conducted, without commission from an outside agency. The funding agency, Boston Scientific will provide IVUS catheters and related devices.

## 5. Background and Hypothesis

### 1) Background

Percutaneous coronary intervention (PCI) is the current standard treatment for coronary artery diseases.(1) Especially, after the adoption of drug-eluting stents (DES), restenosis and revascularization has significantly decreased. However, due to the increased CAD population and the complexity of lesions treated with PCI, adverse effects after treatment is still a major issue. Therefore, there has been many effort to improve the outcome of PCI, where fractional flow reserve (FFR) and intravascular ultrasound (IVUS) are two strategies that are widely used.

First, FFR-guided PCI is a method to measure the coronary blood flow, and physiologically interpret the stenotic lesion. FFR-guided PCI strategy for coronary artery disease has proved its benefit over angiography-guided PCI or medical treatment by previous randomized clinical trials.(2-5)

Second, IVUS-guided PCI strategy is a method that can provide information about the lesion and PCI appropriateness.(6) Recent clinical studies and meta-analysis also showed that IVUS-guided PCI strategy could also reduce the incidence of major clinical events after drug-eluting stents implantation.(7-9) Also, a recent trial has shown that IVUS-guided PCI strategy can reduce adverse effects up to 50%.(10) Especially, diabetic patients with coronary artery disease are patients with high risk of adverse clinical events, who need more meticulous evaluation for the necessity and extent of intervention. Therefore, comparing FFR-guided and IVUS-guided PCI will give valuable information for the treatment strategy in these patients.

However, there has been no randomized study to compare the outcomes of FFR-guided vs. IVUS-guided PCI in patients of intermediate stenosis. The FFR-guided PCI have been known to reduce the number of treated lesions, used stents, and peri-procedural myocardial infarction (MI) with better stratification of lesions which could be significantly benefit by the revascularization. Although previous study showed that FFR-guided PCI strategy reduced the number of intervention compared with IVUS-guided strategy with comparable rates of major adverse cardiovascular events(11), small number of patients and non-randomized design of the study was the major limitations. In this regards, the randomized comparison between physiology (FFR)-guided strategy and imaging (IVUS)-guided PCI will provide valuable insights to enhance the patient's clinical outcomes with fewer number of intervention. The **F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis **(FLAVOUR) is a** randomized controlled prospective multi-center trial. This study aims to compare safety and efficacy of physiology (FFR)-guided PCI strategy and imaging (IVUS)-guided PCI strategy in patients with intermediate coronary stenosis.

Although FFR is the current standard of car for the functional assessment of lesion severity in patients with intermediate-grade stenosis, FFR guided PCI is still underused in real world practice due to the concerns for prolonged procedural time, increased costs, and potential complications by pressure wire. The quantitative flow ratio (QFR) is a novel angiography based approach allowing calculation of FFR by 3-dimensional coronary artery reconstruction and fluid dynamic computation. There are many clinical studies supporting the QFR value and identifying of patients at risk from cardiovascular events.(12, 13) Therefore, we will confirm the accuracy of QFR, the relationship between IVUS and QFR findings, and incremental value of QFR for predicting cardiovascular events.

### 2) Hypothesis

The FFR-guided strategy for PCI with a drug-eluting stent (DES) will show non-inferiority in rates of patients-oriented composite outcomes at 24 months after randomization, compared with IVUS-guided strategy for PCI with a DES in patients with intermediate coronary stenosis.

## 6. Research Materials and Indication for Revascularization

**1) FFR-guided strategy arm**

Pressure-Sensor Wire System

**Criteria for revascularization: The FFR ≤ 0.80 will be targeted for PCI.**

**2) IVUS-guided strategy arm**

iLab$^{TM}$ ultrasound imaging system (Boston Scientific)

**Criteria for revascularization: Minimum lumen area (MLA) ≤ 3mm$^2$ or 3< MLA ≤ 4mm$^2$**

**AND Plaque burden >70%)**

**3) Administrator of study device**

Jung-won, Jo (Cardiovascular center, Seoul National University Hospital)

**4) PCI with a DES**

The usage of any specific DES is decided by the operators' discretion

## 7. Study Population

1,700 patients derived from Korea and China with angina and de novo intermediate coronary stenosis in coronary angiography who clinically need FFR or IVUS for PCI with a DES will be enrolled in the present trial.

## 8. Study Period

From the 'IRB approval date of each participating center' to 2022.12.31

## 9. Eligible criteria, Sample size calculation

### 1) Eligible Criteria

**(1) Inclusion Criteria**

⑥ Subject must be ≥ 19 years

⑦ Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving invasive physiologic or imaging evaluation and PCI and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure.

⑧ Patients suspected with ischemic heart disease

⑨ Patients with de novo intermediate degree of stenosis (40-70% stenosis by visual estimation) eligible for stent implantation who need FFR or IVUS clinically for further evaluation

⑩ Target vessel size ≥ 2.5mm

⑪ Target vessels are limited to proximal to mid LAD, proximal to distal LCX, and RCA proximal to the PL-PDA bifurcation

**(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.

### 2) Definition of FFR or IVUS guided strategy groups

The FFR or IVUS guided strategy groups are defined as the patients who will be evaluated by FFR or IVUS to decide the revascularization with a DES for the intermediate coronary stenosis in major coronary artery. The patients who will be deferred by FFR-guided or IVUS guided strategy will be also included as each assigned group as with the patients who will be treated by PCI according to the pre-defined criteria of revascularization.

### 3) Sample Size Calculation

**Hypothesis:** The FFR-guided strategy for PCI with a drug-eluting stent (DES) will show non-inferiority in rates of patients-oriented composite outcomes at 24 months after randomization, compared with IVUS-guided strategy for PCI with a DES in patients with intermediate coronary stenosis.

**Sample size:** Based on the event rates of previous trials which evaluated FFR-guided PCI strategy in patients with intermediate stenosis, we predicted the rates of POCO at 24 months after PCI in the FFR-guided arm to be 10%.(3, 14, 15) Also, according to previous clinical trials and meta-analysis of IVUS-guided PCI, we predicted the rate of 24 month POCO to be 12% in the IVUS-guided arm.(7, 8, 10, 16, 17)

- Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any revascularization) at 24 months after PCI
- Design: non-inferiority , delta = 2.5%
- Sampling ratio: FFR-guided strategy : IVUS-guided strategy = 1:1
- Type I error (α): One-sided 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 or IVUS-guided strategy, respectively
- Statistical power (1- β): 90%
- Primary statistical method : Kaplan-Meier survival analysis with log-rank test
- Potential withdrawal rates : total 2%
- Stratification in Randomization: Presence of Diabetes Mellitus (600 patients (35%) will be Diabetic patients, with 300 patients in each group)

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

### 4) Recruitment

All consecutive patients with diameter stenosis > 40-70% of coronary artery by visual estimation will be

screened for enrollment in this study and if PCI with a DES is planned, should be invited to participate in the study. A member of each research team should review the patients' medical history for eligibility. If all eligibility criteria are met and written informed consent is provided, the patient may be enrolled in the study. Prior to collecting study data, the details of the study will be explained to the participant including: (1) that the study represents a phase IV clinical trial, (2) that participation is voluntary, and there is no penalty for withdrawal, (3) potential risks and benefits for participation, and (4) contact information for additional concerns. Vulnerable subjects are excluded according to the eligible criteria.

## 10. Methods

### 1) Study designs

Following angiography, patients with intermediate diameter stenosis 40-70% of coronary artery by visual estimation and have lesions that are eligible for coronary intervention without any exclusion criteria, will be randomized 1:1 to receive either FFR-guided strategy or IVUS-guided strategy for evaluation of the lesions.

**According to the pre-defined criteria for revascularization (FFR ≤ 0.80 in FFR-guided strategy group; MLA ≤ 3mm$^2$ or 3 <MLA ≤ 4mm$^2$ and plaque burden > 70% in IVUS-guided strategy group), the patient's will be treated with PCI or not. Optimization of PCI will be recommended to meet the criteria as follows.**

| Group | Criteria for PCI optimization |
|---|---|
| **IVUS-guided PCI group** | Plaque burden at stent edge ≤ 55%<br>Minimal stent area ≥ 5.5mm$^2$, or minimal stent area ≥ distal reference lumen area |
| **FFR-guided PCI group** | Post PCI FFR ≥ 0.88, or<br>Post PCI delta FFR ([FFR at stent distal edge] – [FFR at stent proximal edge]) < 0.05 |

If any violation of the protocols (for example, PCI was performed despite of FFR > 0.80, PCI was performed despite of MLA > 3mm$^2$, PCI was deferred despite of FFR ≤ 0.80, or PCI was deferred despite of MLA < 3mm$^2$) are presented according to the operator's discretion, the specific reasons will be mandatorily described in electronic case report form.

**In FFR-guided strategy group, the method of hyperemia induction and hyperemic agents will be restricted with intravenous adenosine infusion.**

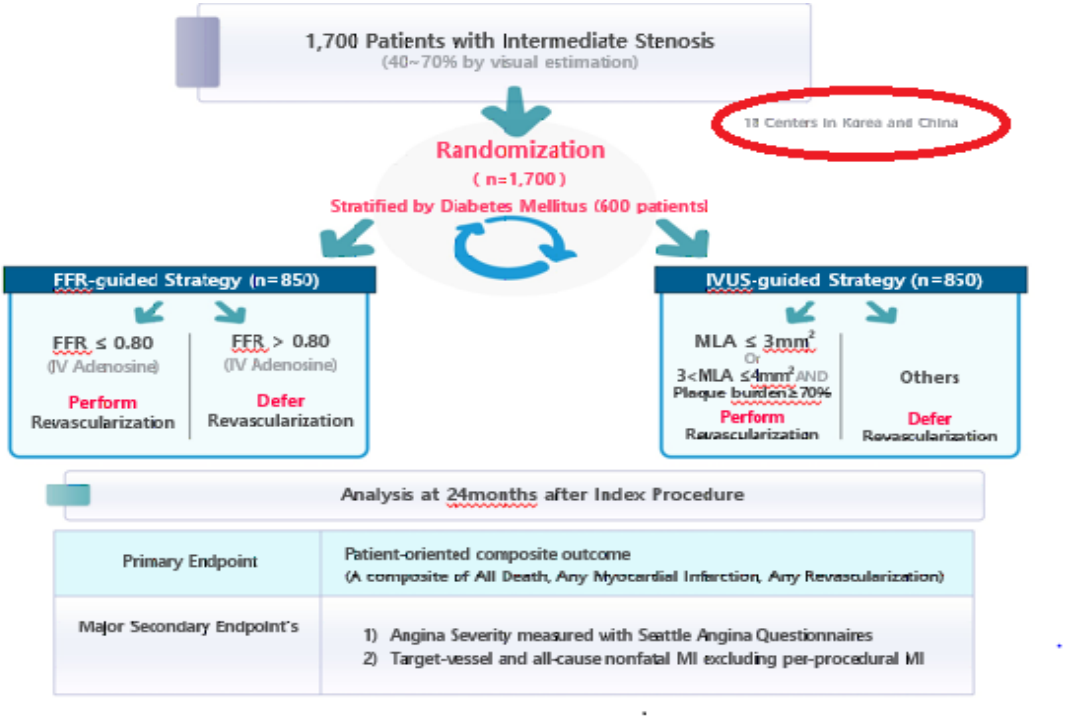
**In case of multivessel disease, PCI to the non-intermediate stenosis (more than 70% stenosis by visual estimation) will be permitted and left to the operator's discretion, however, this vessel will not be eligible as a target vessel for this study. In addition, the use of IVUS or FFR according to the assigned group will be permitted as tools for the optimizing PCI in stent type, PCI procedures and any adjunctive pharmacologic treatment will be left to the operator's discretion.**

The QFR analysis is only performed on a coronary angiograms that can be analyzed. The Post-procedural QFR will be analyzed in case the PCI is performed.

There will be **NO** regulation for any specific usage of the DES. The usage of any specific DES is decided by the operators' discretion. If the operator does not perform PCI with a DES (for example, PCI with plain old balloon angioplasty or PCI with a bare metal stent), this will be a protocol violation, and the specific reasons will be mandatorily described in electronic case report form.

If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available.

## 2) Flow chart




## 3) Randomization

Patients will be randomized to either the FFR-guided strategy or IVUS-guided strategy at the time of enrollment with 1:1 ratio. Stratified randomization by participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

**4) Follow-up data**

| | Baseline | Post-Procedure | Follow Up | | |
|---|---|---|---|---|---|
| | | | 1 month ± 14days | 1 year ± 90days | 2 years ± 90days |
| **Medical/Clinical/ History (age, sex, risk factors, clinical dx, angina status, cardiac history)** | × | | | | |
| **Informed Consent** | × | | | | |
| **Inclusion/Exclusion Criteria** | × | | | | |
| Seattle Angina Questionnaires | × | | | × | × |
| **Brief Physical Examination** | × | | | | |
| **Vital status** | × | | × | × | × |
| **Weight, height** | × | | | | |
| **12 lead ECG**[#] | × | × | | | |
| **Angiogram**[#] | × | | | | |
| FFR-tracing raw data* | × | × | | | |
| IVUS-imaging raw data* | × | × | | | |
| QFR analysis data[†] | × | × | | | |
| **CBC** | × | | | | |
| **Electrolytes, LFT** | × | | | | |
| **Creatinine, BUN** | × | | △ | △ | △ |
| **Fasting plasma TG, HDL, total cholesterol, LDL** | × | | △ | △ | △ |
| **Fasting glucose level** | × | | △ | △ | △ |
| **HgbA1C (only in diabetic patients)** | × | | △ | △ | △ |
| **Medications**[‡] | × | | × | × | × |
| **CK, CK-MB, Troponin I or Troponin T** | △ | × | | | |

[#] There will be no mandatory angiographic follow-up. There will be no mandatory laboratory follow up. ECG and coronary angiographic data (baseline and follow-up) will be collected only if endpoints occur.

* The raw data of FFR measurement data will be analyzed in the Core-Laboratory in Seoul National University Hospital. And The IVUS imaging data will be analyzed in the Core-Laboratory in Ulsan University Hospital. The Post-procedural data will be collected in case the PCI is performed.

[†] The QFR data will be analyzed in the Core-Laboratory in Seoul National University Hospital. The Post-procedural QFR will be analyzed in case the PCI is performed. The QFR analysis is only performed on a coronary angiograms that can be analyzed.

[§] The baseline and post-procedural cardiac enzyme (CK, CK-MB, Troponin I (or Troponin T)) measurement is mandatory to assess the peri-procedural myocardial infarction

‡Medication data included medication at baseline (before admission) and post-discharge

△ Not mandatory, but recommended tests

## 5) Primary and Secondary Endpoints

### (1) Primary endpoint

Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction [MI, including peri-procedural MI(14, 15)] or any revascularization at 24 months after randomization according to the ARC consensus(18)

### (2) Secondary endpoint

1. POCO at 12months after randomization according to the ARC consensus
2. Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)
3. Cost-effectiveness
4. All-cause and cardiac death
5. Target-vessel and all-cause nonfatal MI without peri-procedural MI
6. Target-vessel and all-cause nonfatal MI with peri-procedural MI(14, 15)
7. Periprocedural MI defined as referred.(19-21)
8. Target vessel/lesion revascularization (ischemia-driven or all)
9. Non-target vessel/lesion revascularization (ischemia-driven or all)
10. Any revascularization (ischemia-driven or all)
11. Stent thrombosis (definite/probable/possible)
12. Stroke (ischemic and hemorrhagic)
13. Acute success of procedure (device, lesion and procedure)
14. Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month
15. Plaque characteristics by IVUS (including plaque burden, eccentricity, posterior attenuation, positive remodeling, calcification, etc.)
16. QFR analysis (fixed QFR, contrast QFR, delta QFR, and post PCI QFR)

- Definition of Periprocedural MI
  - Periprocedural MI will be defined as prior studies.
  - Definition of Periprocedural MI in the DEFINE FLAIR & SWEDEHEART trials(14, 15)
    - #. 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"

- #. 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 centile" 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

- Definition of Periprocedural MI in the EXCEL trial(19, 20)
  - Periprocedural MI was defined for PCI as the occurrence of (i) CK-MB >10× URL or (ii) CK-MB >5× URL plus one of the following: (i) new pathological Q-waves in at least two contiguous leads or new persistent non-rate-related left bundle branch block; (ii) angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow; or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. For patients with elevated baseline biomarkers at baseline the peak CK-MB level was required to rise from the baseline value by an increment equal to the values above.

- Definition of Periprocedural MI in the ISCHEMIA trial(21)
  - For subjects with normal baseline biomarker level pre-PCI, peri-PCI MI requires a rise in CK-MB to >5-fold the ULN (or a rise in troponin to >35 times the MI Decision Limit/ULN, when CKMB is unavailable). If pre-PCI cardiac markers (CKMB or cTn) are elevated, they must be stable or falling as indicated by two samples at least 6h apart. The post-PCI CKMB level should reflect a rise of >20% over pre-PCI levels. In addition to biomarker criteria, peri-PCI MI requires at least one of the following:
    - Post- procedure angiographic TIMI 0/1 flow in a major coronary artery or aside branch with reference vessel diameter ≥2.0 mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter ≥3.0 mm which had TIMI 3 flow at baseline or Type C dissection (NHLBI classification) or greater in the target vessel.
    - New ECG changes (ST segment elevation or depression >0.1mV in 2contiguous leads), new pathologic Q-waves in ≥2 contiguous leads, or new persistent LBBB present on a post-PCI ECG obtained in the absence of any intervening coronary event between the time of the PCI procedure and the ECG showing changes.
  - Or stand-alone biomarker definition
    - CK-MB to > 10-fold the ULN (or when CK-MB is unavailable, arise in troponin to > 70-fold the MI decision Limit/ULN)

### 6) Potential risk and adequacy of protection against risks

Complications of FFR measurements include coronary dissection, thrombus formation, side branch occlusion, arterial rupture/perforation, and embolization. IVUS-evaluation will be shared similar complications. However, the evaluation of presence of myocardial ischemia in supplying territory of intermediate coronary stenosis with FFR or IVUS evaluation is standard procedure in real-world practice, and there will be no additional hazard from FFR-measurement conducting in this study

### 7) Patient withdrawal

Once enrolled, each patient should remain in the study until the required follow-up period is completed. However, all patients have the right to withdraw at any point during the study without penalty or loss of benefit. The investigator may discontinue any patient at any time if medically necessary.

The following events will result in terminating the patient's follow-up:

④ Patient voluntary withdrawal

⑤ Patient withdrawn by investigator as clinically indicated

⑥ Patient lost to follow-up (unofficial withdrawal)

If the study treatment(s) or observations are discontinued in any patient, the reason will be recorded and the data coordinating center must be notified promptly.

## 8) Compensation or treatment protocol when trial-related indemnity is needed

Any side effect or adverse effect that should occur within the trial will be thoroughly observed. All effects will be notified to investigators, and the best treatment strategy will be performed. Therefore, the patient should inform the investigator for any adverse effect that happens within, or after the trial. For adverse effects that are clearly related to the trial, the investigators will have obligation on compensation for indemnity for all costs.

## 9) Violence of study protocol

Although the evaluation strategy of intermediate coronary stenosis will be decided by randomization process to either FFR-guided strategy or IVUS-guided strategy, whether revascularized the target lesion or not will be decided by operator according to the clinical decision. **However, the followings will be recorded as protocol violation and the reason will be recorded and the data coordinating center must be notified promptly.**

**⑦ Revascularization is not performed despite of FFR ≤ 0.80 (FFR-guided group)**

**⑧ Revascularization is performed despite of FFR > 0.80 (FFR-guided group)**

**⑨ Revascularization is not performed despite of MLA ≤ 3mm$^2$ or (3 < MLA ≤ 4mm$^2$ AND Plaque burden >70%) (IVUS-guided group)**

**⑩ Revascularization is performed despite of MLA > 3mm$^2$ or (MLA > 4mm$^2$ AND Plaque burden ≤ 70%) (IVUS-guided group)**

**⑪ Both FFR-guided strategy and IVUS-guided strategy are used for one or more coronary artery in one subject.**

**⑫ PCI is performed without a DES (for example, PCI with plain old balloon angioplasty or PCI with a Bare-metal stent)**

## 10) Event adjudication and reporting, Data safety and monitoring plan (DSMP)

### (1) Data safety and monitoring plan

| Type of Report | Prepared by Staffs for: | Time limit of notification |
|---|---|---|
| **Serious adverse event** | IRB | Submitted per 6 months |
| | DCC/EC/Principal investigator | Within 48 hours |
| | DSMB | |

| | | |
|---|---|---|
| **Annual progress report** | EC/Principal investigator | Submitted per 1 year |
| **Deviations from** | IRB | Submitted per 6 months |
| **investigational plan** | EC/Principal investigator | Notify within 7 days. |
| **Final summary report** | EC/Principal investigator | Within 1 month |

*DCC: Data Coordinating Center, EC: Executive Committee (Co-researchers)

**(2) Executive Committee**

| | Name | Center | Position |
|---|---|---|---|
| **Chairman** | Seung-Jea Tahk | Ajou University Hospital | Professor |
| **Co-Chairman** | Bon-Kwon Koo | Seoul National University Hospital | Professor |
| **Committee members** | Bong-Ki Lee | Kangwon National University Hospital | Professor |
| | Changwook Nam | Keimyung University Dongsan Medical Center | Professor |
| | Joonhyung Doh | Inje University Ilsan Paik Hospital | Professor |
| | Eun-Seok Shin | Ulsan University Hospital | Professor |
| | Jianan Wang | Second affiliated hospital of Zhejiang university school of medicine | Professor |
| | Xinyang Hu | Second affiliated hospital of Zhejiang university school of medicine | Professor |

**(3) Serious Adverse Events**

The definition of serious adverse events is in the following paragraph. **It must be reported to the principal investigator within 48hours after recognition of the event and to the IRB every 6 months.**

⑤ Results in persistent or significant disability or incapacity (significant, persistent or permanent change or disruption in patient's body function/structure, physical activity or quality of life

⑥ Requires in-patient hospitalization or prolongs hospitalization

⑦ Results in a congenital anomaly/birth defect or,

⑧ Life-threatening events or death

Clinical events include not only POCO, all death, stent thrombosis, stroke, but also other endpoint events. Clinical events and safety data will be reported to principal investigator regularly, and examined by staffs for patient's safety throughout the study.

