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Validation of the diagnostic performance of 'HeartMedi 1.0', a novel CT-derived fractional flow reserve measurement, for patients with coronary artery disease: a study protocol.

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Abstract

Introduction: Coronary computed tomographic angiography (CCTA) is widely used for noninvasive coronary artery evaluation, but it is limited in identifying the nature of functional characteristics that cause ischemia. Recent computational fluid dynamic (CFD) techniques applied to CCTA images permit noninvasive computation of fractional flow reserve (FFR), a measure of lesion-specific ischemia. However, this technology has limitations, such as long computational time and the need for expensive equipment, which hinder widespread use.

Methods and analysis: This study is a prospective, multicenter, comparative, and confirmatory trial designed to evaluate the diagnostic performance of Heartmedi 1.0, a novel CT-derived FFR measurement for the detection of hemodynamically significant coronary artery stenoses identified by CCTA, based on invasive FFR (i-FFR) as a reference standard. i-FFR values ≤ 0.80 will be considered hemodynamically significant. The study will enroll 184 patients who underwent CCTA, invasive coronary angiography, and i-FFR. Computational FFR (c-FFR) will be analyzed by CFD techniques using a lumped parameter model based on vessel length method. Blinded core laboratory interpretation will be performed for CCTA, invasive coronary angiography, i-FFR, and c-FFR. The primary objective of the study is to compare the area under the receiver-operator characteristic curve between c-FFR and CCTA to noninvasively detect the presence of hemodynamically significant coronary stenosis. The secondary endpoints include diagnostic accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and correlation of c-FFR with i- FFR.

Ethics and dissemination

The study was approved by the ethics committee of Seoul National University Bundang Hospital and informed consent will be obtained for all enrolled patients. The result will be published in a peer-reviewed journal.

Trial Registration: Clinical Research Information Service [Internet]; Osong (Chungcheongbuk-do): Korea Centers for Disease Control and Prevention, Ministry of Health and Welfare (Republic of Korea), 2010: KCT0002725; Pre-results.

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Strengths and limitations of this study

The non-invasive measurement of FFR can improve diagnostic performance for the severity of coronary disease and enhance the quality of patient outcomes.

The novel simulating method for predicting FFR in the study allows shorter time and easier access using an on-site personal computer.

The study aims to reduce the biases associated with selection and referrals through a multicenter, prospective study design.

The study excludes patients with acute myocardial infarction, previous percutaneous coronary intervention, or coronary artery bypass graft, so there is a limitation that the generalization potential of computed FFR for the overall patients with coronary artery disease is unknown.

Keywords

Computed tomography, Coronary CT angiography, Fractional flow reserve, Computational fluid dynamics, Coronary artery disease

Introduction

Fractional flow reserve (FFR) has become the standard of care for functional assessment of the extent and severity of coronary disease.[1 2] Recent advances in computed tomography (CT) and computational fluid dynamics (CFD) have enabled estimation of FFR with routine CT angiography acquired at rest. Hemodynamics of the aorta and coronary arteries calculated using CFD are coupled with parameter models of the cardiovascular system. The current technology has shown acceptable diagnostic accuracy compared with invasive FFR (i-FFR).[3-5] However, there are several limitations with it, such as prolonged time for calculation and the need for high-performance computational power; these hamper its widespread use in clinical practice.

Recently, a novel simulating method for predicting FFR with coronary CT angiography (CCTA) has been developed.[6 7] It represents a simple simulation method using a personal computer to estimate FFR values. CT images of coronary arteries and basal physiological data of patients are the only requirements for patient-specific simulation model.[6] For the construction of a patient-specific CFD model, a fast segmentation system of CT images is used, which enables the on-site solution of computational FFR (c-FFR). The lumped parameter model used to reflect the effect of microvasculature and veins adopts only the coronary circulation rather than using the entire cardiovascular system (Figure 1, 2). Potential advantages include shorter computational time and no need for supercomputers.

A recent retrospective analysis demonstrated acceptable diagnostic performance of the simulation method.[8] In this study, we will prospectively perform a trial to confirm the diagnostic performance of c-FFR. c-FFR estimated using the routine CCTA images will be compared with anatomical assessment alone with i-FFR as the reference standard.

Methods

Study Aim

This study will be a prospective, multicenter, comparative, and confirmatory trial. The primary objective of the trial is to assess the diagnostic performance of c-FFR based on routinely acquired CCTA (HeartMedi 1.0, SiliconSapiens, Korea) in patients with coronary artery disease. The i-FFR acquired during invasive coronary angiography (ICA) will be the reference standard, and non-invasive CCTA will be the comparator diagnostic method. The primary endpoint is to test the superiority of c-FFR compared to CCTA alone in terms of identification of significant hemodynamic stenosis validated by i-FFR with ICA.