The coordinating center needs to report progress to Executive committee and principal investigator annually. This study will not be stopped early based on efficacy results.

**(4) Event adjudication Committee**

All primary and secondary events will be independently adjudicated by Event Adjudication Committee.

| | Name | Center | Position |
|---|---|---|---|
| **Chairman** | Jang-Whan Bae | Chungbuk National University Hospital, Cheongju, Korea | Professor |
| **Committee members** | Sang Hyun Park | Eulji University Hospital, Daejeon, Korea | Assistant Professor |
| | Jin-Sin Koh | Gyeongsang National University Hospital, Jinju, Korea | Assistant Professor |

**(5) Data Safety and Monitoring Board**

All serious adverse events will be reviewed by independent DSMB.

| | Name | Center | Position |
|---|---|---|---|
| **Chairman** | Jung-Sun Kim | Yonsei University College of Medicine, Seoul, Korea | Professor |
| **Committee members** | Hyun-Kuk Kim | Chosun University Hospital, Gwangju, Republic of Korea | Professor |
| | Woojoo Lee | Seoul National University, School of Public Health, Seoul, Korea | Associate Professor |

## 11) Data safety monitoring plan

The principal investigator will make the monitoring manager to visit and examine coordinating centers regularly, every 3 months. A designated trial monitor will review data not only for completeness, but also for accordance of the hospital data and eCRF data. Compliance with the protocol and adverse events will be also examined. This trial monitor may inspect all documents and required records that are maintained by the Investigator/site, including medical records (office, clinic, or hospital) for the subjects in this trial. The coordinating centers will permit access to such records.

**The monitoring manager: Jeong Hee Jang (The cardiovascular center of Seoul National University Hospital), Jinlong Zhang with MRCC**

## 12) Statistical Consideration and Analysis

**(1) Analysis Population**

All patients are to be randomized in a 1:1 fashion to either FFR-guided strategy or IVUS-guided strategy group. All primary and secondary endpoints will be analyzed both on an intention-to-treat basis (all patients a nalyzed as part of their assigned treatment group). Patients receiving multi-lesion evaluation by FFR or IVUS, the target lesion/vessel will be declared by the operator prior to the interventional procedure.

For intention-to-treat analysis, all patients who signed the written informed consent form and are ran domized in the study will be included in the analysis sample, regardless of whether or not the correct treatment was administered, or whether crossover occurred.

Per-protocol population will be defined as population who did not violate the study protocol. The definition of protocol following is as follows;

III. **Revascularization is performed when FFR ≤ 0.80 and revascularization is not performed when FFR > 0.80 (FFR-guided group)**

IV. **Revascularization is performed when MLA ≤ 3mm2 or (**3 < **MLA ≤ 4mm2 AND Plaque burden >70%) (IVUS-guided group) and revascularization is not performed when of MLA > 3mm2 or (MLA > 4mm2 AND Plaque burden ≤ 70%) (IVUS-guided group)**

The definition of protocol violation is as follows;

⑦ **Revascularization is not performed despite of FFR ≤ 0.80 (FFR-guided group)**

⑧ **Revascularization is performed despite of FFR > 0.80 (FFR-guided group)**

⑨ **Revascularization is not performed despite of MLA ≤ 3mm$^2$ or (**3 < **MLA ≤ 4mm$^2$ AND Plaque burden >70%) (IVUS-guided group)**

⑩ **Revascularization is performed despite of MLA > 3mm$^2$ or (MLA > 4mm$^2$ AND Plaque burden ≤ 70%) (IVUS-guided group)**

⑪ **Both FFR-guided strategy and IVUS-guided strategy are used for one or more coronary artery in one subject.**

⑫ **PCI is performed without a DES (PCI with Plain Old balloon Angioplasty or PCI with a Bare-metal stent)**

Analysis with Per-protocol population will be performed as exploratory and sensitivity analysis for that of intention-to-treat population.

**(2) Primary Endpoint Analysis**

Primary endpoints (the rates of POCO at 2 years) will be analyzed firstly on an intention-to-treat basis (all patients analyzed as part of their assigned treatment group), and then, per-protocol basis at 12 months and 24 months after randomization. The null hypothesis will be evaluated with Kaplan-Meier survival with log rank test. All primary and secondary endpoints will be analyzed on per-patient basis.

**(3) Secondary Endpoint Analysis**

The individual components of primary composite outcome (POCO) will be analyzed on an intention-to-treat basis and peri-protocol basis at 24 months after randomization.

Stent-oriented composite endpoint (Target lesion failure: a composite of cardiac death, target-vessel MI, or target lesion revascularization) will be analyzed using $\chi^2$-test and Kaplan-Meier survival with log rank test. Other secondary endpoints including all-cause and cardiac death, target vessel/lesion revascularization, non-target vessel/lesion revascularization, any revascularization, target-vessel and all-cause (including non-target vessel) nonfatal MI, stent thrombosis, stroke (ischemic or hemorrhagic), will be analyzed using $\chi^2$-test and Kaplan-Meier survival with log rank test. Acute success of procedure (device, lesion, and procedure) and adherence to study dose of drug (prasugrel) will be analyzed using $\chi^2$-test.

The Angina severity measured with Seattle Angina Questionnaires (Appendix #1) will be compared between the two groups with independent sample t-test.

The baseline coronary angiographic characteristics will be analyzed on per-lesion.

| **Primary Endpoint** | **Statistical methods** | **Time point of analysis** |
|---|---|---|
| Patient-oriented composite outcome (POCO) | Kaplan-Meier survival estimates and log-rank tests,<br>Chi-square test | 2 years after randomization |
| **Secondary Endpoint** | **Statistical methods** | **Time point of analysis** |
| Patient-oriented composite outcome (POCO) | Kaplan-Meier survival estimates and log-rank tests | 1 years after randomization |
| Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization) | $\chi^2$-test<br>Kaplan-Meier survival | 1 and 2 years after randomization |

| | | |
|---|---|---|
| | estimates and log-rank tests | |
| All-cause and cardiac death | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Target-vessel and all-cause nonfatal MI | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Target vessel/lesion revascularization (ischemia-driven or all) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Non-target vessel/lesion revascularization (ischemia-driven or all) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Any revascularization (ischemia-driven or all) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Stent thrombosis (definite/probable/possible) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Stroke (ischemic and hemorrhagic) | $\chi^2$-test<br>Kaplan-Meier survival estimates and log-rank tests | 1 and 2 years after randomization |
| Acute success of procedure (device, lesion and procedure) | $\chi^2$-test | 1 and 2 years after randomization |
| Angina severity measured with Seattle Angina Questionnaires | Independent sample t-test | Baseline, 1 and 2 years after randomization |

**(4) Treatment of Missing Values**

The primary analysis of the study endpoints will not be covariate adjusted. No imputation methods will be used to infer missing values of baseline variables. For the study endpoints, patients lost to follow-up and subsequently lost to assessment of primary endpoint, will be considered to be censored in the estimation of Kaplan-Meier event rates. As a secondary analysis, we will also examine the patients who have been lost to follow-up. We will perform a comparison of baseline characteristics in patients with vs. without 2-year follow up. The baseline characteristics will include as followed Table. In addition, a sensitivity analysis will be performed to assess the impact of these patients on the study outcomes. For patients lost to follow-up, multiple imputation techniques will be used to calculate pooled estimates of the treatment effect and confidence intervals which will then be compared to the primary statistical analysis.

**Table. Baseline Characteristics**

| ***Demographics*** | ***Cardiac Risk Factors*** | ***Clinical Indication of PCI*** |
|---|---|---|
| Age, years | Current smoker | Stable angina |
| Gender | Previous PCI | Unstable angina |
| Diabetes mellitus | Previous CABG | Acute myocardial infarction |
| Hypertension | Previous MI | NSTEMI |
| Dyslipidemia | Previous CHF | STEMI |
| Peripheral artery disease | Previous CVA | |
| Chronic renal failure | Family history of CAD | |
| | LV ejection fraction | |
| | LV dysfunction (LVEF<30%) | |
| ***Complexity of CAD*** | ***Medication at discharge*** | |
| Angiographic disease extent | Aspirin | |
| 1VD | Prasugrel | |
| 2VD | Clopidogrel | |
| 3VD | Statin | |
| No. of treated lesion/patients | ACE inhibitor/ Angiotensin-II receptor blocker | |
| Type B2 or C lesions† | | |
| At least 1 ISR | Beta-blocker | |
| At least thrombus present | Calcium-channel blocker | |
| At least 1 Bifurcation | | |
| At least 1 Small vessel* | | |
| At least 1 Long lesion** | | |
| Severe calcification | | |
| Multivessel PCI | | |

† Type B2 or C lesions according to ACC/AHA classification.

*small vessel denotes lesion with reference diameter ≤2.75mm

**long lesion denotes lesion with length ≥20mm

**(5) Multivariate Analyses**

Multivariate predictors of all primary and secondary endpoints will be determined using multivariate regression models, using either binary or Cox's proportional hazard method. Forward or backward stepwise selection algorithms will be used to select predictors as needed. Baseline demographic and clinical variables that are predictive at the 0.1 level will be included in the models. The purpose of this is twofold: to do a covariate adjusted analysis of treatment for all primary and secondary endpoints and to identify the risk factors which are associated with the study endpoints. The included covariates in univariate analysis will be as with Table 1.

**(6) Survival Analyses**

All time-to-event outcomes will be summarized using Kaplan-Meier survival estimates and compared between treatment groups using log-rank tests.

**(7) Economic evaluation**

This study aims to conduct economic evaluation for the physiology-guided PCI strategy and imaging-guided PCI strategy in patients with intermediate stenosis. Base-case analysis will be performed from the healthcare system perspective. Accordingly, the cost will be estimated based on the direct medical costs. For cost estimation, health insurance claim data will be used as one of the data sources. As for health insurance claim data, customized health information data provided by the National Health Insurance Service will be used. After this IRB approval, the application for use of the data will be made on the data providing site NHISS (http://nhiss.nhis.or.kr) operated by the National Health Insurance Service, which provides data after deliberation based on the research protocol and IRB approval. The data can be accessed and analyzed at locations within the National Health Insurance Service. The data is provided in the form of an alternative identification number for the resident registration number to ensure anonymity, and the alternative identification number is not used in presenting the analysis results.

### 13) Study Schedule

Patient enrollment: IRB approval date ~ 2019.08

End of follow-up period: 2021. 08 (2 years of follow-up)

Analysis and report: ~2022.12.31

## 11. Care for the safety of the subjects

### 1) Institutional Review Board (IRB) / Ethical Committee Approval

Institutional Review Board / Ethical Committee approval for the protocol and informed consent form will be obtained by the investigator prior to study participation. The approval letter must be signed by the IRB Chairperson or authorized representative prior to beginning the present study. No changes will be made to the protocol or informed consent form without appropriate approval from the IRB. According to IRB requirements, the investigator will report study progress until it is completed. Further, any protocol amendments as well as associated informed consent changes will be submitted to the IRB and written approval must be obtained prior to implementation.

### 2) Elements of Informed Consent

This trial will involve patients with CHD, who have been deemed eligible for coronary revascularization. We anticipate enrolling 1,700 patients with a mean age in the 60s. Pregnant women and patients under the age of 18 will be excluded from the trial for ethical and safety concerns.

Prior to collecting study data, the details of the study will be explained to the potential participant in an independent area, including: (1) that the study represents a phase IV clinical trial, (2) that participation is voluntary,

and there is no penalty for withdrawal, (3) Withdrawal from this study is possible at any time (4) potential risks and benefits for participation, and (5) contact information for additional concerns.

Potential participants should have sufficient time to overview the study and make inquiries. Patients are informed of the purpose of the study, the treatment alternative, the random manner of assignment to treatment, the need to be available for telephone follow-up and return clinic visits at regular intervals for questionnaires and/or medical tests, and of their options to accept or refuse entry into the study without affecting their clinical care.

All patients or legally authorized patient representatives must sign the current IRB approved informed consent form prior to any study-related activities and the index procedure. After sufficient comprehension of the study, the patient or legally authorized patient representative should sign the consent form along with the present date. Failure to obtain signed informed consent will render the patient ineligible for the study. The signed informed consent will be kept in the patient's medical records and a copy given to the patient or legally authorized patient representative. All sources of research materials will be in the form of medical records, coronary angiograms, electrocardiograms and routine blood work. This material will obtained both for routine medical care as well as for research purposes.

### 3) Confidentiality

The confidentiality of protected health information shall be maintained by all parties involved at all times throughout the clinical trial. All data should be secured against unauthorized access. Study patients will be assigned a unique coded identifier on eCRFs. Patient data will be protected by the use of locked cabinets at the Clinical Centers and use of passwords, data encryption and secure, limited access storage of electronic data. The explicit issue of privacy and confidentiality is outlined in the Informed Consent Form. Under the limits of protected health information and prescribed regulations, personnel form regional health authorities may access study data.

### 4) Storage and Disposal of Data

Research records will be maintained for at least three years after the last expenditure report (including articles, research papers etc.) For the recorded data, unauthorized access or disposing data should be forbidden, without permission from the research organization. If the data are recorded electronically, the data should be regularly backed up on disc; a hard copy should be made of particularly important data; relevant software must be retained to ensure future access, and special attention should be given to guaranteeing the security of electronic data.

A regulatory authority or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements

## 12. References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**Fractional Flow Reserve versus Intravascular Ultrasound to Guide Percutaneous Coronary Intervention**

Fractional Flow Reserve and Intravascular Ultrasound-guided Intervention Strategy for Clinical Outcomes

in Patients with Intermediate Stenosis

**: The FLAVOUR Randomized Controlled Trial**

# Study Protocol - Summary of Amendments

| Previous Version Number<br>Ver. 3.0 (May 03. 2016) | Latter Version Number<br>Ver. 4.0 (Nov 10. 2016) | Specific Reason of Modification |
|---|---|---|
| 1-2p, Principal investigator<br>Seoul National University Hospital<br>Bon-Kwon Koo | Co-Principal investigators<br>Ajou Unversity Hospital, Seung-Jea Tahk<br>Seoul National University Hospital Bon-Kwon Koo | Added Dr. Tahk as a co-principal investigator |
| 2p, Funding agencies<br>Boston Scientific & St Jude Medical | Funding agencies<br>Boston Scientific | 'St Jude Medical' declined funding due to internal affairs. However, Boston Scientific has agreed funding for the IVUS catheters used in our study. |
| 2p,Patient enrollment 9 centers | Patient enrollment 12 centers | Added additional participating centers |
| 2p, (1) Inclusion Criteria<br>① Subject must be ≥ 18 years | (1) Inclusion Criteria<br>① Subject must be ≥ 19 years | Modified the inclusion criteria to exclude those underage |
| 2p, 8p, (1) Inclusion Criteria<br>⑫ Subject must be ≥ 18 years<br>⑬ Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving invasive physiologic or imaging evaluation and PCI with a drug-eluting stent (DES) and he/she or his/her legally authorized representative provides written informed consent prior to any study related | (1) Inclusion Criteria<br>① Subject must be ≥ 19 years<br>② Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving invasive physiologic or imaging evaluation and PCI with a drug-eluting stent (DES) and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure. | Specified and modified the inclusion criteria, so as to clarify the study. |

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| procedure.<br><br>⑭ Patients suspected with ischemic heart disease<br><br>⑮ Patients with intermediate degree of stenosis (40-70% stenosis by visual estimation) eligible for stent implantation who need FFR or IVUS clinically for further evaluation<br><br>16 Target vessel size > 2.5mm in visual estimation | ③ Patients suspected with ischemic heart disease<br><br>④ Patients with intermediate degree of stenosis (40-70% stenosis by visual estimation) eligible for stent implantation who need FFR or IVUS clinically for further evaluation<br><br>⑤ Target vessel size > 2.5mm in visual estimation<br><br>⑥ Target vessels are limited to proximal to mid LAD, proximal to mid LCX, and RCA proximal to the PL-PDA bifurcation | |
| 4p, (1) Seoul National University Hospital<br>101, Daehak-ro, Jongno-gu, Seoul, Korea<br>(2) Ajou University Hospital<br>164 World Cup-ro, Yeongtong-gu, Suwon, Korea<br>(3) Inje University Ilsan Paik Hospital,<br>170 Juhwa-ro, Ilsanseo-gu,Goyang, Korea<br>(4) Ulsan University Hospital, University of Ulsan College of Medicine<br>877 Bangeojinsunhwando-ro, Dong-gu, Ulsan, Korea<br>(5) Keimyung University Dongsan Medical Center<br>56 Dalseong-Ro, Jung-Gu, Daegu, Korea<br>(6) Second Affiliated Hospital of Zhejiang University School of Medicine<br>88 Jiefang Road, Hangzhou, Zhejiang, China<br>(7) The General Hospital of Shenyang Military<br>No.83 Cultural Road Shenhe District Shenyang City | (1) Seoul National University Hospital<br>101, Daehak-ro, Jongno-gu, Seoul, Korea<br>(2) Ajou University Hospital<br>164 World Cup-ro, Yeongtong-gu, Suwon, Korea<br>(3) Inje University Ilsan Paik Hospital,<br>170 Juhwa-ro, Ilsanseo-gu,Goyang, Korea<br>(4) Ulsan University Hospital, University of Ulsan College of Medicine<br>877 Bangeojinsunhwando-ro, Dong-gu, Ulsan, Korea<br>(5) Keimyung University Dongsan Medical Center<br>56 Dalseong-Ro, Jung-Gu, Daegu, Korea<br>(6) Samsung Medical Center<br>81 Irwon-Ro Gangnam-gu. Seoul, Korea<br>(7) Kangwon National University Hospital<br>Baengnyeong-ro 156, Chuncheon-Si, Gangwon-Do<br>(8) Second Affiliated Hospital of Zhejiang University | Modified participating centers |

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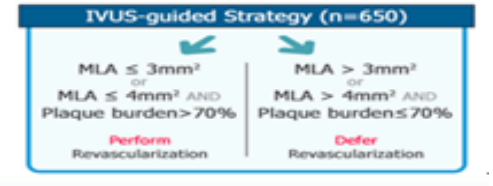
|---|---|---|
| (8) The 2nd Affiliated Hospital of Wenzhou Medical University<br>109 Xueyuan West Road, Wenzhou, Zhejiang<br>(9) Ningbo First Hospital<br>59 Liu ting street, Ningbo, Zhejiang | School of Medicine<br>88 Jiefang Road, Hangzhou, Zhejiang, China<br>(9) The 1st Affiliated Hospital of Wenzhou Medical University<br>2 Fuxuexiang Luchengqu, Wenzhou, Zhejiang<br>(10) The 2nd Affiliated Hospital of Wenzhou Medical University<br>109 Xueyuan West Road, Wenzhou, Zhejiang<br>(11) Ningbo First Hospital<br>59 Liu ting street, Ningbo, Zhejiang<br>(12) Hangzhou First people's Hospital<br>261 Huansha Road Shangchengqu, Hangzhou, Zhejiang | |
| 5p, Co-researchers<br>Eun-Seok Shin, Changwook Nam, Joonhyung Doh, HongSeok Lim, Xinyang Hu, Yaling Hang, Jifei Tang, Xiaomin Chen | Co-researchers<br>Eun-Seok Shin, Changwook Nam, Joo Yong Hahn, Joonhyung Doh, Mung ho Yun, HongSeok Lim, , Hyung Mo Yang, Bong Ki Lee Joo Myung Lee, Xinyang Hu, Xinguo Tong, Peiren Shan, Peng Chen, Hanbin Cui | Modified and added additional co-researchers and updated the affiliations |
| 6p, Boston Scientific & St Jude Medical | Boston Scientific | Modified the funding agencies. |
| 10p, 2) Flow chart<br>  | 2) Flow chart<br>  | Modified and specified the definition of the revascularization criteria (i.e. the defer group). |
| 11p, 4) **Follow-up data** | 4) **Follow-up data**<br>ㄱ. LDL, BNP or Pro-BNP or NT-pro BNP | 1) Added LDL level in laboratory findings. |

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| | ㄴ. HgbA1C (in case of DM) | 2) Modified ‘Pro-BNP’ to ‘BNP or Pro-BNP or NT-pro BNP’<br>3) Modified to check HbA1C level only in DM patients |
| 15p, 10) (2) **Executive Committee**<br>Chairman: Bon-Kwon Koo<br>Committee members: Seung-Jea Tahk,<br>Eun-Seok Shin, Changwook Nam, Joonhyung Doh | 10) (2) **Executive Committee**<br>Chairman: Seung-Jea Tahk<br>Co-Chairman: Bon-Kwon Koo<br>Committee members: Bong-Ki Lee, Eun-Seok Shin, Changwook Nam, Joonhyung Doh | Modified roles of co-researchers. |

| Previous Version Number<br>Ver 4.0 (Nov 10. 2016) | Latter Version Number<br>Ver 5.0.1 (Dec 19. 2016) | Specific Reason of Modification |
|---|---|---|
| 1.<br>FLAVOUR Protocol Version 4.0_Korean_17_October_2016 | 1.<br>FLAVOUR Protocol Version 5.0_Korean_08_December_2016 | |
| **3. 5~6 page Co-researchers**<br>Eun-Seok Shin, Changwook Nam, Joo Yong Hahn, Joonhyung Doh, Mung ho Yun, HongSeok Lim, Hyung Mo Yang, Bong Ki Lee, Joo Myung Lee, Xinyang Hu, Xinguo Tong, Peiren Shan,<br>Peng Chen, Hanbin Cui | **3. 5~6 page Co-researchers**<br>Eun-Seok Shin, Changwook Nam, Joo Yong Hahn, So Yeon Choi , Byeong Joo Choi , Joonhyung Doh, Mung ho Yun, Hong Seok Lim, Hyung Mo Yang, Kyeong Woo Seo , Bong Ki Lee, Joo Myung Lee, Xinyang Hu, Xinguo Tong, Peiren Shan,<br>Peng Chen, Hanbin Cui | Modified participating centers and co-investigators. |
| **2. 2page & 8page (1) Inclusion Criteria**<br>④ Patients with intermediate degree of stenosis (40-70% stenosis by visual estimation) eligible for stent implantation who need FFR or IVUS clinically for further evaluation | **2. 2page & 10page (1) Inclusion Criteria**<br>④ Patients with intermediate degree of stenosis (40-70% stenosis by visual estimation**) in a de novo lesion,** eligible for stent implantation who need FFR or IVUS clinically for further evaluation | Specified and modified the inclusion criteria, so as to clarify the study. |

| Previous Version Number<br>Ver 5.0.1 (Dec 19. 2016) | Latter Version Number<br>Ver 5.0.2 (Jun 19. 2017) | Specific Reason of Modification |
|---|---|---|
| **2p Research Summary & 8P 7. Study Population &**<br>**22p 2) Elements of Informed Consent**<br>**Patient enrollment**<br>1,300 patients enrolled at 12 centers in Republic of Korea and China | **2p Research Summary & 8P 7. Study Population &**<br>**22p 2) Elements of Informed Consent**<br>**Patient enrollment**<br>1,700 patients enrolled at 12 centers in Republic of Korea and China | Modified total enrollment target |
| **5p 3. Principal Investigator, Staff, Co-researchers**<br>**Co-researchers**<br>Eun-Seok Shin, Changwook Nam, Joo Yong Hahn, Joonhyung Doh, Mung ho Yun, HongSeok Lim, Hyung Mo Yang, Bong Ki Lee, Joo Myung Lee, Xinyang Hu, Xinguo Tong, Peiren Shan,<br>Peng Chen, Hanbin Cui | **5p 3. Principal Investigator, Staff, Co-researchers**<br>**Co-researchers**<br>Kyung Woo Park , Han-mo Yang , Jung Kyu Han , Eun-Seok Shin, Changwook Nam, Joo Yong Hahn, Joonhyung Doh, Mung ho Yun,<br>Soyoun Choi, Byung-Joo Choi , Kyung Woo Suh , HongSeok Lim, Hyung Mo Yang, Bong Ki Lee, Joo Myung Lee, Xinyang Hu, Xinguo Tong, Peiren Shan,<br>Peng Chen, Hanbin Cui | Modified participating centers and co-investigators |
| **6p 4. Funding Agencies**<br>Boston Scientific | **6p 4. Funding Agencies**<br>Boston Scientific<br>The current study is an Investigator initiated trial. Boston Scientific will provide IVUS for the current study. | Specify the role of funding agencies |
| **8p 5. Background and Hypothesis**<br>**1) Background**<br>~ Also, a recent trial has shown that IVUS-guided PCI strategy can reduce adverse effects up to 50%.(10) | **8p 5. Background and Hypothesis**<br>**1) Background**<br>~ Also, a recent trial has shown that IVUS-guided PCI strategy can reduce adverse effects up to 50%.(10) | Specify the background of this study |

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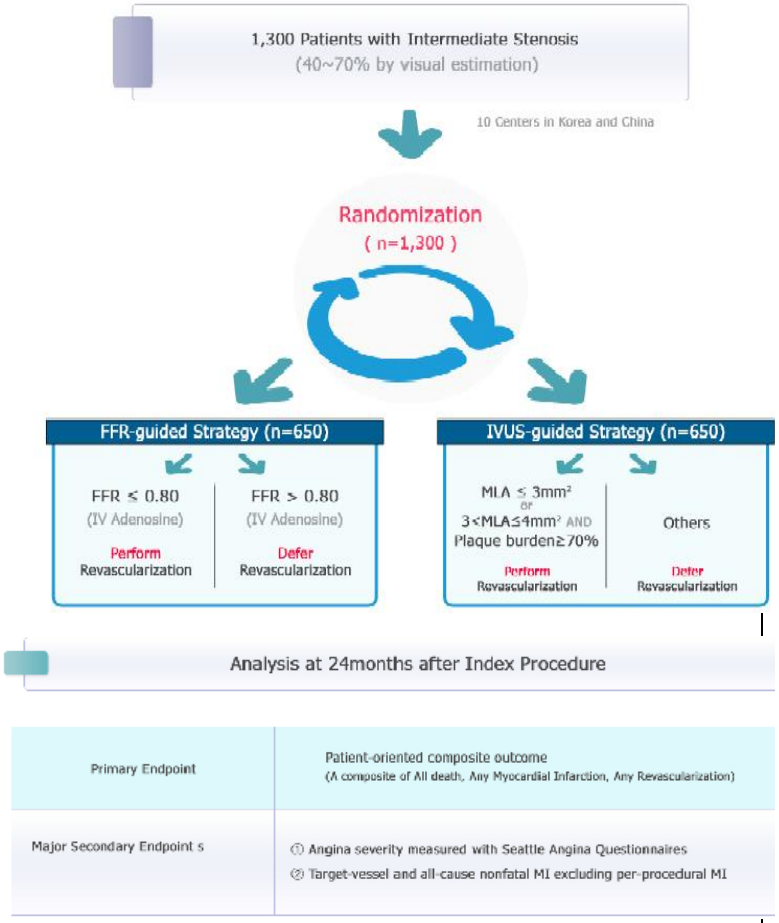
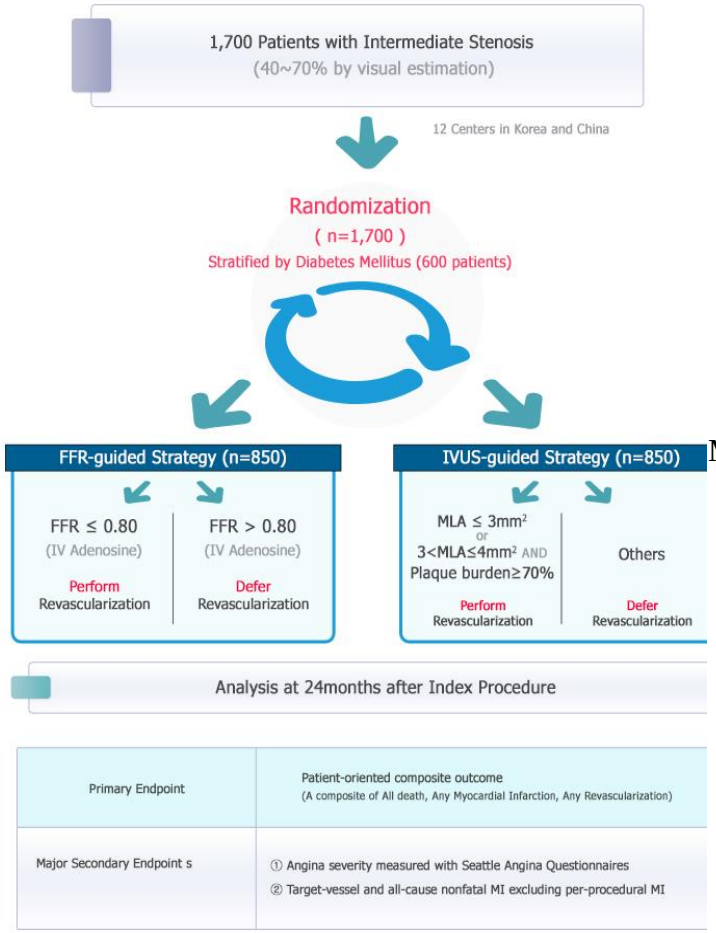
| However, there has been no randomized study to compare the outcomes of FFR-guided vs.~ FFR)-guided PCI strategy and imaging (IVUS)-guided PCI strategy in patients with intermediate coronary stenosis. | Especially, diabetic patients with coronary artery disease are patients with high risk of adverse clinical events, who need more meticulous evaluation for the necessity and extent of intervention. Therefore, comparing FFR-guided and IVUS-guided PCI will give valuable information for the treatment strategy in these patients.<br><br>However, there has been no randomized study to compare the outcomes of FFR-guided vs.~ FFR)-guided PCI strategy and imaging (IVUS)-guided PCI strategy in patients with intermediate coronary stenosis. | |
| **9p 3) Sample Size Calculation**<br><br>• Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any repeat revascularization) at 24 months after PCI<br>• Design: Superiority (one-sided test)<br>• Sampling ratio: FFR-guided strategy : IVUS-guided strategy = 1:1<br>• Type I error (α): one-sided 2.5%<br>• Accrual time : 2 years<br>• Total time : 4 years (accrual 2 year + follow-up 2 years)<br>• Assumption: POCO 15.0% vs. 20.0% in FFR or IVUS-guided strategy, respectively<br>• Statistical power (1- β): 80%<br>• Primary statistical method : Kaplan-Meier survival analysis with log-rank test<br>• Potential withdrawal rates : total 2%<br>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. | **9p 3) Sample Size Calculation**<br><br>• Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any repeat revascularization) at 24 months after PCI<br>• Design: non-inferiority (one-sided test)<br>• Sampling ratio: FFR-guided strategy : IVUS-guided strategy = 1:1<br>• Type I error (α): One-sided 5%<br>• Accrual time : 2 years<br>• Total time : 4 years (accrual 2 year + follow-up 2 years)<br>• Assumption: POCO 10.0% vs. 12.0% in FFR or IVUS-guided strategy, respectively<br>• Statistical power (1- β): 90%<br>• Primary statistical method : Kaplan-Meier survival analysis with log-rank test<br>• Potential withdrawal rates : total 2%<br>• Stratification in Randomization: Presence of Diabetes Mellitus (600 patients (35%) will be Diabetic patients, with 300 patients in each group)<br>Based on the above assumption, we would need total 1,700 patients (850 patients in each group) with consideration of withdrawal rates. | Specify the sample size calculation |

**12p 2) Flow chart**




**12p 2) Flow chart**




Modified the study flow

**12p 4) Follow-up data**

| | Baselin | Post- | Follow Up |
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**12p 4) Follow-up data**

| | Baselin | Post- | Follow Up |
|---|---|---|---|

Modified mandatorily collecting data

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | e | Proced ure | 1 month ± 14days | 1 year ± 90days | 2 years ± 90days | | e | Proced ure | 1 month ± 14days | 1 year ± 90days | 2 years ± 90days |
| **CK, CK-MB, Troponin I or Troponin T** | × | × | | | | **CK, CK-MB, Troponin I or Troponin T** | △ | × | | | |
| Pro-BNP or BNP or NT-pro BNP | × | | × | × | | × Pro-BNP or BNP or NT-pro BNP | △ | | △ | △ | △ |

△ Not mandatory, but recommended tests

| Previous Version Number<br>Ver 5.0.2 (Jun 19. 2017) | Latter Version Number<br>Ver 5.1 (Jun 28. 2017) | Specific Reason of Modification |
|---|---|---|
| **7p 2) Hypothesis**<br><br>The FFR-guided strategy for PCI with a drug-eluting stent (DES) will show significantly lower rates of patients-oriented composite outcomes at 24 months after randomization, compared with IVUS-guided strategy for PCI with a DES in patients with intermediate coronary stenosis. | **7p 2) Hypothesis**<br><br>The FFR-guided strategy for PCI with a drug-eluting stent (DES) will show non-inferiority in rates of patients-oriented composite outcomes at 24 months after randomization, compared with IVUS-guided strategy for PCI with a DES in patients with intermediate coronary stenosis. | Specify the hypothesis of this study, as per the IRB recommendations. |
| **9p 3) Sample Size Calculation**<br><br>Hypothesis: The FFR-guided strategy will show significantly lower rates of patients-oriented composite outcomes at 24 months after randomization, compared with IVUS-guided strategy in patients with intermediate coronary stenosis.<br><br>Based on the event rates of a previous trials evaluated FFR-guided PCI strategy (FAME I 2 year results)(3) or meta-analysis compared IVUS-guided PCI versus angiography-guided PCI strategy(8), we predicted the rates of patient-oriented composite outcomes (POCO) at 24 months after PCI to be 15% and 20%, respectively.<br><br>• Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any repeat revascularization) at 24 months after PCI<br>• Design: non-inferiority (two-sided test)<br>• Sampling ratio: FFR-guided strategy : IVUS-guided strategy = 1:1<br>• Type I error (α): One-sided 5% | **9p 3) Sample Size Calculation**<br><br>Hypothesis: The FFR-guided strategy for PCI with a drug-eluting stent (DES) will show non-inferiority in rates of patients-oriented composite outcomes at 24 months after randomization, compared with IVUS-guided strategy for PCI with a DES in patients with intermediate coronary stenosis.<br><br>Based on the event rates of a previous trials evaluated FFR-guided PCI strategy (FAME I 2 year results)(3) or meta-analysis compared IVUS-guided PCI versus angiography-guided PCI strategy(8), we predicted the rates of patient-oriented composite outcomes (POCO) at 24 months after PCI to be 10% and 12%, respectively.<br><br>• Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any repeat revascularization) at 24 months after PCI<br>• Design: non-inferiority , delta = 2.5%<br>• Sampling ratio: FFR-guided strategy : IVUS-guided strategy = 1:1<br>• Type I error (α): One-sided 5% | Specify the sample size calculation, as per the IRB recommendations. |

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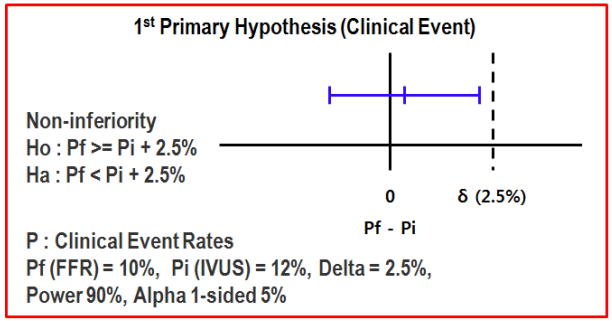
| • Accrual time : 2 years<br>• Total time : 4 years (accrual 2 year + follow-up 2 years)<br>• Assumption: POCO 10.0% vs. 12.0% in FFR or IVUS-guided strategy, respectively<br>• Statistical power (1- β): 90%<br>• Primary statistical method : Kaplan-Meier survival analysis with log-rank test<br>• Potential withdrawal rates : total 2%<br>• Stratification in Randomization: Presence of Diabetes Mellitus (600 patients (35%) will be Diabetic patients, with 300 patients in each group)<br><br>Based on the above assumption, we would need total 1,700 patients (850 patients in each group) with consideration of withdrawal rates. | • Accrual time : 2 years<br>• Total time : 4 years (accrual 2 year + follow-up 2 years)<br>• Assumption: POCO 10.0% vs. 12.0% in FFR or IVUS-guided strategy, respectively<br>• Statistical power (1- β): 90%<br>• Primary statistical method : Kaplan-Meier survival analysis with log-rank test<br>• Potential withdrawal rates : total 2%<br>• Stratification in Randomization: Presence of Diabetes Mellitus (600 patients (35%) will be Diabetic patients, with 300 patients in each group)<br><br>  <br><br>Based on the above assumption, we would need total 1,700 patients (850 patients in each group) with consideration of withdrawal rates. | |

| Previous Version Number<br>Ver 5.1 (Jun 28. 2017) | Latter Version Number<br>Ver 6.0 (Nov 17. 2017) | Specific Reason of Modification |
|---|---|---|
| **2page Research Summary, Study Period** &<br>**9 page Study Period**<br>Study Period: From the 'IRB approval date of each participating center' to 2021.12.31 | **2page Research Summary, Study Period & 9 page Study Period**<br>Study Period: From the 'IRB approval date of each participating center' to 2022.12.31 | Updated IRB approval date, as the recruiting time had to be prolonged. |
| **4page 2. Clinical Research Center**<br>(1) Seoul National University Hospital<br>101, Daehak-ro, Jongno-gu, Seoul, Korea<br>(2) Ajou University Hospital<br>164 World Cup-ro, Yeongtong-gu, Suwon, Korea<br>(3) Inje University Ilsan Paik Hospital,<br>170 Juhwa-ro, Ilsanseo-gu,Goyang, Korea<br>(4) Ulsan University Hospital, University of Ulsan College of Medicine<br>877 Bangeojinsunhwando-ro, Dong-gu, Ulsan, Korea<br>(5) Keimyung University Dongsan Medical Center<br>56 Dalseong-Ro, Jung-Gu, Daegu, Korea<br>(6) Samsung Medical Center<br>81 Irwon-Ro Gangnam-gu. Seoul, Korea<br>(7) Kangwon National University Hospital<br>Baengnyeong-ro 156, Chuncheon-Si, Gangwon-Do<br>(8) Second Affiliated Hospital of Zhejiang University | **4page 2. Clinical Research Center**<br>(1) Seoul National University Hospital<br>101, Daehak-ro, Jongno-gu, Seoul, Korea<br>(2) Ajou University Hospital<br>164 World Cup-ro, Yeongtong-gu, Suwon, Korea<br>(3) Inje University Ilsan Paik Hospital,<br>170 Juhwa-ro, Ilsanseo-gu,Goyang, Korea<br>(4) Ulsan University Hospital, University of Ulsan College of Medicine<br>877 Bangeojinsunhwando-ro, Dong-gu, Ulsan, Korea<br>(5) Keimyung University Dongsan Medical Center<br>56 Dalseong-Ro, Jung-Gu, Daegu, Korea<br>(6) Samsung Medical Center<br>81 Irwon-Ro Gangnam-gu. Seoul, Korea<br>(7) Kangwon National University Hospital<br>Baengnyeong-ro 156, Chuncheon-Si, Gangwon-Do<br>(8) Second Affiliated Hospital of Zhejiang University | Modified participating centers and co-investigators. |

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| School of Medicine<br>88 Jiefang Road, Hangzhou, Zhejiang, China<br>(9) The 1st Affiliated Hospital of Wenzhou Medical University<br>2 Fuxuexiang Luchengqu, Wenzhou, Zhejiang<br>(10) The 2nd Affiliated Hospital of Wenzhou Medical University<br>109 Xueyuan West Road, Wenzhou, Zhejiang<br>(11) Ningbo First Hospital<br>59 Liu ting street, Ningbo, Zhejiang<br>(12) Hangzhou First people's Hospital<br>261 Huansha Road Shangchengqu, Hangzhou, Zhejiang | School of Medicine<br>88 Jiefang Road, Hangzhou, Zhejiang<br>(9) The 1st Affiliated Hospital of Wenzhou Medical University<br>2 Fuxuexiang Luchengqu, Wenzhou, Zhejiang<br>(10) The 2nd Affiliated Hospital of Wenzhou Medical University<br>109 Xueyuan West Road, Wenzhou, Zhejiang<br>(11) Ningbo First Hospital<br>59 Liu ting street, Ningbo, Zhejiang<br>(12) Hangzhou First people's Hospital<br>261 Huansha Road Shangchengqu, Hangzhou, Zhejiang<br>(13) KyungHee University Medical Center<br>23, Kyung Hee Dae-ro, Dongdaemun-gu, Seouk, Korea<br>(14) Yonsei University Wonju Severance Hospital<br>20,Ilsan-ro, Wonju, Gangwon-do, Korea | |
| **7page 3. Principal Investigator, Staff, Co-researchers**<br>Staff – Jeehoon Kang, Jinlong Zhang, Jeong Hee Jang<br>Co-researchers - Kyung Woo Park, Han-mo Yang, Jung Kyu Han, Eun-Seok Shin, Changwook Nam, Joo Yong Hahn, Joonhyung Doh, Mung-ho Yun, Soyoun Choi, Byung-Joo Choi, Kyung Woo Suh, Hong Seok Lim, Hyung Mo Yang, Bong Ki Lee, Joo Myung Lee,<br>Xinyang Hu, Xinguo Tong, Peiren Shan, Peng Chen, | **7page 3. Principal Investigator, Staff, Co-researchers**<br>Staff – Jeehoon Kang, Jinlong Zhang, Jeong Hee Jang,<br>Lee Sun Hwa<br>Co-researchers - Kyung Woo Park, Han-mo Yang, Jung Kyu Han, Eun-Seok Shin, Changwook Nam, Joo Yong Hahn, Joonhyung Doh, Mung-ho Yun, Soyoun Choi, Byung-Joo Choi, Kyung Woo Suh, Hong Seok Lim, Hyung Mo Yang, Bong Ki Lee, Joo Myung Lee, | Modified staff and co-investigators. |