Study Population

Patients with coronary artery disease undergoing non-emergent ICA and i-FFR will be eligible for inclusion in the trial. All study subjects will provide written informed consent. CCTA with ≥64 multidetector slices needs to be taken within 90 days before enrollment. ICA and i-FFR will be performed with a clinical indication that will be left on physicians' discretion. Patients will be enrolled after completion of ICA and i-FFR if he/she provides informed consent (Figure 3). The key inclusion criteria include the presence of CCTA within 90 days, available ICA, and i-FFR measurements. Key exclusion criteria include resting anginal symptom, chronic kidney disease, tachycardia, hypotension, and high coronary artery calcium score. The inclusion and exclusion criteria are detailed in Table 1. The study subjects will be enrolled from 12 medical centers in Korea.

Table 1. Inclusion and Exclusion criteria

Inclusion criteria	Exclusion criteria
1. Men and women age ≥ 19 2. Voluntary agreement to a written consent 3. 64 Multidetector row CCTA taken within 90 days of coronary angiography 4. Subjects who needs a preliminary test for FFR during coronary angiography	1. Needs for emergency procedures 2. Difficult cooperating with medical staff for reasons such as cognitive impairment 3. Experienced acute myocardial infarction within the last 30 days 4. Complains of chest pain during rest (CCS Class IV) 5. Impaired chronic renal function (Serum creatinine > 2.0 mg/dL) 6. Heart rate ≥100 beats/m 7. Systolic BP ≤90 mmHg 8. CAC ≥1000 9. Pregnancy 10. Body mass index > 35 kg/m2 11. Prior PCI or CABG in the subject blood vessel 12. Previous valvular surgery 13. Complicated congenital heart disease 14. Acute pulmonary edema 15. Unstable hemodynamics including cardiogenic shock, abrupt chest pain 16. Pacemaker, or internal defibrillator leads implanted 17. Known hypersensitivity or contraindication to β-blocker, nitroglycerin, adenosine 18. History of contrast dye allergy 19. Significant arrhythmia including Complete AV block, Ventricular arrhythmia 20. Subjects who are currently participating in other clinical trials or have participated in other clinical trials within 30 days before screening 21. Others who is inappropriate subject judged by clinician

FFR, fractional flow reserve; CCTA, coronary CT angiography; CCS, Canadian Cardiovascular Society; BP, blood pressure; CAC, Coronary artery calcium

Study Process

Study images such as CCTA, ICA, and i-FFR will be transferred to blinded independent core laboratories where study images of CCTA and i-FFR will be interpreted independently. CCTA images will be anonymized and sent to the vendor (c-FFR core laboratory), where measurements of c-FFR will be performed. All study processes will be blinded, and measurements will be conducted independently. All measurement data will be recorded in electronic case report forms, which will be blinded to other participants of the study. Specifically, the c-FFR core laboratory of SiliconSapiens will be completely blinded to the findings of the CCTA, quantitative coronary angiography, and i-FFR core laboratories. The independent statistical core laboratory will collect the data after completion of the trial.

Coronary CT angiography

Patients who underwent CCTA as part of routine clinical care will be enrolled in the study. The minimum requirement for CCTA includes ≥64 multidetector slices and a row width of ≤0.75 mm. CT angiography scanning protocols in the participating centers are consistent with the quality standards by the Society of Cardiac Computed Tomography.[9] The quality of CCTA images of each participating center has been confirmed by the core laboratory before the trial initiation. Study CCTA images will be transmitted to the core laboratory, where the characteristics and severity of coronary atherosclerotic lesions will be quantified by two independent, blinded radiologists. Any disagreement between the two radiologists will be resolved by discussion. The coronary system will be divided into the left anterior descending artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA), and then further into 15 segments according to the American Heart Association (AHA) classification guidelines.[10 11] Using a semi-automated

dedicated three-dimensional workstation (Intellispace Portal, Philips Healthcare, Cleveland, OH), curved multiplanar reformatted images will be reconstructed for assessment. The degree of stenosis of the vessels will be measured around the narrowest area at a rate based on the average of the normal coronary arteries above and below the stenosis site. Quantitative analysis of stenosis grade will be classified as normal (0%), minimal (1-24%), mild (26-49%), moderate (50-69%), severe (70-99%), and occlusion (100%) according to Society of Cardiovascular Computed Tomography (SCCT) guidelines.[9]

Coronary angiography

ICA and i-FFR procedures will be performed according to the American College of Cardiology/American Heart Association for guidelines for coronary angiography and intervention.[12] Intracoronary nitroglycerine (100–200 mg) will be administered in the coronary arteries before initial cine angiograms unless contraindicated. Coronary arterial images will be obtained with selective catheterization of the left and right coronary arteries. The coronary angiography images will be analyzed using an automated edge-detection system (Cardiovascular Angiography Analysis Systems, Maastricht, the Netherlands) at the core laboratory by an experienced technician who is blinded to the study. After calibration with the outer diameter of the coronary catheter, the minimal lumen diameter, reference vessel diameter, % diameter stenosis, will be measured. If there are two or more stenosed vessels over 2.0 mm, the most severe lesion will be chosen as the index lesion.