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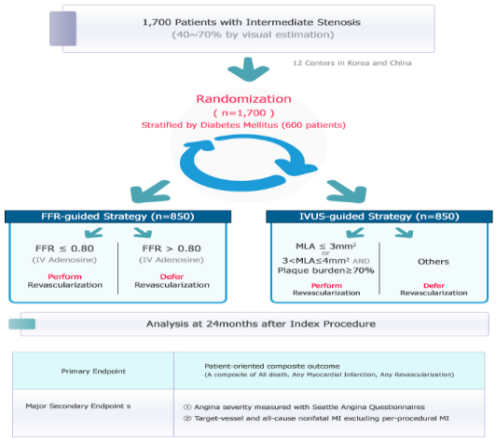
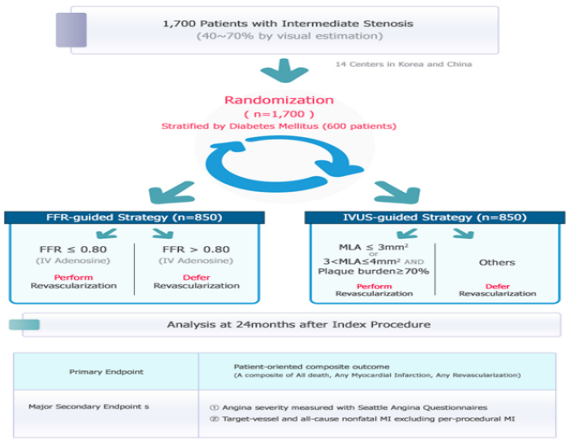
| Hanbin Cui | Xinyang Hu, Xinguo Tong, Peiren Shan, Peng Chen, Hanbin Cui, Won Kim, Sung Gyun Ahn | |
| **6page 4. Funding Agencies**<br><br>Boston Scientific<br><br>The current study is an Investigator initiated trial. Boston Scientific will provide IVUS for the current study. | **6page 4. Funding Agencies**<br><br>Boston Scientific<br><br>This study is a research project independently conducted, without commission from an outside agency. The funding agency, Boston Scientific will provide IVUS catheters and related devices. | Specified the role of the funding agency. |
| **23page 13) Study Schedule**<br><br>Patient enrollment: IRB approval date ~ 2018.04 (**roughly** 24 months of enrollment)<br><br>End of follow-up period: 2020. 04 (2 years of follow-up)<br><br>Analysis and report: ~2021.12.31 | **23page 13) Study Schedule**<br><br>Patient enrollment: IRB approval date ~ 2019.04 (**roughly** 36 months of enrollment)<br><br>End of follow-up period: 2021. 04 (2 years of follow-up)<br><br>Analysis and report: ~2022.12.31 | Updated IRB approval date, as the recruiting time had to be prolonged. |

| 13page Flow chart | 13page Flow chart | |
|---|---|---|
|  |  | Added participating centers to the flow chart. |

| Previous Version Number<br>Ver 6.0 (Nov 17. 2017) | Latter Version Number<br>Ver 6.1 (Dec 06. 2017) | Specific Reason of Modification |
|---|---|---|
| **2page Research Summary, Eligible criteria**<br><br>**(1) Inclusion Criteria**<br><br>⑥Target vessels are limited to proximal to mid LAD, proximal to mid LCX, and RCA proximal to the PL-PDA bifurcation<br><br>**9~10page 9. Eligible criteria, Sample size calculation, 1) Eligible Criteria, (1) Inclusion Criteria**<br><br>⑦ Target lesions located at the proximal to mid part of coronary artery<br><br>⑧ | **2page Research Summary Eligible criteria**<br><br>**(1) Inclusion Criteria**<br><br>⑥Target vessels are limited to proximal to mid LAD, proximal to distal LCX, and RCA proximal to the PL-PDA bifurcation<br><br>**9~10page 9. Eligible criteria, Sample size calculation, 1) Eligible Criteria, (1) Inclusion Criteria**<br><br>⑥ Target vessels are limited to proximal to mid LAD, proximal to distal LCX, and RCA proximal to the PL-PDA bifurcation | Modified the inclusion criteria, so as to clarify the study. |
| **6page Principal Investigator, Staff, Co-researchers**<br>  <br>Co-researchers: Kyung Woo Park, Seoul National University Hospital, Professor<br>Han-mo Yang, Seoul National University Hospital, Professor<br>Jung Kyu Han, Seoul National University Hospital, Professor | **6page Principal Investigator, Staff, Co-researchers**<br>  <br>Co-researchers: Kyung Woo Park, Seoul National University Ho<br>Hyun-Jai Cho, Seoul National University Ho<br>Han-mo Yang, Seoul National University Ho | Added additional co-researchers. |

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| Eun-Seok Shin | Ulsan University Hospital | Professor | |
| Changwook Nam | Keimyung University Dongsan Medical Center | Professor | |
| Joo Yong Hahn | Samsung Medical Center | Professor | |
| Joonhyung Doh | Inje University Ilsan Paik Hospital | Professor | |
| Mung-ho Yun | Ajou University Hospital | Professor | |
| Soyoun Choi | Ajou University Hospital | Professor | |
| Byung-Joo Choi | Ajou University Hospital | Professor | |
| Kyung Woo Suh | Ajou University Hospital | Professor | |
| Hong Seok Lim | Ajou University Hospital | Professor | |
| Hyung Mo Yang | Ajou University Hospital | Professor | |
| Bong Ki Lee | Kangwon National University Hospital | Professor | |
| Joo Myung Lee | Samsung Medical Center | Professor | |
| Won Kim | KyungHee University Medical Center | Professor | |
| Sung Gyun Ahn | Yonsei University Wonju Severance Hospital | Professor | |
| Xinyang Hu | 2nd Affiliated Hospital of Zhejiang University | Professor | |
| Xinguo Tong | Hangzhou First people's Hospital | Professor | |
| Peiren Shan | 1st Affiliated Hospital of Wenzhou Medical University | Professor | |
| Peng Chen | 2nd Affiliated Hospital of Wenzhou Medical University | Professor | |
| Hanbin Cui | Ningbo First Hospital | Professor | |

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| Jung Kyu Han | Seoul National University H |
| Eun-Seok Shin | Ulsan University Hospit |
| Changwook Nam | Keimyung University Dongsan Me |
| Joo Yong Hahn | Samsung Medical Cent |
| Joonhyung Doh | Inje University Ilsan Paik Ho |
| Mung-ho Yun | Ajou University Hospit |
| Soyoun Choi | Ajou University Hospit |
| Byung-Joo Choi | Ajou University Hospit |
| Kyung Woo Suh | Ajou University Hospit |
| Hong Seok Lim | Ajou University Hospit |
| Hyung Mo Yang | Ajou University Hospit |
| Bong Ki Lee | Kangwon National University |
| Joo Myung Lee | Samsung Medical Cent |
| Won Kim | KyungHee University Medical |
| Sung Gyun Ahn | Yonsei University Wonju Severanc |
| Xinyang Hu | 2nd Affiliated Hospital of Zhejian |
| Xinguo Tong | Hangzhou First people's Ho |
| Peiren Shan | 1st Affiliated Hospital of Wenzh University |
| Peng Chen | 2nd Affiliated Hospital of Wenzh University |
| Hanbin Cui | Ningbo First Hospital |

| Previous Version Number<br>Ver 6.1 (Dec 06. 2017) | Latter Version Number<br>Ver 6.2 (Apr 17. 2018) | Specific Reason of Modification |
|---|---|---|
| **2page Research Summary, Patient enrollment**<br>1,700 patients enrolled at 14 centers in Republic of Korea and China | **2page Research Summary, Patient enrollment**<br>1,700 patients enrolled at 18 centers in Republic of Korea and China | Added participating centers. |
| **5~6page 2. Clinical Research Center**<br>**(11) Ningbo First Hospital**<br>**59 Liu ting street, Ningbo, Zhejiang**<br>**(12) Hangzhou First people's Hospital**<br>**261 Huansha Road Shangchengqu, Hangzhou, Zhejiang**<br>**(13) KyungHee University Medical Center**<br>**23, Kyung Hee Dae-ro, Dongdaemun-gu, Seouk, Korea**<br>**(14) Yonsei University Wonju Severance Hospital**<br>**20,Ilsan-ro, Wonju, Gangwon-do, Korea** | **5~6page 2. Clinical Research Center**<br>**, Zhejiang**<br>**(12) Hangzhou First people's Hospital**<br>**261 Huansha Road Shangchengqu, Hangzhou, Zhejiang**<br>**(13) KyungHee University Medical Center**<br>**23, Kyung Hee Dae-ro, Dongdaemun-gu, Seouk, Korea**<br>**(14) Yonsei University Wonju Severance Hospital**<br>**20,Ilsan-ro, Wonju, Gangwon-do, Korea**<br>**(15) Hangzhou Normal University's affiliated Hospital**<br>**126 Wenzhou Road, Gongshu District, Hangzhou**<br>**(16) Taizhou Hospital of Zhejiang Province**<br>**150 Ximen Road of Linhai City, Taizhou P.R China 317000**<br>**(17) Zhejiang Hospital** | Added participating centers |

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| | **12 Lingyin Road , Hangzhou**<br><br>**(18) Yeungnam University Medical Center**<br><br>**170, Hyeonchung-ro, Nam-gu, Daegu, Republic of Korea** | |
| **6~7 page 3. Principal Investigator, Staff, Co-researchers**<br><br>Xinguo Tong Hangzhou First people's Hospital Profes<br>Peiren Shan 1st Affiliated Hospital of Wenzhou Medical University Profes<br>Peng Chen 2nd Affiliated Hospital of Wenzhou Medical University Profes<br>Hanbin Cui Ningbo First Hospital Profes | **6~7 page 3. Principal Investigator, Staff, Co-researchers**<br><br>Peng Chen 2nd Affiliated Hospital of Wenzhou Medical University Professo<br>Hanbin Cui Ningbo First Hospital Professo<br>Jiang Fan The Affiliated Hospital Of Hangzhou Normal University Professo<br>Jiang Jianjun Taizhou Hospital Professo<br>Ujiang Tang Zhejiang Hospital Professo<br>Kim Woong Yeungnam University Medical Center Professo | Added participating co-investigators |
| **9 page 6. Research Materials and Indication for Revascularization**<br><br>**2) IVUS-guided strategy arm**<br><br>iLabTM ultrasound imaging system (Boston Scientific)<br><br>Criteria for revascularization: Minimum lumen area (MLA) ≤ 3mm2 or (MLA ≤ 4mm2<br><br>AND Plaque burden >70%) | **9 page 6. Research Materials and Indication for Revascularization**<br><br>**2) IVUS-guided strategy arm**<br><br>iLabTM ultrasound imaging system (Boston Scientific)<br><br>Criteria for revascularization: Minimum lumen area (MLA) ≤ 3mm$^2$ or 3< MLA ≤ 4mm$^2$<br><br>AND Plaque burden >70%) | Specified and modified the inclusion criteria, so as to clarify the study. |

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| **12page 10. Methods**<br><br>According to the pre-defined criteria for revascularization (FFR ≤ 0.80 in FFR-guided strategy group; MLA < 3mm2 or MLA < 4mm2 and plaque burden > 70% in IVUS-guided strategy group), the patient's will be treated with PCI or not. Optimization of PCI will be recommended to meet the criteria as follows. | **12page 10. Methods**<br><br>According to the pre-defined criteria for revascularization (FFR ≤ 0.80 in FFR-guided strategy group; MLA ≤ 3mm2 or 3 <MLA ≤ 4mm2 and plaque burden > 70% in IVUS-guided strategy group), the patient's will be treated with PCI or not. Optimization of PCI will be recommended to meet the criteria as follows | |

| Previous Version Number<br>Ver 6.2 (Apr 17. 2018) | Latter Version Number<br>Ver 6.3 (Apr 19. 2018) | Specific Reason of Modification |
|---|---|---|
| **2page Research Summary, Patient enrollment**<br>1,700 patients enrolled at 18centers in Republic of Korea and China | **2page Research Summary, Patient enrollment**<br>1,700 patients enrolled at 19centers in Republic of Korea and China | Added a participating center |
| **5~6page 2. Clinical Research Center**<br>12) Hangzhou First people's Hospital<br>261 Huansha Road Shangchengqu, Hangzhou, Zhejiang<br>(13) KyungHee University Medical Center<br>23, Kyung Hee Dae-ro, Dongdaemun-gu, Seouk, Korea<br>(14) Yonsei University Wonju Severance Hospital<br>20,Ilsan-ro, Wonju, Gangwon-do, Korea<br>(15) Hangzhou Normal University's affiliated Hospital<br>126 Wenzhou Road, Gongshu District, Hangzhou<br>(16) Taizhou Hospital of Zhejiang Province<br>150 Ximen Road of Linhai City, Taizhou P.R China 317000<br>(17) Zhejiang Hospital<br>12 Lingyin Road , Hangzhou<br>(18) Yeungnam University Medical Center<br>170, Hyeonchung-ro, Nam-gu, Daegu, Republic of | **5~6page 2. Clinical Research Center**<br>(12) Hangzhou First people's Hospital<br>261 Huansha Road Shangchengqu, Hangzhou, Zhejiang<br>(13) KyungHee University Medical Center<br>23, Kyung Hee Dae-ro, Dongdaemun-gu, Seouk, Korea<br>(14) Yonsei University Wonju Severance Hospital<br>20,Ilsan-ro, Wonju, Gangwon-do, Korea<br>(15) Hangzhou Normal University's affiliated Hospital<br>126 Wenzhou Road, Gongshu District, Hangzhou<br>(16) Taizhou Hospital of Zhejiang Province<br>150 Ximen Road of Linhai City, Taizhou P.R China 317000<br>(17) Zhejiang Hospital<br>12 Lingyin Road , Hangzhou<br>(18) Yeungnam University Medical Center<br>170, Hyeonchung-ro, Nam-gu, Daegu, Republic of | Added a participating center |

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| Korea | Korea<br>(19) Sejong Hospital<br>28, Hohyeon-ro 489, Bucheon-si, Gyeonggi-do, Republic of Korea | |
| **6~7 page 3. Principal Investigator, Staff, Co-researchers**<br>Peng Chen — University<br>Hanbin Cui — Ningbo First Hospital<br>Jiang Fan — The Affiliated Hospital Of Hangzhou Normal University<br>Jiang Jianjun — Taizhou Hospital<br>Lijiang Tang — Zhejiang Hospital<br>Kim Woong — Yeungnam University Medical Center | **6~7 page 3. Principal Investigator, Staff, Co-researchers**<br>Xinguo Tong — Hangzhou First people's Hospital<br>Peiren Shan — 1st Affiliated Hospital of Wenzhou Medical University<br>Peng Chen — 2nd Affiliated Hospital of Wenzhou Medical University<br>Hanbin Cui — Ningbo First Hospital<br>Jiang Fan — The Affiliated Hospital Of Hangzhou Normal University<br>Jiang Jianjun — Taizhou Hospital<br>Lijiang Tang — Zhejiang Hospital<br>Kim Woong — Yeungnam University Medical Center<br>Lee Hyun Jong — Sejong Hospital | Added a co-researcher |

| Previous Version Number<br>Ver 6.3 (Apr 19. 2018) | Latter Version Number<br>Ver 6.4 (Jun 07. 2018) | Specific Reason of Modification |
|---|---|---|
| **2page Research Summary, Patient enrollment**<br>1,700 patients enrolled at 19centers in Republic of Korea and China | **2page Research Summary, Patient enrollment**<br>1,700 patients enrolled at 18centers in Republic of Korea and China | Modified participating centers. |
| **5~6page 2. Clinical Research Center**<br>12) Hangzhou First people's Hospital<br>261 Huansha Road Shangchengqu, Hangzhou, Zhejiang<br>(13) KyungHee University Medical Center<br>23, Kyung Hee Dae-ro, Dongdaemun-gu, Seouk, Korea<br>(14) Yonsei University Wonju Severance Hospital<br>20,Ilsan-ro, Wonju, Gangwon-do, Korea<br>(15) Hangzhou Normal University's affiliated Hospital<br>126 Wenzhou Road, Gongshu District, Hangzhou<br>(16) Taizhou Hospital of Zhejiang Province<br>150 Ximen Road of Linhai City, Taizhou P.R China 317000<br>(17) Zhejiang Hospital<br>12 Lingyin Road , Hangzhou<br>(18) Yeungnam University Medical Center<br>170, Hyeonchung-ro, Nam-gu, Daegu, Republic of Korea | **5~6page 2. Clinical Research Center**<br>(12) Hangzhou First people's Hospital<br>261 Huansha Road Shangchengqu, Hangzhou, Zhejiang<br>(13) KyungHee University Medical Center<br>23, Kyung Hee Dae-ro, Dongdaemun-gu, Seouk, Korea<br>(14) Yonsei University Wonju Severance Hospital<br>20,Ilsan-ro, Wonju, Gangwon-do, Korea<br>(15) Hangzhou Normal University's affiliated Hospital<br>126 Wenzhou Road, Gongshu District, Hangzhou<br>(16) Taizhou Hospital of Zhejiang Province<br>150 Ximen Road of Linhai City, Taizhou P.R China 317000<br>(17) Zhejiang Hospital<br>12 Lingyin Road , Hangzhou<br>(18) Yeungnam University Medical Center<br>170, Hyeonchung-ro, Nam-gu, Daegu, Republic of Korea | Modified participating centers. |

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| ~~(19) Sejong Hospital~~<br><br>~~28, Hohyeon-ro 489, Bucheon-si, Gyeonggi-do, Republic of Korea~~ | | |
| **6~7 page 3. Principal Investigator, Staff, Co-researchers**<br><br>Xinguo Tong — Hangzhou First people's Hospital — P<br>Peiren Shan — 1st Affiliated Hospital of Wenzhou Medical University — P<br>Peng Chen — 2nd Affiliated Hospital of Wenzhou Medical University — P<br>Hanbin Cui — Ningbo First Hospital — P<br>Jiang Fan — The Affiliated Hospital Of Hangzhou Normal University — P<br>Jiang Jianjun — Taizhou Hospital — P<br>Lijiang Tang — Zhejiang Hospital — P<br>Kim Woong — Yeungnam University Medical Center — P<br>~~Lee Hyun Jong — Sejong Hospital~~ | **6~7 page 3. Principal Investigator, Staff, Co-researchers**<br><br>Peng Chen — University<br>Hanbin Cui — Ningbo First Hospital<br>Jiang Fan — The Affiliated Hospital Of Hangzhou Normal University<br>Jiang Jianjun — Taizhou Hospital<br>Lijiang Tang — Zhejiang Hospital<br>Kim Woong — Yeungnam University Medical Center | Removed 1 co-investigator |

| Previous Version Number<br>Ver 6.4 (Jun 07. 2018) | Latter Version Number<br>Ver 7.0 (Aug 07. 2018) | Specific Reason of Modification |
|---|---|---|
| **2page Objectives**<br>To compare~ intermediate coronary stenosis. | **2page Objectives**<br>To compare~ de novo intermediate coronary stenosis. | Specified and modified the objective, so as to clarify the study. – Specified the inclusion criteria to exclude in-stent restenosis lesions to be included in the study. |
| **2page Patient enrollment**<br>18center | **2page Patient enrollment**<br>20center | Added participating centers |
| 2page & 10page Eligible criteria (1) Inclusion Criteria<br>③ Patients with intermediate~FFR or IVUS clinically for further evaluation | 2page & 10page Eligible criteria (1) Inclusion Criteria<br>④ Patients with de novo intermediate~ FFR or IVUS clinically for further evaluation | Specified and modified the objective, so as to clarify the study. – Specified the inclusion criteria to exclude in-stent restenosis lesions to be included in the study. |
| 2page & 11page Eligible criteria **(2) Exclusion Criteria**<br>① ~⑦ | 2page & 11page Eligible criteria **(2) Exclusion Criteria**<br>①~⑦<br>⑧ Target lesion located in previous PCI segment with in-stent restenosis. | |
| 5page 2. **Clinical Research Center**<br>**(1)** Seoul National University Hospital~<br>~~(4) Ulsan University Hospital, University of Ulsan College of Medicine~~ ~<br>(18) Yeungnam University Medical Center | 5page 2. **Clinical Research Center**<br>**(1)** Seoul National University Hospital~<br>(17) Yeungnam University Medical Center<br>(18) Wenzhou People's Hospital<br>(19) Ningbo University<br>(20) Chosun University Hospital | Removed 1 center, added 2 centers |
| 6page **3. Principal Investigator, Staff, Co-researchers**<br>~~Staff Jeehoon Kang (Clinical Fellow)~~ | 6page **3. Principal Investigator, Staff, Co-researchers**<br>Co-researchers Jeehoon Kang (Professor) | Modified the affiliation and position of co-investigators. |

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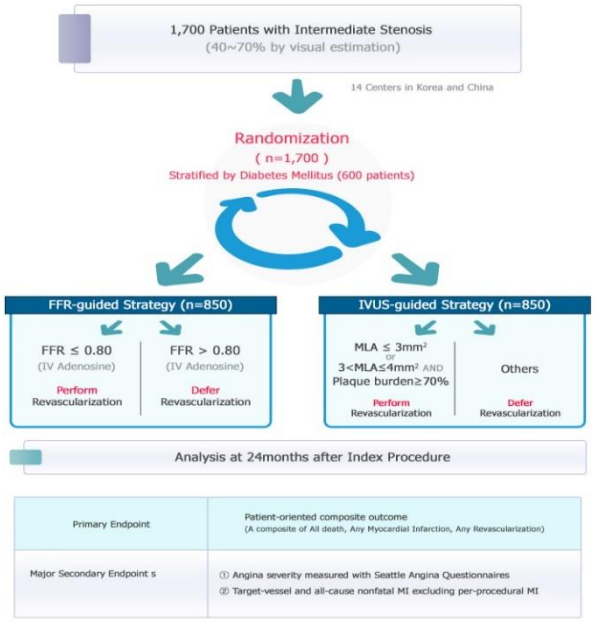
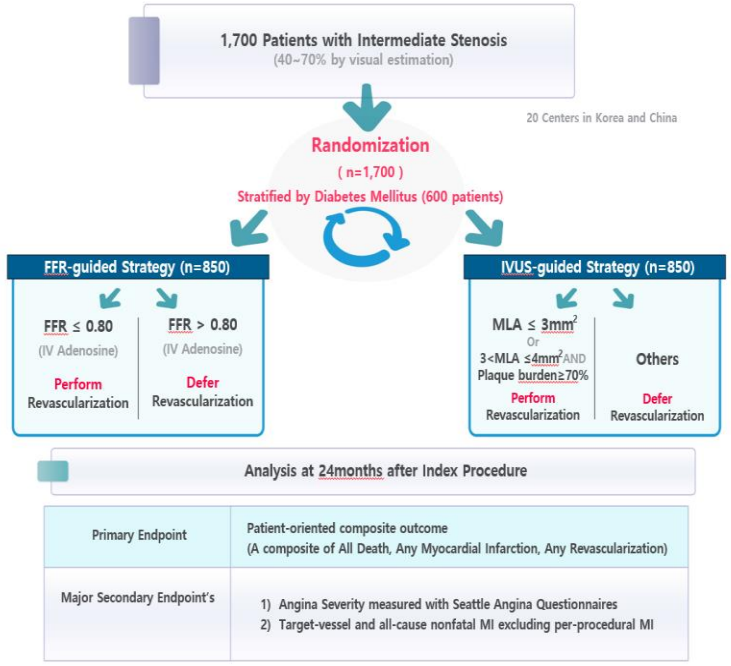
| ~~Eun-Seok Shin~~ | **Hyeonguk Kim,** Wenbing Jiang, Wenming He | |
| 10page 7. **Study Population**<br><br>1,700 patients derived from Korea and China with angina and intermediate coronary stenosis in coronary angiography who~ enrolled in the present trial. | 10page 7. **Study Population**<br><br>1,700 patients derived from Korea and China with angina and<br><br>de novo intermediate coronary stenosis in coronary angiography who~ enrolled in the present trial. | Specified and modified the objective, so as to clarify the study. – Specified the inclusion criteria to exclude in-stent restenosis lesions to be included in the study. |
|  |  | Modified the study flow |
| 18 page **(2) Executive Committee**<br><br>Committee members<br><br>~~Eun-Seok Shin,~~<br><br>Bong-Ki Lee, Changwook Nam, Joonhyung Doh | 18 page **(2) Executive Committee**<br><br>Committee members<br><br>Bong-Ki Lee, Changwook Nam, Joonhyung Doh | Removed 1 co-investigator |

| Previous Version Number<br>Ver 7.0 (Aug 07. 2018) | Latter Version Number<br>Ver 8.0 (Feb 27. 2019) | Specific Reason of Modification |
|---|---|---|
| **FLAVOUR Protocol Version 7.0** | **FLAVOUR Protocol Version 8.0** | Update the version |
| 1page Co-Principal investigators<br>Seung-Jae Tahk, Ajou University Hospital | 1page Co-Principal investigators<br>Mung-ho Yun, Ajou University Hospital | Modified co-investigators. |
| 2page Co-Principal investigator<br>Seung-Jae Tahk, Ajou University Hospital<br>Bon-Kwon Koo, Seoul National University Hospital | 2page Co-Principal investigator<br>Mung-ho Yun, Ajou University Hospital<br>Bon-Kwon Koo, Seoul National University Hospital | |
| 2page Patient enrollment<br>1,700 patients enrolled at 20 centers in Republic of Korea and China | 2page Patient enrollment<br>1,700 patients enrolled at 18centers in Republic of Korea and China | Removed 2 participating centers |
| 5~6 page **2. Clinical Research Center**<br>(1) Seoul National University Hospital<br>(2) Ajou University Hospital<br>(3) Inje University Ilsan Paik Hospital,<br>(4) Keimyung University Dongsan Medical Center<br>(5) Samsung Medical Center<br>(6) Kangwon National University Hospital<br>(7) Second Affiliated Hospital of Zhejiang University School of Medicine<br>(8) The 1st Affiliated Hospital of Wenzhou Medical University<br>(9) The 2nd Affiliated Hospital of Wenzhou Medical University | 5~6 page **2. Clinical Research Center**<br>(1) Seoul National University Hospital<br>(2) Ajou University Hospital<br>(3) Inje University Ilsan Paik Hospital,<br>(4) Keimyung University Dongsan Medical Center<br>(5) Samsung Medical Center<br>(6) Kangwon National University Hospital<br>(7) Second Affiliated Hospital of Zhejiang University School of Medicine<br>(8) The 1st Affiliated Hospital of Wenzhou Medical University<br>(9) The 2nd Affiliated Hospital of Wenzhou Medical University | Removed 2 participating centers |

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| (10) Ningbo First Hospital<br>(11) Hangzhou First people's Hospital<br>(12) KyungHee University Medical Center<br>(13) Yonsei University Wonju Severance Hospital<br>(14) Hangzhou Normal University's affiliated Hospital<br>~~(15) Taizhou Hospital of Zhejiang Province~~<br>(16) Zhejiang Hospital<br>(17) Yeungnam University Medical Center<br>**(18)** Wenzhou People's Hospital<br>(19) Ningbo University<br>~~**(20)** Chosun University Hospital~~ | (10) Ningbo First Hospital<br>(11) Hangzhou First people's Hospital<br>(12) KyungHee University Medical Center<br>(13) Yonsei University Wonju Severance Hospital<br>(14) Hangzhou Normal University's affiliated Hospital<br>(15) Zhejiang Hospital<br>(16) Yeungnam University Medical Center<br>**(17)** Wenzhou People's Hospital<br>(18) Ningbo University | |
| 6page Principal investigator<br>Seung-Jae Tahk | 6page Principal investigator<br>Mung-ho Yun | Modified co-investigators. |
| 7page **3. Principal Investigator, Staff, Co-researchers**<br><br>Kyung Woo Park, Hyun-Jai Cho, Han-mo Yang, Jung Kyu Han, Jeehoon Kang, ~~**Hyeonguk Kim,**~~ Changwook Nam, Joo Yong Hahn, Joonhyung Doh, ~~Mung-ho Yun,~~ Soyoun Choi, Byung-Joo Choi, Kyung Woo Suh, Hong Seok Lim, Hyung Mo Yang, Bong Ki Lee, Joo Myung | 7page **3. Principal Investigator, Staff, Co-researchers**<br><br>Kyung Woo Park, Hyun-Jai Cho, Han-mo Yang, Jung Kyu Han, Jeehoon Kang, Changwook Nam, YoonKung-cho, Joo Yong Hahn, Joonhyung Doh, Soyoun Choi, Byung-Joo Choi, Kyung Woo Suh, Hong Seok Lim, Hyung Mo Yang, Bong Ki Lee, Joo Myung Lee, Won | Modified co-investigators. |

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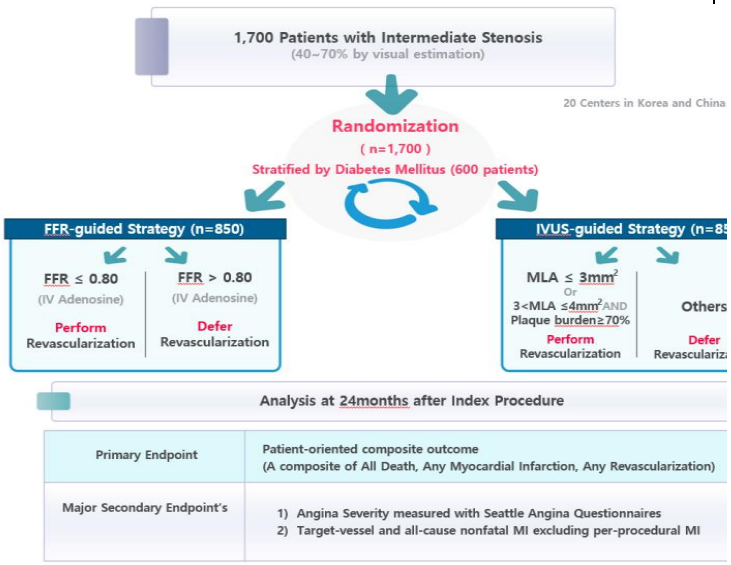
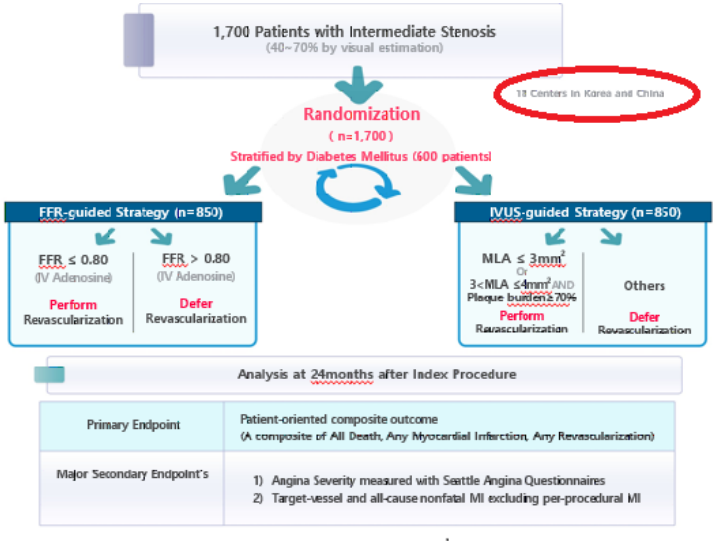
| Lee, Won Kim, Sung Gyun Ahn, Xinyang Hu, Xinguo Tong, Peiren Shan, Peng Chen, Hanbin Cui, Jiang Fan, ~~Jiang Jianjun,~~ Lijiang Tang, Kim Woong, Wenbing Jiang, Wenming He | Kim, Sung Gyun Ahn, Xinyang Hu, Xinguo Tong, Peiren Shan, Peng Chen, Hanbin Cui, Jiang Fan, Lijiang Tang, Kim Woong, Wenbing Jiang, Wenming He | |
| 13 page **2) Flow chart**<br>  | 13 page **2) Flow chart**<br>  | Modified the study flow |
| 17page **(2) Executive Committee**<br><br>Chairman Seung-Jae Tahk | 17page **(2) Executive Committee**<br><br>Chairman Mung-ho Yun | Modifed the chairman of Executive Committee |

| Previous Version Number<br>Ver 8.0 (Feb 27. 2019) | Latter Version Number<br>Ver8.1 (Jul 05. 2019) | Specific Reason of Modification |
|---|---|---|
| **1p**<br>Co-Principal investigators:<br>Seoul National University Hospital, Korea Bon-Kwon Koo<br>Ajou University Hospital, Korea Mung-ho Yun | **1p**<br>Co-Principal investigators:<br>Seoul National University Hospital, Korea Bon-Kwon Koo<br>Ajou University Hospital, Korea Mung-ho Yun<br>Second affiliated hospital of Zhejiang Univ School of Medicine, Jianan Wang | Modified the error on cover page |
| **5p 2. Clinical Research Center**<br>(1) Seoul National University Hospital ~<br>(3) Inje University Ilsan Paik Hospital<br>(4) Keimyung University Dongsan Medical Center<br>56 Dalseong-Ro, Jung-Gu, Daegu, Korea<br>(5) Samsung Medical Center~~(18) Ningbo University | **5p 2. Clinical Research Center**<br>(1) Seoul National University Hospital ~<br>(3) Inje University Ilsan Paik Hospital<br>(4) Keimyung University Dongsan Medical Center<br>1035, Dalgubeol-daero, Dalseo-gu, Daegu, Korea<br>(5) Samsung Medical Center~~(18) Ningbo University | Modified one center's address |
| **7p Co-researchers**<br>~~Kyung Woo Park, Hyun Jai Cho, Han mo Yang, Jung Kyu~~<br>~~Han~~, Jeehoon Kang, YoonKung-cho, Joo Yong Hahn, Joonhyung Doh, Soyoun Choi, Byung-Joo Choi, Kyung Woo Suh, Hong Seok Lim, Hyung Mo Yang, Bong Ki Lee,<br>Joo Myung Lee, Won Kim, Sung Gyun Ahn, Xinyang Hu, Xinguo Tong, Peiren Shan, Peng Chen, Hanbin Cui, Jiang Fan, Lijiang Tang, Kim Woong, Wenbing Jiang, | **7p Co-researchers**<br>Jeehoon Kang, YoonKung-cho, Joo Yong Hahn, Joonhyung Doh, Soyoun Choi, Byung-Joo Choi, Kyung Woo Suh, Hong Seok Lim, Hyung Mo Yang, Bong Ki Lee,<br>Joo Myung Lee, Won Kim, Sung Gyun Ahn, Xinyang Hu, Xinguo Tong, Peiren Shan, Peng Chen, Hanbin Cui, Jiang Fan, Lijiang Tang, Kim Woong, Wenbing Jiang, Wenming He | Removed 4 investigators. |

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| Wenming He | | |
| **23p 13) Study Schedule**<br>Patient enrollment: IRB approval date ~ 2019.04<br>(roughly 36 months of enrollment)<br>End of follow-up period: 2021. 04 (2 years of follow-up)<br>Analysis and report: ~2022.12.31 | **23p 13) Study Schedule**<br>Patient enrollment: IRB approval date ~ 2019.07<br>End of follow-up period: 2021. 07 (2 years of follow-up)<br>Analysis and report: ~2022.12.31 | Updated IRB approval date, as the recruiting time had to be prolonged |

| Previous Version Number<br>Ver 8.1 (Jul 05. 2019) | Latter Version Number<br>Ver9.0 (Dec 23. 2019) | Specific Reason of Modification |
|---|---|---|
| **1p Co-Principal investigators**<br>-Seoul National University Hospital, Korea, Bon-Kwon Koo<br>-Ajou University Hospital, Korea, ~~Mung-ho Yun~~<br>-Send affiliated hospital of Zhejiang Univ School of Medicine, China, Jianan Wang | **1p Co-Principal investigators**<br>-Seoul National University Hospital, Korea, Bon-Kwon Koo<br>-Ajou University Hospital, Korea, Seung-Jae Tahk<br>-Send affiliated hospital of Zhejiang Univ School of Medicine, China, Jianan Wang | Modified co-investigators. |
| 2p ~~Co-~~ Principal investigator<br>-Bon-Kwon Koo, Seoul National University Hospital, Korea<br>~~-Mung-ho Yun, Ajou University Hospital, Korea~~<br>~~-Jianan Wang, Send affiliated hospital of Zhejiang Univ School of Medicine, China~~ | 2p Principal investigator<br>Seoul National University Hospital, Korea, Bon-Kwon Koo | Modified information of the PI. |
| 6p **Principal Investigator, Staff, Co-researchers**<br>Bon-Kwon Koo, ~~**Mung-ho Yun,**~~ Jian An Wang | 6p **Co-Principal Investigator, Co-researchers, Staff**<br>Bon-Kwon Koo, Seung-Jae Tahk, Jian An Wang | Modified co-investigators. |
| **7p Co-researchers**<br>Jeehoon Kang, Won Kim, Changwook Nam, YoonKung-cho, Joo Yong Hahn, Joonhyung Doh, Sung Gyun Ahn,<br>Hyung Mo Yang, Soyoun Choi, Byung-Joo Choi, Hong Seok Lim, Kyung Woo Suh, Bong Ki Lee, Joo Myung Lee,<br>Xinyang Hu, Xinguo Tong, Peiren Shan, Peng Chen,<br>Hanbin Cui, Jiang Fan, Lijiang Tang, Kim Woong, | **7p Co-researchers**<br>Jeehoon Kang, Won Kim, Changwook Nam, **Seungho Heo** , YoonKung-cho, **Jincheol Kim**, **Cheolhyeon Lee** , Joo Yong Hahn, Joonhyung Doh, Sung Gyun Ahn, Mung-ho Yun, Hyung Mo Yang, Soyoun Choi, Byung-Joo Choi, Hong Seok Lim, Kyung Woo Suh, Bong Ki Lee, Joo Myung Lee, Xinyang Hu, Xinguo Tong, Peiren Shan, Peng Chen, Hanbin Cui, Jiang Fan, Lijiang Tang, Kim Woong, Wenbing Jiang, Wenming He | Modified co-investigators. |

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| Wenbing Jiang, Wenming He | | |
| 17p **9) Violence of study protocol**<br>③ Revascularization is not performed despite of MLA ≤ 3mm$^2$ or (MLA ≤ 4mm$^2$ AND Plaque burden >70%) (IVUS-guided group) | 17p **9) Violence of study protocol**<br>③ Revascularization is not performed despite of MLA ≤ 3mm$^2$ or (3 < MLA ≤ 4mm$^2$ AND Plaque burden > 70%) (IVUS-guided group) | Synchronized the violation definition within the study protocol. |
| 17p 10) **(2) Executive Committee**<br>Chairman : ~~Mung-ho Yun~~ | 17p 10) **(2) Executive Committee**<br>Chairman : **Seung-Jae Tahk** | Modified the Chairman of Executive Committee. |
| 17p 10) **(2) Executive Committee**<br>Committee members<br>Bong-Ki Lee, Changwook Nam, Joonhyung Doh | 17p 10) **(2) Executive Committee**<br>Committee members<br>Bong-Ki Lee, Changwook Nam, Joonhyung Doh,<br>Eun-Seok Shin, Jianan Wang, Xinyang Hu | Added the Executive Committee members. |
| 19p **12) (1) Analysis Population**<br>Per-protocol population will be defined as populati on who did not violate the study protocol. The definition of protocol following is as follows;<br>**II. Revascularization is performed when MLA ≤ 3mm2 or (MLA ≤ 4mm2 AND Plaque burden >70%) (IVUS-guided group) and revascularization is not performed when of MLA > 3mm2 or (MLA > 4mm2 AND Plaque burden ≤ 70%) (IVUS-guided group)** | 20p **12) (1) Analysis Population**<br>Per-protocol population will be defined as populatio n who did not violate the study protocol. The definition of protocol following is as follows;<br>**II. Revascularization is performed when MLA ≤ 3mm2 or (MLA ≤ 4mm2 AND Plaque burden >70%) (IVUS-guided group) and revascularization is not performed when of MLA > 3mm2 or (3 < MLA > 4mm2 AND Plaque burden ≤ 70%) (IVUS-guided group)** | Synchronized the violation definition within the study protocol. |
| 19p **12) (1) Analysis Population**<br>The definition of protocol violation is as follows;<br>**③ Revascularization is not performed despite of MLA ≤ 3mm$^2$ or (MLA ≤ 4mm$^2$ AND Plaque burden** | 20p **12) (1) Analysis Population**<br>The definition of protocol violation is as follows;<br>**③ Revascularization is not performed despite of MLA ≤ 3mm$^2$ or (3 < MLA ≤ 4mm$^2$ AND Plaque** | |

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| **>70%) (IVUS-guided group)** | **burden > 70%) (IVUS-guided group)** | |
| 24p **13) Study Schedule**<br>Patient enrollment: IRB approval date ~ 2019.07<br>End of follow-up period: 2021. 07 (2 years of follow-up)<br>Analysis and report: ~2022.12.31 | 24p **13) Study Schedule**<br>**13) Study Schedule**<br>Patient enrollment: IRB approval date ~ 2019.08<br>End of follow-up period: 2021. 08 (2 years of follow-up)<br>Analysis and report: ~2022.12.31 | Updated IRB approval date, as the recruiting time had to be prolonged |

| Previous Version Number | Latter Version Number | Specific Reason of Modification |
|---|---|---|
| **Ver 9.0 (Dec 23. 2019)** | **Ver10.0 (Jan 07. 2020)** | |
| **19p 10(5) Data Safety and Monitoring Board**<br>Committee members<br>~~Cheol Woong Yu (Korea University Anam Hospital)~~<br>Soo-Jung Kim (Kyung-Hee University Hospital) | **19p 10(5) Data Safety and Monitoring Board**<br>Committee members<br>Hyun-Kuk Kim (Chosun University Hospital)<br>Soo-Jung Kim (Kyung-Hee University Hospital) | .Modified one DSMB member |

| Previous Version Number<br>Ver 10.0 (Jan 07. 2020) | Latter Version Number<br>Ver 11.0 (Apr 17. 2020) | Specific Reason of Modification |
|---|---|---|
| **3p & 15p Primary endpoint**<br><br>Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction (MI) or any ~~repeat~~ revascularization at 24 months after randomization according to the ARC consensus | **3p & 15p Primary endpoint**<br><br>Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction [MI, including peri-procedural MI (12,13)] or any revascularization at 24 months after randomization according to the ARC consensus(16) | Modified the terminology, to prevent misunderstanding |
| **3p Secondary endpoint**<br><br>① POCO at 12months after randomization according to the ARC consensus<br><br>② Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)<br><br>③ All-cause and cardiac death<br><br>④ Target-vessel and all-cause nonfatal MI without peri-procedural MI<br><br>⑤ Target-vessel and all-cause nonfatal MI with peri-procedural MI<br><br>⑥ Target vessel/lesion revascularization (ischemia-driven or all)<br><br>⑦ Non-target vessel/lesion revascularization (ischemia-driven or all)<br><br>⑧ Any revascularization (ischemia-driven or all) | **3p Secondary endpoint**<br><br>① POCO at 12months after randomization according to the ARC consensus<br><br>② Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)<br><br>③ Cost-effectiveness analysis<br><br>④ All-cause and cardiac death<br><br>⑤ Target-vessel and all-cause nonfatal MI without peri-procedural MI<br><br>⑥ Target-vessel and all-cause nonfatal MI with peri-procedural MI (12,13)<br><br>⑦ Peri-procedural MI using referred definitions (17~19)<br><br>⑧ Target vessel/lesion revascularization (ischemia-driven or all)<br><br>⑨ Non-target vessel/lesion revascularization (ischemia- | Added secondary endpoints for an extended study, and references to specify the secondary endpoints |