Invasive FFR

i-FFR measurements performed in the coronary arteries with a diameter of ≥ 2 mm will be

included in the study. i-FFR should be measured using a sensor-tipped 0.014-inch guidewire (PressureWire; St. Jude Medical, St. Paul, MN or Verrata wire; Philips, Eindhoven, the Netherlands) through a 5- to 7-Fr guiding catheter. Pressure calibration should be confirmed as zero at the ascending aorta or proximal segment of the coronary arteries. The location of the pressure wire distal to the index lesion should be recorded on a coronary angiographic image. Maximal myocardial hyperemia should be induced by continuous intravenous adenosine infusion via a central or peripheral vein with an infusion rate of 140 mg/kg per minute. The i-FFR will be calculated as the mean distal coronary pressure divided by the mean aortic pressure during hyperemia. A pullback recording should be performed and recorded. The absence of pressure signal drift (0.97–1.03) needs to be confirmed at the distal end of the guiding catheter. The raw data of the i-FFR measurements will be sent to the i-FFR core laboratory, where potential bias such as maximum hyperemia and pressure drift will be confirmed, and the measurements will be validated. The validated i-FFR values will be transmitted to the statistical core laboratory.

Computational FFR

The vendor (c-FFR core laboratory) will receive the segmented CCTA images from the CCTA core laboratory. The i-FFR core laboratory will demarcate the location of i-FFR measurement on the reconstructed CCTA, which will be transmitted to SiliconSapiens via the study coordinator. SiliconSapiens will analyze c-FFR according to the method of using medical devices for clinical trials. The simulations use a three-dimensional model of epicardial coronary arteries derived from CCTA image segmentation, and the estimation is based on vessel lengths but not on myocardial volume. The parameters will be assigned by physiological data customized to each individual patient-specific model. Coronary blood flow will be simulated under conditions that

mimic maximal hyperemia. For suboccluded or chronically occluded arteries by coronary CTA (i.e., stenosis >90%) default c-FFR values of 0.50 will be assigned to that vessel.

Primary efficacy analysis

The primary measure of performance will be the area under the receiver-operator characteristic curve (AUC) to detect hemodynamically significant stenosis. The gold standard for significant stenosis will be defined as invasive FFR ≤ 0.80. The measurements will be % stenosis and simulated FFR based on CT for CCTA and c-FFR, respectively. Sensitivity will be plotted against (1-Specificity) for different cut-off points of the study measurements. The AUC, standard error, and 95% confidence intervals will be presented. Delong's test will be used to compare two correlated C-statistics.[13]

Secondary efficacy analysis

Diagnostic accuracy, sensitivity, specificity, PPV, NPV, and correlation will be presented as secondary analyses. The cutoff for significant obstruction of CCTA will be defined as a diameter stenosis of $\geq 50\%$. The cutoff for c-FFR will the simulated c-FFR measured by the software HeartMedi 1.0 of ≤ 0.8. Each value will be calculated as shown below.

$$\text{Predictive accuracy} = \frac{TP + TN}{TP + FP + FN + TN}$$

$$\text{Sensitivity} = \frac{TP}{TP + FN}$$

$$\text{Specificity} = \frac{TN}{TN + FP}$$

$$\text{Positive predictive value} = \frac{TP}{TP + FP}$$

$$\text{Negative predictive value} = \frac{TN}{TN + FN}$$

Each value and 95% confidence interval will be presented. The performance will be compared using McNemar's test. Correlation will be assessed with the use of Pearson or Spearman Correlation, whereby coefficient (r) and p-values will be determined.

Statistical hypotheses and sample size calculation

The study hypothesis is that the AUC of c-FFR would be greater than that of CCTA. The NXT trial previously reported the AUC of FFRct (HeartFlow) and CCTA to be 0.90 and 0.81, respectively.[3 14] The NOVEL-FLOW study also showed similar discriminatory functions (AUC, 0.93 for CT-FFR and 0.74 for CCTA).[8] In the present study, the AUC of c-FFR and CCTA were assumed to be 0.90 and 0.81, respectively. We expected the prevalence of hemodynamically significant stenosis to be 31.5% based on the previous studies.[3 15-17] The assumptions included 0.6 of the correlation coefficient of AUCs between c-FFR and CCTA and the attrition rate of 15%. With these assumptions, 184 study participants would be required to achieve a one-sided significance level of 0.025 and power of 80%.