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| ⑨ Stent thrombosis (definite/probable/possible)<br><br>⑩ Stroke (ischemic and hemorrhagic)<br><br>⑪ Acute success of procedure (device, lesion and procedure)<br><br>⑫ Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month | driven or all)<br><br>⑩ Any revascularization (ischemia-driven or all)<br><br>⑪ Stent thrombosis (definite/probable/possible)<br><br>⑫ Stroke (ischemic and hemorrhagic)<br><br>⑬ Acute success of procedure (device, lesion and procedure)<br><br>⑭ Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month<br>⑮ Plaque characteristics by IVUS (including plaque burden, eccentricity, posterior attenuation, positive remodeling, calcification, etc.) | |
| **7p Co-researchers**<br><br>Keimyung University Dongsan Medical Center<br><br>**Jincheol Kim** | **7p Co-researchers**<br><br>Keimyung University Dongsan Medical Center<br><br>**incheol Kim** | Modified the typing error |
| **11p 3) Sample Size Calculation**<br><br>• Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any ~~repeat~~ revascularization) at 24 months after PCI | **11p 3) Sample Size Calculation**<br><br>• Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any revascularization) at 24 months after PCI | Modified the terminology, to prevent misunderstanding |
| **3p & 15p 5) (1) Primary endpoint**<br><br>Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction (MI, including peri-procedural MI) or any ~~repeat~~ revascularization at 24 months after randomization according to the ARC consensus | **3p & 15p 5) (1) Primary endpoint**<br><br>Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction [MI, including peri-procedural MI (12,13)] or any revascularization at 24 months after randomization according to the ARC consensus(16) | Modified the terminology, to prevent misunderstanding and added references |
| 15p 5) (2) **Secondary endpoint** | 15p 5) (2) **Secondary endpoint** | Added secondary endpoints for an |

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| ⑬ POCO at 12months after randomization according to the ARC consensus<br><br>⑭ Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)<br><br>⑮ All-cause and cardiac death<br><br>16 Target-vessel and all-cause nonfatal MI without peri-procedural MI<br><br>17 Target-vessel and all-cause nonfatal MI with peri-procedural MI<br><br>18 Target vessel/lesion revascularization (ischemia-driven or all)<br><br>19 Non-target vessel/lesion revascularization (ischemia-driven or all)<br><br>20 Any revascularization (ischemia-driven or all)<br><br>21 Stent thrombosis (definite/probable/possible)<br><br>22 Stroke (ischemic and hemorrhagic)<br><br>23 Acute success of procedure (device, lesion and procedure)<br><br>24 Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month<br><br>25 Plaque characteristics by IVUS (including plaque burden, eccentricity, posterior attenuation, positive remodeling, calcification, etc.)” | ① POCO at 12months after randomization according to the ARC consensus<br><br>② Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)<br><br>③ Cost-effectiveness<br><br>④ All-cause and cardiac death<br><br>⑤ Target-vessel and all-cause nonfatal MI without peri-procedural MI<br><br>⑥ Target-vessel and all-cause nonfatal MI with peri-procedural MI(12,13)<br><br>⑦ Periprocedural MI defined as referred.(17-19)<br><br>⑧ Target vessel/lesion revascularization (ischemia-driven or all)<br><br>⑨ Non-target vessel/lesion revascularization (ischemia-driven or all)<br><br>⑩ Any revascularization (ischemia-driven or all)<br><br>⑪ Stent thrombosis (definite/probable/possible)<br><br>⑫ Stroke (ischemic and hemorrhagic)<br><br>⑬ Acute success of procedure (device, lesion and procedure)<br><br>⑭ Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month | extended study, and references to specify the secondary endpoints |

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| | ⑮ Plaque characteristics by IVUS (including plaque burden, eccentricity, posterior attenuation, positive remodeling, calcification, etc.)” | |
| 16p Definition of Periprocedural MI<br><br>[Blank] | 16p Definition of Periprocedural MI<br><br>■ Periprocedural MI will be defined as prior studies.<br><br>■ Definition of Periprocedural MI in the DEFINE FLAIR & SWEDEHEART trials (12, 13)<br><br>◆ Periprocedural MI is considered an event within the first 48 hours after randomisation:<br><br>◆ #. 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"<br><br>◆ #. 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 centile within 24 hours post index PCI" 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 | Added the definition of peri-procedural MI from newly published studies. This was to specify the definition of a secondary endpoint. |

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| | 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<br><br>■Definition of Periprocedural MI in the EXCEL trial (17, 18)<br><br>◆Periprocedural MI was defined for PCI as the occurrence within 72 h after either procedure of (i) CK-MB >10× URL or (ii) CK-MB >5× URL plus one of the following: (i) new pathological Q-waves in at least two contiguous leads or new persistent non-rate-related left bundle branch block; (ii) angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow; or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. For patients with elevated baseline biomarkers at baseline the peak CK-MB level was required to rise from the baseline value by an increment equal to the values above.<br><br>■ Definition of Periprocedural MI in the ISCHEMIA trial (19)<br><br>◆ For subjects with normal baseline biomarker level pre-PCI, peri-PCI MI requires a rise in CK-MB to >5-fold the ULN (or a rise in troponin to >35 times the MI Decision Limit/ULN, whenCKMB is unavailable) within 48 hours post-PCI. If pre-PCI cardiac markers (CKMB or cTn) are elevated, they | |

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| | must be stable or falling as indicated by two samples at least 6h apart. The post-PCI CKMB level should reflect a rise of >20% over pre-PCI levels. In addition to biomarker criteria, peri-PCI MI requires at least one of the following:<br><br>● Post- procedure angiographic TIMI 0/1 flow I n a major coronary artery or aside branch with reference vessel diameter ≥2.0 mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter ≥3.0 mm which had TIMI 3 flow at baseline or Type C dissection (NHLBI classification) or greater in the target vessel.<br><br>● New ECG changes (ST segment elevation or depression >0.1mV in 2contiguous leads), new pathologic Q-waves in ≥2 contiguous leads, or new persistent LBBB present on a post-PCI ECG obtained at least 30 minutes and up to 48 hours post procedure in the absence of any intervening coronary event between the time of the PCI procedure and the ECG showing changes.<br><br>◆ Or stand-alone biomarker definition<br><br>● CK-MB to > 10-fold the ULN (or when CK-MB is unavailable, arise in troponin to > 70-fold the MI decision Limit/ULN) | |

| Previous Version Number<br>Ver 11.0 (Apr 17. 2020) | Latter Version Number<br>Ver 11.1 (Sep 09. 2020) | Specific Reason of Modification |
|---|---|---|
| **4p & 16p Secondary endpoint**<br><br>16. [Blank] | **4p & 16p Secondary endpoint**<br><br>16. QFR analysis (fixed QFR, contrast QFR, delta QFR, and post PCI QFR) | Added a secondary endpoint |
| 9 p 5. 1) **Background**<br><br>Percutaneous coronary intervention (PCI) is ~ This study aims to compare safety and efficacy of physiology (FFR)-guided PCI strategy and imaging (IVUS)-guided PCI strategy in patients with intermediate coronary stenosis. | 10 p 5. 1) **Background**<br><br>Percutaneous coronary intervention (PCI) is ~ This study aims to compare safety and efficacy of physiology (FFR)-guided PCI strategy and imaging (IVUS)-guided PCI strategy in patients with intermediate coronary stenosis.<br><br>Although FFR is the current standard of car for the functional assessment of lesion severity in patients with intermediate-grade stenosis, FFR guided PCI is still underused in real world practice due to the concerns for prolonged procedural time, increased costs, and potential complications by pressure wire. The quantitative flow ratio (QFR) is a novel angiography based approach allowing calculation of FFR by 3-dimensional coronary artery reconstruction and fluid dynamic computation. There are many clinical studies supporting the QFR value and identifying of patients at risk from cardiovascular events.(12, 13) Therefore, we will confirm the accuracy of QFR, the relationship between IVUS and QFR findings, and incremental value of QFR for predicting cardiovascular events. | Added a secondary endpoint and its background. |
| 12 p 10. 1) **Study designs**<br><br>Following angiography, patients with intermediate diameter stenosis 40-70% ~ **In addition, the use of IVUS or FFR according to the assigned group will be permitted as tools for the optimizing PCI in stent type,** | 12 p 10. 1) **Study designs**<br><br>Following angiography, patients with intermediate diameter stenosis 40-70% ~ **In addition, the use of IVUS or FFR according to the assigned group will be permitted as tools for the optimizing PCI in stent type,** | Added a secondary endpoint and its analysis plan. |

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| **PCI procedures and any adjunctive pharmacologic treatment will be left to the operator's discretion.**<br><br>There will be **NO** regulation for any specific usage of the DES.~ If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available. | **PCI procedures and any adjunctive pharmacologic treatment will be left to the operator's discretion.**<br><br>The QFR analysis is only performed on a coronary angiograms that can be analyzed. The Post-procedural QFR will be analyzed in case the PCI is performed.<br><br>There will be **NO** regulation for any specific usage of the DES.~ If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available. | |
| 14 p 4) **Follow-up data**<br><br>[Blank] | 14 p 4) **Follow-up data**<br><br>**QFR analysis data :** Baseline / Post-Procedure**:**<br><br>† The QFR data will be analyzed in the Core-Laboratory in Seoul National University Hospital. The Post-procedural QFR will be analyzed in case the PCI is performed. The QFR analysis is only performed on a coronary angiograms that can be analyzed. | Added a secondary endpoint and its analysis plan as a footnote under the table. |

| Previous Version Number<br>Ver 11.1 (Apr 17. 2020) | Latter Version Number<br>Ver 11.2 (Oct 23. 2020) | Specific Reason of Modification |
|---|---|---|
| 6p 3. Co-Principal Investigator, Co-researchers, Staff<br>Staff :<br>Jinlong Zhang (~~Seoul National University Hospital~~) | 6p 3. Co-Principal Investigator, Co-researchers, Staff<br>Staff<br>Jinlong Zhang (Second affiliated hospital of Zhejiang university school of medicine) | Modified 1 investigator's affiliation |

| Previous Version Number<br>Ver 11.2 (Oct 23. 2020) | Latter Version Number<br>Ver 11.3 (Jan 18. 2021) | Specific Reason of Modification |
|---|---|---|
| **20p (5) Data Safety and Monitoring Board-Committee members**<br>Hyun-Kuk Kim (Chosun University Hospital)<br>~~Soo-Jung Kim (Kyung-Hee University Hospital)~~ | **20p (5) Data Safety and Monitoring Board-Committee members**<br>Hyun-Kuk Kim (Chosun University Hospital)<br>Woojoo Lee (Seoul National University, School of Public Health, Associate Professor) | Modified the DSMP member, due to request from the previous member |

| Previous Version Number<br>Ver 11.3 (Jan 18. 2021) | Latter Version Number<br>Ver 11.4 (Jun 03. 2021) | Specific Reason of Modification |
|---|---|---|
| 15p below of Follow-up data table<br>* The raw data of FFR measurement or IVUS imaging data will be analyzed in the Core-Laboratory in Seoul National University Hospital. The Post-procedural data will be collected in case the PCI is performed. | 15p below of Follow-up data table<br>* The raw data of FFR measurement data will be analyzed in the Core-Laboratory in Seoul National University Hospital. And The IVUS imaging data will be analyzed in the Core-Laboratory in Ulsan University Hospital. The Post-procedural data will be collected in case the PCI is performed. | Added an independent core-laboratory for IVUS evaluation. |
| 19p (2) Executive Committee<br>- Committee members<br>Bong-Ki Lee, Changwook Nam, Joonhyung Doh,<br>Eun-Seok Shin(~~Ulsan Hospital~~), Jianan Wang, Xinyang Hu | 19p (2) Executive Committee<br>- Committee members<br>Bong-Ki Lee, Changwook Nam, Joonhyung Doh,<br>Eun-Seok Shin(Ulsan University Hospital), Jianan Wang, Xinyang Hu | Modified the affiliation of a co-investigator. |

| Previous Version Number<br>Ver 11.4 (Jun 03. 2021) | Latter Version Number<br>Ver 11.5 (Nov 05. 2021) | Specific Reason of Modification |
|---|---|---|
| 25p (7) Economic evaluation<br><br>[None] | 25p (7) Economic evaluation<br><br>**(7) Economic evaluation**<br><br>This study aims to conduct economic evaluation for the physiology-guided PCI strategy and imaging-guided PCI strategy in patients with intermediate stenosis. Base-case analysis will be performed from the healthcare system perspective. Accordingly, the cost will be estimated based on the direct medical costs. For cost estimation, health insurance claim data will be used as one of the data sources. As for health insurance claim data, customized health information data provided by the National Health Insurance Service will be used. After this IRB approval, the application for use of the data will be made on the data providing site NHISS (http://nhiss.nhis.or.kr) operated by the National Health Insurance Service, which provides data after deliberation based on the research protocol and IRB approval. The data can be accessed and analyzed at locations within the National Health Insurance Service. The data is provided in the form of an alternative identification number for the resident registration number to ensure anonymity, and the alternative identification number is not used in presenting the analysis results. | Added the “Economic evaluation” evaluation to the protocol |

**Original Statistical Analysis Plan**

# Statistical Analysis Plan

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|---|---|
| TRIAL FULL TITLE | **F**ractionalF**L**owReserve **A**ndI**V**USfor Clinical**OU**tcomesin Patients with Inte**R**mediate Stenosis |
| ClinicalTrials.gov Identifier | NCT02673424 |
| SAP VERSION | Version 1.3 |
| SAP VERSION DATE | 2019.9.20 |
| TRIAL STATISTICIAN | Jeehoon Kang |
| TRIAL CHIEF INVESTIGATOR | Seung-Jae Tahk, Bon-Kwon Koo, JianAn Wang |
| SAP AUTHOR | Jeehoon Kang |

## 1 SAP Signatures

I give my approval for the attached SAP entitled <**F**ractionalF**L**owReserve **A**ndI**V**USfor Clinical**OU**tcomesin Patients with Inte**R**mediate Stenosis>dated <Version 1.3, 2019.9.20>.

**Chief Investigator**

Name:

Signature: _____ Date: _____

Name:

Signature: _____ Date: _____

Name:

Signature: _____ Date: _____

**Statistician**

Name:

Signature: _____ Date: _____

# Statistical Analysis Plan

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|---|---|
| TRIAL FULL TITLE | FractionalFLowReserve AndIVUSfor ClinicalOUtcomesin Patients with InteRmediate Stenosis |
| ClinicalTrials.gov Identifier | NCT02673424 |
| SAP VERSION | Version 1.3 |
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| TRIAL STATISTICIAN | Jeehoon Kang |
| TRIAL CHIEF INVESTIGATOR | Seung-Jae Tahk, Bon-Kwon Koo, JianAn Wang |
| SAP AUTHOR | Jeehoon Kang |

## 1 SAP Signatures

I give my approval for the attached SAP entitled <FractionalFLowReserve AndIVUSfor ClinicalOUtcomesin Patients with InteRmediate Stenosis>dated <Version 1.3, 2019.9.20>.

**Chief Investigator**

Name: JianAn Wang

Signature: J. A. Wang Date: 27. Sep. 2019

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**Statistician**

Name: Jeehoon Kang

Signature: Date: 29. Sep. 2019

# 1 Table of Contents

# 2 Abbreviations and Definitions

| | |
|---|---|
| AE | Adverse Event |
| CRF | Case Report Form |
| DES | drug-eluting stents |
| SAP | Statistical Analysis Plan |
| PCI | Percutaneous coronary intervention |
| FFR | fractional flow reserve |
| IVUS | intravascular ultrasound |
| POCO | Patient-oriented composite outcome |
| MI | myocardial infarction |
| MLA | Minimal lumen area |
| LAD | Left anterior descending coronary artery |
| LCX | Left circumflex coronary artery |
| RCA | Right coronary artery |
| DMC | Data Monitoring Committee |
| CEC | Clinical Events Committee |

# 3 Introduction

## 3.1 Preface

Percutaneous coronary intervention (PCI) is the current standard treatment for coronary artery diseases.(1) Especially, after the adoption of drug-eluting stents (DES), restenosis and revascularization has significantly decreased. However, due to the increased CAD population and the complexity of lesions treated with PCI, adverse effects after treatment is still a major issue. Therefore, there has been many effort to improve the outcome of PCI, where fractional flow reserve (FFR) and intravascular ultrasound (IVUS) are two strategies that are widely used.

First, FFR-guided PCI is a method to measure the coronary blood flow, and physiologically interpret the stenotic lesion. FFR-guided PCI strategy for coronary artery disease has proved its benefit over angiography-guided PCI or medical treatment by previous randomized clinical trials.(2-5)

Second, IVUS-guided PCI strategy is a method that can provide information about the lesion and PCI appropriateness.(6) Recent clinical studies and meta-analysis also showed that IVUS-guided PCI strategy could also reduce the incidence of major clinical events after drug-eluting stents implantation.(7-9) Also, a recent trial has shown that IVUS-guided PCI strategy can reduce adverse effects up to 50%.(10) Especially, diabetic patients with coronary artery disease are patients with high risk of adverse clinical events, who need more meticulous evaluation for the necessity and extent of intervention. Therefore, comparing FFR-guided and IVUS-guided PCI will give valuable information for the treatment strategy in these patients.

However, there has been no randomized study to compare the outcomes of FFR-guided vs. IVUS-guided PCI in patients of intermediate stenosis. The FFR-guided PCI have been known to reduce the number of treated lesions, used stents, and peri-procedural myocardial infarction (MI) with better stratification of lesions which could be significantly benefit by the revascularization. Although previous study showed that FFR-guided PCI strategy reduced the number of intervention compared with IVUS-guided strategy with comparable rates of major adverse cardiovascular events(11), small number of patients and non-randomized design of the study was the major limitations. In this regards, the randomized comparison between physiology (FFR)-guided strategy and imaging (IVUS)-guided PCI will provide valuable insights to enhance the patient's clinical outcomes with fewer number of intervention. The **F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis **(FLAVOUR) is a** randomized controlled prospective multi-center trial. This study aims to compare safety and efficacy of physiology (FFR)-guided PCI strategy and imaging (IVUS)-guided PCI strategy in patients with intermediate coronary stenosis.

## 3.2 Purpose of the analyses

This analyses will compare the patients-oriented composite outcomes at 24 months of FFR-guided strategy for PCI with a drug-eluting stent (DES) in comparison with IVUS-guided strategy for PCI with a DES in patients with intermediate coronary stenosis.

# 4 Study Objectives and Endpoints

## 4.1 Study Objectives

To compare the safety and efficacy of physiology (FFR)-guided percutaneous coronary intervention strategy with imaging (IVUS)-guided PCI strategy in patients with de novo intermediate coronary stenosis

.

## 4.2 Endpoints

#### 4.2.1 Primary endpoint

Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction (MI, including peri-procedural MI) or any repeat revascularization at 24 months after randomization according to the ARC consensus

#### 4.2.2. Secondary endpoint

① POCO at 12months after randomization according to the ARC consensus

② Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)

③ All-cause and cardiac death

④ Target-vessel and all-cause nonfatal MI without peri-procedural MI

⑤ Target-vessel and all-cause nonfatal MI with peri-procedural MI

⑥ Target vessel/lesion revascularization (ischemia-driven or all)

⑦ Non-target vessel/lesion revascularization (ischemia-driven or all)

⑧ Any revascularization (ischemia-driven or all)

⑨ Stent thrombosis (definite/probable/possible)

⑩ Stroke (ischemic and hemorrhagic)

⑪ Acute success of procedure (device, lesion and procedure)

⑫ Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month

⑬ Plaque characteristics by IVUS (including plaque burden, eccentricity, posterior attenuation, positive remodeling, calcification, etc.)

# 5 Study Methods

## 5.1 General Study Design and Plan

Following angiography, patients with intermediate diameter stenosis 40-70% of coronary artery by visual estimation and have lesions that are eligible for coronary intervention without any exclusion criteria, will be randomized 1:1 to receive either FFR-guided strategy or IVUS-guided strategy for evaluation of the lesions.

According to the pre-defined criteria for revascularization (FFR ≤ 0.80 in FFR-guided strategy group; MLA ≤ 3mm2 or 3 <MLA ≤ 4mm2 and plaque burden > 70% in IVUS-guided strategy group), the patient's will be treated with PCI or not. Optimization of PCI will be recommended to meet the criteria as follows.

| Group | Criteria for PCI optimization |
|---|---|
| **IVUS-guided PCI group** | Plaque burden at stent edge ≤ 55%<br>Minimal stent area ≥ 5.5mm$^2$, or minimal stent area ≥ distal reference lumen area |
| **FFR-guided PCI group** | Post PCI FFR ≥ 0.88, or<br>Post PCI delta FFR ([FFR at stent distal edge] – [FFR at stent proximal edge]) < 0.05 |

If any violation of the protocols (for example, PCI was performed despite of FFR > 0.80, PCI was performed despite of MLA > 3mm2, PCI was deferred despite of FFR ≤ 0.80, or PCI was deferred despite of MLA < 3mm2) are presented according to the operator's discretion, the specific reasons will be mandatorily described in electronic case report form.

In FFR-guided strategy group, the method of hyperemia induction and hyperemic agents will be restricted with intravenous adenosine infusion. In case of multivessel disease, PCI to the non-intermediate stenosis (more than 70% stenosis by visual estimation) will be permitted and left to the operator's discretion, however, this vessel will not be eligible as a target vessel for this study. In addition, the use of IVUS or FFR according to the assigned group will be permitted as tools for the optimizing PCI in stent type, PCI procedures and any adjunctive pharmacologic treatment will be left to the operator's discretion.

There will be NO regulation for any specific usage of the DES. The usage of any specific DES is decided by the operators' discretion. If the operator does not perform PCI with a DES (for example, PCI with plain old balloon angioplasty or PCI with a bare metal stent), this will be a protocol violation, and the specific reasons will be mandatorily described in electronic case report form.

If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available.

## 5.2 Inclusion-Exclusion Criteria and General Study Population

**(1) Inclusion Criteria**

⑫ Subject must be ≥ 19 years

⑬ Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of receiving invasive physiologic or imaging evaluation and PCI and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure.

⑭ Patients suspected with ischemic heart disease

⑮ Patients with de novo intermediate degree of stenosis (40-70% stenosis by visual estimation) eligible for stent implantation who need FFR or IVUS clinically for further evaluation

16 Target vessel size ≥ 2.5mm

17 Target vessels are limited to proximal to mid LAD, proximal to distal LCX, and RCA proximal to the PL-PDA bifurcation

**(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.)

⑨ Patients with active pathologic bleeding

⑩ Gastrointestinal or genitourinary major bleeding within the prior 3 months.

⑪ History of bleeding diathesis, known coagulopathy (including heparin-induced thrombocytopenia)

⑫ Non-cardiac co-morbid conditions with life expectancy < 2 years

⑬ Target lesion located in coronary arterial bypass graft

⑭ Target lesion located in the left main coronary artery

⑮ Target lesion located in previous PCI segment with in-stent restenosis.

## 5.3 Randomisation and Blinding

Patients will be randomized to either the FFR-guided strategy or IVUS-guided strategy at the time of enrollment with 1:1 ratio. Stratified randomization by participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

## 5.4 Study Variables

| | Baseline | Post-Procedure | Follow Up | | |
|---|---|---|---|---|---|
| | | | 1 month ± 14days | 1 year ± 90days | 2 years ± 90days |
| **Medical/Clinical/ History (age, sex, risk factors, clinical dx, angina status, cardiac history)** | × | | | | |
| **Informed Consent** | × | | | | |
| **Inclusion/Exclusion Criteria** | × | | | | |
| **Seattle Angina Questionnaires** | × | | | × | × |
| **Brief Physical Examination** | × | | | | |
| **Vital status** | × | | × | × | × |
| **Weight, height** | × | | | | |
| **12 lead ECG[#]** | × | × | | | |
| **Angiogram[#]** | × | | | | |
| **FFR-tracing raw data*** | × | × | | | |
| **IVUS-imaging raw data*** | × | × | | | |
| **CBC** | × | | | | |
| **Electrolytes, LFT** | × | | | | |
| **Creatinine, BUN** | × | | △ | △ | △ |
| **Fasting plasma TG, HDL, total cholesterol, LDL** | × | | △ | △ | △ |
| **Fasting glucose level** | × | | △ | △ | △ |
| **HgbA1C (only in diabetic patients)** | × | | △ | △ | △ |
| **Medications[†]** | × | | × | × | × |
| **CK, CK-MB, Troponin I or Troponin T** | △ | × | | | |

# 6 Sample Size

**Hypothesis:** The FFR-guided strategy for PCI with a drug-eluting stent (DES) will show non-inferiority in rates of patients-oriented composite outcomes at 24 months after randomization, compared with IVUS-guided strategy for PCI with a DES in patients with intermediate coronary stenosis.

**Sample size:** Based on the event rates of previous trials which evaluated FFR-guided PCI strategy in patients with intermediate stenosis, we predicted the rates of POCO at 24 months after PCI in the FFR-guided arm to be 10%.(3, 12, 13) Also, according to previous clinical trials and meta-analysis of IVUS-guided PCI, we predicted the rate of 24 month POCO to be 12% in the IVUS-guided arm.(7, 8, 10, 14, 15)

- Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any repeat revascularization) at 24 months after PCI
- Design: non-inferiority , delta = 2.5%
- Sampling ratio: FFR-guided strategy : IVUS-guided strategy = 1:1
- Type I error (α): One-sided 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 or IVUS-guided strategy, respectively
- Statistical power (1- β): 90%
- Primary statistical method : Kaplan-Meier survival analysis with log-rank test
- Potential withdrawal rates : total 2%
- Stratification in Randomization: Presence of Diabetes Mellitus (600 patients (35%) will be Diabetic patients, with 300 patients in each group)

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

# 7 General Considerations

## 7.1 Timing of Analyses

- The final analysis will be performed when all subjects have completed 2-year visit or dropped out prior to the 2-year visit.

## 7.2 Analysis Populations

### 7.2.1 Full Analysis Population

- All subjects who received any treatment strategy
- All subjects who were randomised

### 7.2.2 Per Protocol Population

- All subjects who adhere to the major criteria in the protocol
- All subjects who did not substantially deviate from the protocol as to be determined on a per-subject basis at the trial steering committee immediately before data base lock.

### 7.2.3 Safety Population

- All subjects who received any study treatment (including control) and are confirmed as providing complete follow-up regarding adverse event information.

## 7.3 Missing Data and Protocol violation

#### 8.3.1 Missing Data

The primary analysis of the study endpoints will not be covariate adjusted. No imputation methods will be used to infer missing values of baseline variables. For the study endpoints, patients lost to follow-up and subsequently lost to assessment of primary endpoint, will be considered to be censored in the estimation of Kaplan-Meier event rates. As a secondary analysis, we will also examine the patients who have been lost to follow-up. We will perform a comparison of baseline characteristics in patients with vs. without 2-year follow up. The baseline characteristics will include as followed Table. In addition, a sensitivity analysis will be performed to assess the impact of these patients on the study outcomes. For patients lost to follow-up, multiple imputation techniques will be used to calculate pooled estimates of the treatment effect and confidence intervals which will then be compared to the primary statistical analysis.

#### 8.3.2 Protocol Violation

Although the evaluation strategy of intermediate coronary stenosis will be decided by randomization process to either FFR-guided strategy or IVUS-guided strategy, whether revascularized the target lesion or not will be decided by operator according to the clinical decision. However, the followings will be recorded as protocol violation and the reason will be recorded and the data coordinating center must be notified promptly.

① Revascularization is not performed despite of FFR ≤ 0.80 (FFR-guided group)

② Revascularization is performed despite of FFR > 0.80 (FFR-guided group)

③ Revascularization is not performed despite of MLA ≤ 3mm2 or (MLA ≤ 4mm2 AND Plaque burden >70%) (IVUS-guided group)

④ Revascularization is performed despite of MLA > 3mm2 or (MLA > 4mm2 AND Plaque burden ≤ 70%) (IVUS-guided group)

⑤ Both FFR-guided strategy and IVUS-guided strategy are used for one or more coronary artery in one subject.

⑥ PCI is performed without a DES (for example, PCI with plain old balloon angioplasty or PCI with a Bare-metal stent)

## 7.4 Interim Analyses and Data Monitoring

### 7.4.1 Interim Analyses

No formal interim analyses are planned. Informal interim analyses will be performed if requested by the Data Monitoring Committee (DMC), but findings will be made available to member of the DMC only. Unless advised by the DMC in response to clear evidence of benefit or hazard, the Steering Committee, collaborators, participants and all clinical staff will remain blind to the allocation until the end of the study unless a decision to unblind is made by the DMC.

### 7.4.2 Practical Measures to Minimise Bias

The following methods will be performed to minimize potential sources of bias

- Enrollment of subjects is limited by inclusion and exclusion criteria
- Subjects will be systematically randomized with blinding procedures implemented.
- An external, independent Clinical Events Committee (CEC) blinded to treatment assignment will review and adjudicate, at minimum, all deaths and safety-endpoint related adverse events. Safety endpoint results will be based on CEC adjudications.

- An external, independent Data Monitoring Committee (DMC) will evaluate safety data and advise the Sponsor in regard to continued safety of the study, to ensure the well-being of the subjects.
- An independent Angiographic Core Lab will evaluate all event angiograms.
- Statistical analyses will be independently validated
- Study sites should follow their institutional procedures for maintenance of angiography and laboratory equipment used for assessing the study variables.
- Study monitors will verify subject data and ensure compliance with this Clinical Investigational Plan and other study requirements, ie, blinding and informed consenting processes

# 8 Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment in the order (Control, Experimental) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

## 8.1 Tables to present

**Table 1. Baseline demographic characteristics**

| | Total (N=) | FFR guided PCI (N=) | IVUS guided PCI (N=) |
|---|---|---|---|
| ***Demographics*** | | | |
| **Age (years old)** | | | |
| **Male sex, n (%)** | | | |
| **Body mass index (kg/m$^2$)** | | | |
| **Diabetes mellitus, n (%)** | | | |
| **Hypertension, n (%)** | | | |
| **Dyslipidemia, n (%)** | | | |
| **Current smoking, n (%)** | | | |
| **Prior MI, n (%)** | | | |
| **Prior PCI, n (%)** | | | |
| **LV ejection fraction (%)** | | | |
| ***Laboratory data*** | | | |
| **WBC (/ul)** | | | |
| **Hemoglobin (g/dL)** | | | |
| **Creatinine (mg/dL)** | | | |
| **Total Cholesterol (mg/dL)** | | | |
| **Triglyceride (mg/dL)** | | | |
| **HDL-cholesterol (mg/dL)** | | | |
| **LDL-cholesterol (mg/dL)** | | | |
| ***Discharge medication*** | | | |
| **Aspirin, n (%)** | | | |
| **P2Y12 inhibitor, n (%)** | | | |
| **DAPT, n (%)** | | | |
| **Statin, n (%)** | | | |
| **Beta blocker, n (%)** | | | |
| **ACEinhibitor or ARBs, n (%)** | | | |
| **Calcium channel blocker, n (%)** | | | |

**Table 2. Baseline procedural characteristics**

| | Total (N=) | FFR guided PCI (N=) | IVUS guided PCI (N=) |
|---|---|---|---|
| ***Angiographic findings*** | | | |
| **Angiographic disease extent** | | | |
| **- 1 vessel disease, n (%)** | | | |
| **- 2 vessel disease, n (%)** | | | |
| **- 3 vessel disease, n (%)** | | | |
| ***Target vessel*** | | | |
| **Location** | | | |
| **- LAD, n (%)** | | | |
| **- LCX, n (%)** | | | |
| **- RCA, n (%)** | | | |
| **Target vessel PCI rate (%)** | | | |
| **Lesion length (mm)** | | | |
| **Reference vessel diameter (mm)** | | | |
| **Minimum lumen diameter (mm)** | | | |
| **Diameter stenosis (%)** | | | |
| **Stent diameter, mm** | | | |
| **Stent length, mm** | | | |
| **Non-Target vessel** | | | |
| **Location** | | | |
| **- LAD, n (%)** | | | |
| **- LCX, n (%)** | | | |
| **- RCA, n (%)** | | | |
| **Non-Target vessel PCI rate (%)** | | | |
| **Total PCI rate (%)** | | | |
| **Total Stent length, mm** | | | |
| **Total Stent Number** | | | |
| **SYNTAX score at baseline** | | | |
| **SYNTAX score after PCI (residual)** | | | |
| ***IVUS findings*** | | | |
| **Minimal luminal area ($mm^2$)** | | | |
| **Plaque Burden (%)** | | | |
| **Post PCI** | | | |

| | | |
|---|---|---|
| **i. Minimal stent area ($mm^2$)** | | |
| ***FFR findings*** | | |
| **FFR**<br>**Post PCI FFR** | | |

**Table 3. Clinical outcomes**

| | **Total (N=)** | **FFR guided PCI (N=)** | **IVUS guided PCI (N=)** | **P Value** |
|---|---|---|---|---|
| ***Clinical outcomes*** | | | | |
| **POCO**<br>**All cause death**<br>**Cardiac death**<br>**MI**<br>**TV MI**<br>**Any revascularization**<br>**TLR** | | | | |

## 8.2 Figures to present

**Figure 1. CONSORT diagram of study population**

**Figure 2. Cumulative event rates by the overall treatment groups, for the primary endpoint and its individual components (Intention to treat analysis)**

**Figure 3. Cumulative event rates of patients treated with PCI and the deferred patients, by treatment groups, for the primary endpoint and its individual components**

# 9 Reporting Conventions

For statistical analysis SPSS, R software with a version that is most up-to-date at the time of writing, will be used. A second review statistician will independently reproduce the primary analyses and summary statistics tables. The reviewing statistician will have an overview of the entire analyses

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

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# Statistical Analysis Plan

| | |
|---|---|
| TRIAL FULL TITLE | **F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis |
| ClinicalTrials.gov Identifier | NCT02673424 |
| SAP VERSION | Version 1.5 |
| SAP VERSION DATE | 2020.08.24 |
| TRIAL STATISTICIAN | Jeehoon Kang |
| TRIAL CHIEF INVESTIGATOR | Seung-Jae Tahk, Bon-Kwon Koo, JianAn Wang |
| SAP AUTHOR | Jeehoon Kang |

## SAP Signatures

I give my approval for the attached SAP entitled <**F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis> dated <Version 1.3, 2019.9.20>.

**Chief Investigator**

Name:

Signature: _____ Date: _____

Name:

Signature: _____ Date: _____

Name:

Signature: _____ Date: _____

**Statistician**

Name:

Signature: _____ Date: _____

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# 12 Abbreviations and Definitions

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# 13 Introduction

## 13.1 Preface

Percutaneous coronary intervention (PCI) is the current standard treatment for coronary artery diseases.(1) Especially, after the adoption of drug-eluting stents (DES), restenosis and revascularization has significantly decreased. However, due to the increased CAD population and the complexity of lesions treated with PCI, adverse effects after treatment is still a major issue. Therefore, there has been many effort to improve the outcome of PCI, where fractional flow reserve (FFR) and intravascular ultrasound (IVUS) are two strategies that are widely used.

First, FFR-guided PCI is a method to measure the coronary blood flow, and physiologically interpret the stenotic lesion. FFR-guided PCI strategy for coronary artery disease has proved its benefit over angiography-guided PCI or medical treatment by previous randomized clinical trials.(2-5)

Second, IVUS-guided PCI strategy is a method that can provide information about the lesion and PCI appropriateness.(6) Recent clinical studies and meta-analysis also showed that IVUS-guided PCI strategy could also reduce the incidence of major clinical events after drug-eluting stents implantation.(7-9) Also, a recent trial has shown that IVUS-guided PCI strategy can reduce adverse effects up to 50%.(10) Especially, diabetic patients with coronary artery disease are patients with high risk of adverse clinical events, who need more meticulous evaluation for the necessity and extent of intervention. Therefore, comparing FFR-guided and IVUS-guided PCI will give valuable information for the treatment strategy in these patients.

However, there has been no randomized study to compare the outcomes of FFR-guided vs. IVUS-guided PCI in patients of intermediate stenosis. The FFR-guided PCI have been known to reduce the number of treated lesions, used stents, and peri-procedural myocardial infarction (MI) with better stratification of lesions which could be significantly benefit by the revascularization. Although previous study showed that FFR-guided PCI strategy reduced the number of intervention compared with IVUS-guided strategy with comparable rates of major adverse cardiovascular events(11), small number of patients and non-randomized design of the study was the major limitations. In this regards, the randomized comparison between physiology (FFR)-guided strategy and imaging (IVUS)-guided PCI will provide valuable insights to enhance the patient's clinical outcomes with fewer number of intervention. The **F**ractional F**L**ow Reserve **A**nd I**V**US for Clinical **OU**tcomes in Patients with Inte**R**mediate Stenosis **(FLAVOUR) is a** randomized controlled prospective multi-center trial. This study aims to compare safety and efficacy of physiology (FFR)-guided PCI strategy and imaging (IVUS)-guided PCI strategy in patients with intermediate coronary stenosis.

Although FFR is the current standard of car for the functional assessment of lesion severity in patients with intermediate-grade stenosis, FFR guided PCI is still underused in real world practice due to the concerns for prolonged procedural time, increased costs, and potential complications by pressure wire. The quantitative flow ratio (QFR) is a novel angiography based approach allowing calculation of FFR by 3-dimensional coronary artery reconstruction and fluid dynamic computation. There are many clinical studies supporting the QFR value and identifying of patients at risk from cardiovascular events.(12, 13) Therefore, we will confirm the accuracy of QFR, the relationship between IVUS and QFR findings, and incremental value of QFR for predicting cardiovascular events.

## 13.2 Purpose of the analyses

This analyses will compare the patients-oriented composite outcomes at 24 months of FFR-guided strategy for PCI with a drug-eluting stent (DES) in comparison with IVUS-guided strategy for PCI with a DES in patients with intermediate coronary stenosis.

# 14 Study Objectives and Endpoints

## 14.1 Study Objectives

To compare the safety and efficacy of physiology (FFR)-guided percutaneous coronary intervention strategy with imaging (IVUS)-guided PCI strategy in patients with de novo intermediate coronary stenosis

.

## 14.2 Endpoints

#### 4.2.1 Primary endpoint

Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction (MI, including peri-procedural MI(14, 15)) or any revascularization at 24 months after randomization according to the ARC consensus.(16)

#### 4.2.2. Secondary endpoint

1. POCO at 12months after randomization according to the ARC consensus
2. Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)
3. All-cause and cardiac death
4. Cost-effectiveness analysis
5. Target-vessel and all-cause nonfatal MI without peri-procedural MI
6. Target-vessel and all-cause nonfatal MI with peri-procedural MI
7. Periprocedural MI defined as referred
8. Target vessel/lesion revascularization (ischemia-driven or all)
9. Non-target vessel/lesion revascularization (ischemia-driven or all)
10. Any revascularization (ischemia-driven or all)
11. Stent thrombosis (definite/probable/possible)
12. Stroke (ischemic and hemorrhagic)
13. Acute success of procedure (device, lesion and procedure)
14. Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month
15. Plaque characteristics by IVUS (including plaque burden, eccentricity, posterior attenuation, positive remodeling, calcification, etc.)
16. QFR analysis (fixed QFR, contrast QFR, delta QFR, and post PCI QFR)

- Definition of Periprocedural MI
  - Periprocedural MI will be defined as prior studies.
  - Definition of Periprocedural MI in the DEFINE FLAIR & SWEDEHEART trials(14, 15)
    - #. 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 centile post index PCI" 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.
  - Definition of Periprocedural MI in the EXCEL trial(17, 18)
    - Periprocedural MI was defined for PCI as the occurrence of (i) CK-MB >10× URL or (ii) CK-MB >5× URL plus one of the following: (i) new pathological Q-waves in at least two contiguous leads or new persistent non-rate-related left bundle branch block; (ii) angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow; or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. For patients with elevated baseline biomarkers at baseline the peak CK-MB level was required to rise from the baseline value by an increment equal to the values above.
  - Definition of Periprocedural MI in the ISCHEMIA trial(19)
    - For subjects with normal baseline biomarker level pre-PCI, peri-PCI MI requires a rise in CK-MB to >5-fold the ULN (or a rise in troponin to >35 times the MI Decision Limit/ULN, when CKMB is unavailable) post-PCI. If pre-PCI cardiac markers (CKMB or cTn) are elevated, they must be stable or falling as indicated by two samples at least 6h apart. The post-PCI CKMB level should reflect a rise of >20% over pre-PCI levels. In addition to biomarker criteria, peri-PCI MI requires at least one of the following:
      - Post- procedure angiographic TIMI 0/1 flow in a major coronary artery or aside branch with reference vessel diameter ≥2.0 mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter ≥3.0 mm which had TIMI 3 flow at baseline or Type C dissection (NHLBI classification) or greater in the target vessel.
      - New ECG changes (ST segment elevation or depression >0.1mV in 2contiguous leads), new pathologic Q-waves in ≥2 contiguous leads, or new persistent LBBB present on a post-PCI ECG obtained in the absence of any intervening coronary event between the time of the PCI procedure and the ECG showing changes.
    - Or stand-alone biomarker definition
      - CK-MB to > 10-fold the ULN (or when CK-MB is unavailable, arise in troponin to > 70-fold the MI decision Limit/ULN)

# 15 Study Methods

## 15.1 General Study Design and Plan

Following angiography, patients with intermediate diameter stenosis 40-70% of coronary artery by visual estimation and have lesions that are eligible for coronary intervention without any exclusion criteria, will be randomized 1:1 to receive either FFR-guided strategy or IVUS-guided strategy for evaluation of the lesions.

According to the pre-defined criteria for revascularization (FFR ≤ 0.80 in FFR-guided strategy group; MLA ≤ 3mm2 or 3 <MLA ≤ 4mm2 and plaque burden > 70% in IVUS-guided strategy group), the patient's will be treated with PCI or not. Optimization of PCI will be recommended to meet the criteria as follows.

| Group | Criteria for PCI optimization |
|---|---|
| **IVUS-guided PCI group** | Plaque burden at stent edge ≤ 55%<br>Minimal stent area ≥ 5.5mm$^2$, or minimal stent area ≥ distal reference lumen area |
| **FFR-guided PCI group** | Post PCI FFR ≥ 0.88, or<br>Post PCI delta FFR ([FFR at stent distal edge] – [FFR at stent proximal edge]) < 0.05 |

If any violation of the protocols (for example, PCI was performed despite of FFR > 0.80, PCI was performed despite of MLA > 3mm2, PCI was deferred despite of FFR ≤ 0.80, or PCI was deferred despite of MLA < 3mm2) are presented according to the operator's discretion, the specific reasons will be mandatorily described in electronic case report form.

In FFR-guided strategy group, the method of hyperemia induction and hyperemic agents will be restricted with intravenous adenosine infusion. In case of multivessel disease, PCI to the non-intermediate stenosis (more than 70% stenosis by visual estimation) will be permitted and left to the operator's discretion, however, this vessel will not be eligible as a target vessel for this study. In addition, the use of IVUS or FFR according to the assigned group will be permitted as tools for the optimizing PCI in stent type, PCI procedures and any adjunctive pharmacologic treatment will be left to the operator's discretion.

The QFR analysis is only performed on a coronary angiograms that can be analyzed. The Post-procedural QFR will be analyzed in case the PCI is performed.

There will be NO regulation for any specific usage of the DES. The usage of any specific DES is decided by the operators' discretion. If the operator does not perform PCI with a DES (for example, PCI with plain old balloon angioplasty or PCI with a bare metal stent), this will be a protocol violation, and the specific reasons will be mandatorily described in electronic case report form.

If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available.

## 15.2 Inclusion-Exclusion Criteria and General Study Population

**(1) Inclusion Criteria**

18 Subject must be ≥ 19 years

19 Subject is able to verbally confirm understandings of risks, benefits and treatment alternatives of

receiving invasive physiologic or imaging evaluation and PCI and he/she or his/her legally authorized representative provides written informed consent prior to any study related procedure.

20 Patients suspected with ischemic heart disease

21 Patients with de novo intermediate degree of stenosis (40-70% stenosis by visual estimation) eligible for stent implantation who need FFR or IVUS clinically for further evaluation

22 Target vessel size $\geq$ 2.5mm

23 Target vessels are limited to proximal to mid LAD, proximal to distal LCX, and RCA proximal to the PL-PDA bifurcation

**(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.)

16 Patients with active pathologic bleeding

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

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

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

20 Target lesion located in coronary arterial bypass graft

21 Target lesion located in the left main coronary artery

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

## 15.3 Randomisation and Blinding

Patients will be randomized to either the FFR-guided strategy or IVUS-guided strategy at the time of enrollment with 1:1 ratio. Stratified randomization by participating center will be performed. This process will be done by a web-based randomization program, run by an independent organization.

## 15.4 Study Variables

| | **Baseline** | **Post-Procedure** | **Follow Up** | | |
|---|---|---|---|---|---|
| | | | 1 month ± 14days | 1 year ± 90days | 2 years ± 90days |
| **Medical/Clinical/ History (age, sex, risk factors, clinical dx, angina status, cardiac history)** | × | | | | |
| **Informed Consent** | × | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Inclusion/Exclusion Criteria** | × | | | | |
| **Seattle Angina Questionnaires** | × | | | × | × |
| **Brief Physical Examination** | × | | | | |
| **Vital status** | × | | × | × | × |
| **Weight, height** | × | | | | |
| **12 lead ECG[#]** | × | × | | | |
| **Angiogram[#]** | × | | | | |
| **FFR-tracing raw data*** | × | × | | | |
| **IVUS-imaging raw data*** | × | × | | | |
| **QFR analysis data[†]** | × | × | | | |
| **CBC** | × | | | | |
| **Electrolytes, LFT** | × | | | | |
| **Creatinine, BUN** | × | | △ | △ | △ |
| **Fasting plasma TG, HDL, total cholesterol, LDL** | × | | △ | △ | △ |
| **Fasting glucose level** | × | | △ | △ | △ |
| **HgbA1C (only in diabetic patients)** | × | | △ | △ | △ |
| **Medications[†]** | × | | × | × | × |
| **CK, CK-MB, Troponin I or Troponin T** | △ | × | | | |

# 16 Sample Size

**Hypothesis:** The FFR-guided strategy for PCI with a drug-eluting stent (DES) will show non-inferiority in rates of patients-oriented composite outcomes at 24 months after randomization, compared with IVUS-guided strategy for PCI with a DES in patients with intermediate coronary stenosis.

**Sample size:** Based on the event rates of previous trials which evaluated FFR-guided PCI strategy in patients with intermediate stenosis, we predicted the rates of POCO at 24 months after PCI in the FFR-guided arm to be 10%.(3, 14, 15) Also, according to previous clinical trials and meta-analysis of IVUS-guided PCI, we predicted the rate of 24 month POCO to be 12% in the IVUS-guided arm.(7, 8, 10, 20, 21)

- Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any revascularization) at 24 months after PCI

- Design: non-inferiority , delta = 2.5%
- Sampling ratio: FFR-guided strategy : IVUS-guided strategy = 1:1
- Type I error (α): One-sided 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 or IVUS-guided strategy, respectively
- Statistical power (1- β): 90%
- Primary statistical method : Kaplan-Meier survival analysis with log-rank test
- Potential withdrawal rates : total 2%
- Stratification in Randomization: Presence of Diabetes Mellitus (600 patients (35%) will be Diabetic patients, with 300 patients in each group)

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

# 17 General Considerations

## 17.1 Timing of Analyses

- The final analysis will be performed when all subjects have completed 2-year visit or dropped out prior to the 2-year visit.

## 17.2 Analysis Populations

### 17.2.1 Full Analysis Population

- All subjects who received any treatment strategy
- All subjects who were randomised

### 17.2.2 Per Protocol Population

- All subjects who adhere to the major criteria in the protocol
- All subjects who did not substantially deviate from the protocol as to be determined on a per-subject basis at the trial steering committee immediately before data base lock.

### 17.2.3 Safety Population

- All subjects who received any study treatment (including control) and are confirmed as providing complete follow-up regarding adverse event information.

## 17.3 Missing Data and Protocol violation

#### 7.3.1 Missing Data

The primary analysis of the study endpoints will not be covariate adjusted. No imputation methods will be used to infer missing values of baseline variables. For the study endpoints, patients lost to follow-up and subsequently lost to assessment of primary endpoint, will be considered to be censored in the estimation of Kaplan-Meier event rates. As a secondary analysis, we will also examine the patients who have been lost to follow-up. We will perform a comparison of baseline characteristics in patients with vs. without 2-year follow up. The baseline characteristics will include as followed Table. In addition, a sensitivity analysis will be performed to assess the impact of these patients on the study outcomes. For patients lost to follow-up, multiple imputation techniques will be used to calculate pooled estimates of the treatment effect and confidence intervals which will then be compared to the primary statistical analysis.

#### 7.3.2 Protocol Violation

Although the evaluation strategy of intermediate coronary stenosis will be decided by randomization process to either FFR-guided strategy or IVUS-guided strategy, whether revascularized the target lesion or not will be decided by operator according to the clinical decision. However, the followings will be recorded as protocol violation and the reason will be recorded and the data coordinating center must be notified promptly.

① Revascularization is not performed despite of FFR ≤ 0.80 (FFR-guided group)

② Revascularization is performed despite of FFR > 0.80 (FFR-guided group)

③ Revascularization is not performed despite of MLA ≤ 3mm2 or (3 $mm^2$ <MLA ≤ 4$mm^2$ AND Plaque burden >70%) (IVUS-guided group)

④ Revascularization is performed despite of MLA > 3mm2 or (MLA > 4mm2 AND Plaque burden ≤ 70%) (IVUS-guided group)

⑤ Both FFR-guided strategy and IVUS-guided strategy are used for one or more coronary artery in one subject.

⑥ PCI is performed without a DES (for example, PCI with plain old balloon angioplasty or PCI with a Bare-metal stent)

## 17.4 Interim Analyses and Data Monitoring

### 17.4.1 Interim Analyses

No formal interim analyses are planned. Informal interim analyses will be performed if requested by the Data Monitoring Committee (DMC), but findings will be made available to member of the DMC only. Unless advised by the DMC in response to clear evidence of benefit or hazard, the Steering Committee, collaborators, participants and all clinical staff will remain blind to the allocation until the end of the study unless a decision to unblind is made by the DMC.

### 17.4.2 Practical Measures to Minimise Bias

The following methods will be performed to minimize potential sources of bias

- Enrollment of subjects is limited by inclusion and exclusion criteria
- Subjects will be systematically randomized with blinding procedures implemented.
- An external, independent Clinical Events Committee (CEC) blinded to treatment assignment will review and adjudicate, at minimum, all deaths and safety-endpoint related adverse events. Safety endpoint results will be based on CEC adjudications.
- An external, independent Data Monitoring Committee (DMC) will evaluate safety data and advise the Sponsor in regard to continued safety of the study, to ensure the well-being of the subjects.
- An independent Angiographic Core Lab will evaluate all event angiograms.
- Statistical analyses will be independently validated
- Study sites should follow their institutional procedures for maintenance of angiography and laboratory equipment used for assessing the study variables.
- Study monitors will verify subject data and ensure compliance with this Clinical Investigational Plan and other study requirements, ie, blinding and informed consenting processes

# 18 Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment in the order (Control, Experimental) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

## 18.1 Tables to present

**Table 1. Baseline demographic characteristics**

| | Total (N=) | FFR guided PCI (N=) | IVUS guided PCI (N=) |
|---|---|---|---|
| ***Demographics*** | | | |
| **Age (years old)** | | | |
| **Male sex, n (%)** | | | |
| **Body mass index (kg/m$^2$)** | | | |
| **Diabetes mellitus, n (%)** | | | |
| **Hypertension, n (%)** | | | |
| **Dyslipidemia, n (%)** | | | |
| **Current smoking, n (%)** | | | |
| **Prior MI, n (%)** | | | |
| **Prior PCI, n (%)** | | | |
| **LV ejection fraction (%)** | | | |
| ***Laboratory data*** | | | |
| **WBC (/ul)** | | | |
| **Hemoglobin (g/dL)** | | | |
| **Creatinine (mg/dL)** | | | |
| **Total Cholesterol (mg/dL)** | | | |
| **Triglyceride (mg/dL)** | | | |
| **HDL-cholesterol (mg/dL)** | | | |
| **LDL-cholesterol (mg/dL)** | | | |
| ***Discharge medication*** | | | |
| **Aspirin, n (%)** | | | |
| **P2Y12 inhibitor, n (%)** | | | |
| **DAPT, n (%)** | | | |
| **Statin, n (%)** | | | |
| **Beta blocker, n (%)** | | | |
| **ACEinhibitor or ARBs, n (%)** | | | |
| **Calcium channel blocker, n (%)** | | | |

**Table 2. Baseline procedural characteristics**

| | Total (N=) | FFR guided PCI (N=) | IVUS guided PCI (N=) |
|---|---|---|---|
| ***Angiographic findings*** | | | |
| **Angiographic disease extent** | | | |
| **- 1 vessel disease, n (%)** | | | |
| **- 2 vessel disease, n (%)** | | | |
| **- 3 vessel disease, n (%)** | | | |
| ***Target vessel*** | | | |
| **Location** | | | |
| **- LAD, n (%)** | | | |
| **- LCX, n (%)** | | | |
| **- RCA, n (%)** | | | |
| **Target vessel PCI rate (%)** | | | |
| **Lesion length (mm)** | | | |
| **Reference vessel diameter (mm)** | | | |
| **Minimum lumen diameter (mm)** | | | |
| **Diameter stenosis (%)** | | | |
| **Stent diameter, mm** | | | |
| **Stent length, mm** | | | |
| **Non-Target vessel** | | | |
| **Location** | | | |
| **- LAD, n (%)** | | | |
| **- LCX, n (%)** | | | |
| **- RCA, n (%)** | | | |
| **Non-Target vessel PCI rate (%)** | | | |
| **Total PCI rate (%)** | | | |
| **Total Stent length, mm** | | | |
| **Total Stent Number** | | | |
| **SYNTAX score at baseline** | | | |
| **SYNTAX score after PCI (residual)** | | | |
| ***IVUS findings*** | | | |
| **Minimal luminal area ($mm^2$)** | | | |
| **Plaque Burden (%)** | | | |
| **Post PCI** | | | |

| | | |
|---|---|---|
| **i. Minimal stent area ($mm^2$)** | | |
| ***FFR findings*** | | |
| **FFR**<br>**Post PCI FFR** | | |
| ***QFR findings*** | | |
| **Fixed QFR**<br>**Contrast FFR** | | |

**Table 3. Clinical outcomes**

| | **Total (N=)** | **FFR guided PCI (N=)** | **IVUS guided PCI (N=)** | **P Value** |
|---|---|---|---|---|
| ***Clinical outcomes*** | | | | |
| **POCO**<br>**All cause death**<br>**Cardiac death**<br>**MI**<br>**TV MI**<br>**Any revascularization**<br>**TLR** | | | | |

## 18.2 Figures to present

**Figure 1. CONSORT diagram of study population**

**Figure 2. Cumulative event rates by the overall treatment groups, for the primary endpoint and its individual components (Intention to treat analysis)**

**Figure 3. Cumulative event rates of patients treated with PCI and the deferred patients, by treatment groups, for the primary endpoint and its individual components**

# 19 Reporting Conventions

For statistical analysis SPSS, R software with a version that is most up-to-date at the time of writing, will be used. A second review statistician will independently reproduce the primary analyses and summary statistics tables. The reviewing statistician will have an overview of the entire analyses

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

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**Fractional Flow Reserve versus Intravascular Ultrasound to Guide Percutaneous Coronary Intervention**

Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy for Clinical Outcomes in Patients with Intermediate Stenosis

**: The FLAVOUR Randomized Controlled Trial**

# Statistical Analysis Plan – Summary of Amendments

| Previous Version Number<br>Ver 1.3 (Oct. 11. 2019) | Latter Version Number<br>Ver 1.4 (Apr. 17. 2020) | Specific Reason of Modification |
|---|---|---|
| **5p 4. 2.1 Primary endpoint**<br><br>Patient-oriented composite outcome (POCO), defined as a composite of all death, myocardial infarction (MI, including peri-procedural MI) or any repeat revascularization at 24 months after randomization according to the ARC consensus | **5p 4. 2.1 Primary endpoint**<br><br>Patient-<br>oriented composite outcome (POCO), defined as a compos ite of all death, myocardial infarction (MI, including peri-procedural MI(12, 13)) or any revascularization at 24 mon ths after randomization according to the ARC consensus(1 6) | Specified the definition of outcomes and added applicable references |
| **5p 4.2.2 Secondary endpoint**<br>① POCO at 12months after randomization according to the ARC consensus<br>② Stent-oriented composite endpoint<br>(a composite of cardiac death, target-vessel MI, or target lesion revascularization)<br>③ All-cause and cardiac death<br>④ Target-vessel and all-cause nonfatal MI without peri-procedural MI<br>⑤ Target-vessel and all-cause nonfatal MI with peri-procedural MI<br>⑥ Target vessel/lesion revascularization (ischemia-driven or all)<br>⑦ Non-target vessel/lesion revascularization | **5p 4.2 Secondary endpoint**<br>① POCO at 12months after randomization according to the ARC consensus<br>② Stent-oriented composite endpoint (a composite of cardiac death, target-vessel MI, or target lesion revascularization)<br>③ Cost-effectiveness<br>④ All-cause and cardiac death<br>⑤ Target-vessel and all-cause nonfatal MI without peri-procedural MI<br>⑥ Target-vessel and all-cause nonfatal MI with peri-procedural MI(12,13)<br>⑦ Peri-procedural MI defined as referred(17-19)<br>⑧ Target vessel/lesion revascularization (ischemia- | Added secondary endpoints and applicable references |

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| (ischemia-driven or all)<br><br>⑧ Any revascularization (ischemia-driven or all)<br><br>⑨ Stent thrombosis (definite/probable/possible)<br><br>⑩ Stroke (ischemic and hemorrhagic)<br><br>⑪ Acute success of procedure (device, lesion and procedure)<br><br>⑫ Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month<br><br>⑬ Plaque characteristics by IVUS (including plaque burden, eccentricity, posterior attenuation, positive remodeling, calcification, etc.)” | driven or all)<br><br>⑨ Non-target vessel/lesion revascularization (ischemia-driven or all)<br><br>⑩ Any revascularization (ischemia-driven or all)<br><br>⑪ Stent thrombosis (definite/probable/possible)<br><br>⑫ Stroke (ischemic and hemorrhagic)<br><br>⑬ Acute success of procedure (device, lesion and procedure)<br><br>⑭ Angina severity measured with Seattle Angina Questionnaires at 12-month and 24-month<br><br>⑮ Plaque characteristics by IVUS (including plaque burden, eccentricity, posterior attenuation, positive remodeling, calcification, etc.)” | |
| **5~6p Definition of Peri-procedural MI**<br><br>[Blank] | **5~6p Definition of Peri-procedural MI**<br><br>■ Peri-procedural MI will be defined as prior studies.<br><br>■ Definition of Peri-procedural MI in the DEFINE FLAIR & SWEDEHEART trials (12, 13)<br><br>◆ Peri-procedural MI is considered an event within the first 48 hours after randomisation:<br><br>◆ #. 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 | Specified the definitions of peri-procedural MI referring to recently published reference articles |

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| | 99th percentile of diagnostic value for the specific institution"<br><br>◆ #. 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 centile within 24 hours post index PCI" 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<br><br>■Definition of Peri-procedural MI in the EXCEL trial (17, 18)<br><br>◆Peri-procedural MI was defined for PCI as the occurrence within 72 h after either procedure of (i) CK-MB >10× URL or (ii) CK-MB >5× URL plus one of the following: (i) new pathological Q-waves in at least two contiguous leads or new persistent non-rate-related left bundle branch block; (ii) angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow; or (iii) imaging evidence of new loss of viable | |

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| | myocardium or new regional wall motion abnormality. For patients with elevated baseline biomarkers at baseline the peak CK-MB level was required to rise from the baseline value by an increment equal to the values above.<br><br>■ Definition of Peri-procedural MI in the ISCHEMIA trial (19)<br><br>◆ For subjects with normal baseline biomarker level pre-PCI, peri-PCI MI requires a rise in CK-MB to >5-fold the ULN (or a rise in troponin to >35 times the MI Decision Limit/ULN, whenCKMB is unavailable) within 48 hours post-PCI. If pre-PCI cardiac markers (CKMB or cTn) are elevated, they must be stable or falling as indicated by two samples at least 6h apart. The post-PCI CKMB level should reflect a rise of >20% over pre-PCI levels. In addition to biomarker criteria, peri-PCI MI requires at least one of the following:<br><br>● Post- procedure angiographic TIMI 0/1 flow I n a major coronary artery or aside branch with reference vessel diameter ≥2.0 mm which had TIMI 2-3 flow at baseline, or TIMI 2 flow in a major coronary artery or a side branch with reference vessel diameter ≥3.0 mm which had TIMI 3 flow at baseline or Type C dissection (NHLBI classification) or greater in the target vessel.<br><br>● New ECG changes (ST segment elevation or depression >0.1mV in 2contiguous leads), new | |

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| | pathologic Q-waves in ≥2 contiguous leads, or new persistent LBBB present on a post-PCI ECG obtained at least 30 minutes and up to 48 hours post procedure in the absence of any intervening coronary event between the time of the PCI procedure and the ECG showing changes.<br><br>◆ Or stand-alone biomarker definition<br><br>● CK-MB to > 10-fold the ULN (or when CK-MB is unavailable, arise in troponin to > 70-fold the MI decision Limit/ULN) | |
| 10p 6. **Sample size**<br><br>• Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any ~~repeat~~ revascularization) at 24 months after PCI | 10p 6. **Sample size**<br><br>Primary endpoint: patient-oriented composite outcome (a composite of all-cause death, MI, any revascularization) at 24 months after PCI | Modified the terminology |
| 12p **7.3.2 Protocol Violation**<br><br>③Revascularization is not performed despite of MLA ≤ 3mm2 or (MLA ≤ 4mm2 AND Plaque burden >70%) (IVUS-guided group) | 12p **7.3.2 Protocol Violation**<br><br>③Revascularization is not performed despite of MLA ≤ 3mm2 or (3 mm2 <MLA ≤ 4mm2 AND Plaque burden >70%) (IVUS-guided group) | Specified the definition of protocol violation so as to clear up misunderstandings and clarify the study protocol. |

| Previous Version Number<br>Ver 1.4 (Apr. 17. 2020) | Latter Version Number<br>Ver 1.5 (Sep. 09. 2020) | Specific Reason of Modification |
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| **4p 3.1 Preface**<br>Percutaneous coronary intervention (PCI) is the current standard treatment for coronary artery diseases ~ This study aims to compare safety and efficacy of physiology (FFR)-guided PCI strategy and imaging (IVUS)-guided PCI strategy in patients with intermediate coronary stenosis. | **4p 3.1 Preface**<br>Percutaneous coronary intervention (PCI) is the current standard treatment for coronary artery diseases ~ This study aims to compare safety and efficacy of physiology (FFR)-guided PCI strategy and imaging (IVUS)-guided PCI strategy in patients with intermediate coronary stenosis.<br><br>Although FFR is the current standard of car for the functional assessment of lesion severity in patients with intermediate-grade stenosis, FFR guided PCI is still underused in real world practice due to the concerns for prolonged procedural time, increased costs, and potential complications by pressure wire. The quantitative flow ratio (QFR) is a novel angiography based approach allowing calculation of FFR by 3-dimensional coronary artery reconstruction and fluid dynamic computation. There are many clinical studies supporting the QFR value and identifying of patients at risk from cardiovascular events.(12, 13) Therefore, we will confirm the accuracy of QFR, the relationship between IVUS and QFR findings, and incremental value of QFR for predicting cardiovascular events | Added the background of adding a secondary endpoint. |
| 5p **4.2.2. Secondary endpoint**<br><br>16. [Blank] | 5p **4.2.2. Secondary endpoint**<br><br>16. QFR analysis (fixed QFR, contrast QFR, delta QFR, and post PCI QFR) | Added a secondary endpoint. |
| **7 p 5.1 General Study Design and Plan**<br>Following angiography, patients with intermediate | **7 p 5.1 General Study Design and Plan**<br>Following angiography, patients with intermediate | Added a secondary endpoint and its analysis plan. |

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| diameter stenosis 40-70% ~ In addition, the use of IVUS or FFR according to the assigned group will be permitted as tools for the optimizing PCI in stent type, PCI procedures and any adjunctive pharmacologic treatment will be left to the operator's discretion.<br><br>There will be **NO** regulation for any specific usage of the DES.~ If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available. | diameter stenosis 40-70% ~ In addition, the use of IVUS or FFR according to the assigned group will be permitted as tools for the optimizing PCI in stent type, PCI procedures and any adjunctive pharmacologic treatment will be left to the operator's discretion**.**<br><br>The QFR analysis is only performed on a coronary angiograms that can be analyzed. The Post-procedural QFR will be analyzed in case the PCI is performed.<br><br>There will be **NO** regulation for any specific usage of the DES.~ If the patient misses scheduled follow-up visits, other effort using telephone, e-mail to communicate with the patient will be available. | |
| **9p 5.4 Study Variables Table**<br>[Blank] | **9p 5.4 Study Variables Table**<br>**"QFR analysis data :** Baseline / Post-Procedure" | Specify the additional secondary endpoint. |
| 15p 8.1 **Table 2. Baseline procedural characteristics**<br><br>*Angiographic findings*~ Post PCI FFR | 15p 8.1 **Table 2. Baseline procedural characteristics**<br><br>*Angiographic findings*~ Post PCI FFR: *QFR findings*<br><br>Fixed QFR<br><br>Contrast FFR | Added a secondary endpoint and its analysis plan as a footnote under the table. |