Patient and public involvement statements

There was no patient or public involvement in the design of the present study, and there is no planned patient or public involvement to recruit and conduct the study.

Discussion

FFR-guided coronary revascularization has shown clinical benefits over angiography guidance alone.[18 19] CCTA is currently the most widely used imaging modality for non-invasive coronary evaluation.[20 21] Recent advances in CT imaging enabled high diagnostic accuracy for detecting obstructive coronary artery disease.[22 23] The combination of high image quality of CCTA and functional assessment of FFR has the potential to improve diagnostic performance and enhance the quality of patient outcomes. It allows the functional assessment of coronary stenosis without invasive catheterization, which inevitably is associated with complications.

Previous studies have proven the benefit of such approaches, including FFR_{CT} developed by HeartFlow.[24-26] The limitations of this technology include the need for high-performance computing power, long computation time, and potential simulation errors. The novel simulation method tested in this study (CT-FFR, HeartMedi 1.0) has several advantages over the previous methods. The previous methods use computational fluid dynamics that require myocardial mass estimation based on the whole cardiac anatomy coupled with lumped parameter models (volume-based method).[3 4 27] In contrast, computational fluid dynamics used in the novel c-FFR technology calculates vessel length and three-dimensional coronary artery geometry, which is combined with coronary circulation of lumped parameter models (length-based method). A previous study demonstrated no significant difference in hemodynamic simulation between the two estimation methods.[7] The feature is translated into less need for computational power. Functional assessment can be performed on-site with a personal computer environment without transferring large volume CT images to central laboratories. In addition, this method excludes the possibility of errors due to the segmentation of LV muscle.

One previous study retrospectively analyzed 218 vessels from 117 patients to validate the c-

FFR method compared with invasively measured FFR.[8] The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of c-FFR were shown to be 85.8%, 86.2%, 85.5%, 79.8%, and 90.3%, respectively. The diagnostic performance measured by the area under the receiver operating characteristic curve was significantly higher for c-FFR than those for CCTA. c-FFR showed a slight underestimation of the functional severity of the lesions. The present study is designed to prospectively validate the performance of the novel simulation method. Eligible subjects who have coronary artery disease with CCTA and i-FFR available will be prospectively enrolled. The sample size is planned based on statistical power calculation.

In conclusion, the present study will prospectively assess the diagnostic performance of c-FFR. The values will be compared with that of CCTA with i- FFR as the gold standard.

Protocol amendments

All changes in the study protocol were reviewed by the ethics committee of Seoul National University Bundang Hospital and reported to the sponsor and funder. Significant protocol changes were recorded in Clinical Research Information Servic (KCT0002725).

Ethics and dissemination

Written informed consent will be obtained for all enrolled patients. The result will be published in a peer-reviewed journal.

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Footnotes

Authors' contributions: Kang SH and Youn TJ conceived and design the study. Kim SH and Kang SH wrote the draft of the paper. Youn TJ and Chae IH were involved in critical revision of the study for important intellectual content. All authors contributed to revision and approved the final version of the manuscript.

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Competing interests: None declared.

Ethics approval: This study was approved by the ethics committee of Seoul National University Bundang Hospital (E-1709/420-001).

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Data availability statement: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. On completion of the trial, and after publication of the primary manuscript, data requests can be submitted.

Patient consent for publication: Not required.

Acknowledgments: None

Figures

Figure 1. Process of computational FFR calculation. (A) DICOM data sets from segmented CCTA image and physiological data required for hemodynamic calculations. (B) FFR is calculated through computational fluid dynamic (CFD) technique and three-dimensional vascular modeling. Blood flow is calculated using coronary artery length instead of the volume of myocardium based on lumped parameter model (LPM) resistance. (C) Visualized results are derived based on the computed FFR.

DICOM, digital imaging and communications in medicine; FFR, fractional flow reserve.

Figure 2. An example case of computed and invasive FFR. (A) 3D model reconstruction derived from CCTA image segmentation and FFR simulated using the novel methods. (B) Coronary angiography shows significant stenosis at the proximal LAD, an intermediate lesion at the distal LCX, and an insignificant lesion at the mid-RCA. The arrow indicates the position of the pressure sensor when measuring FFR. The measured FFR was 0.79 for LAD, 0.87 for LCX, and 0.99 for RCA, respectively. (C) The computed FFR at the corresponding point was 0.77, 0.90, and 0.96.

3D, three-dimensional; CCTA, coronary CT angiogram; FFR, fractional flow reserve; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

Figure 3. Study flow. CCTA, coronary CT angiography; FFR, fractional flow reserve.

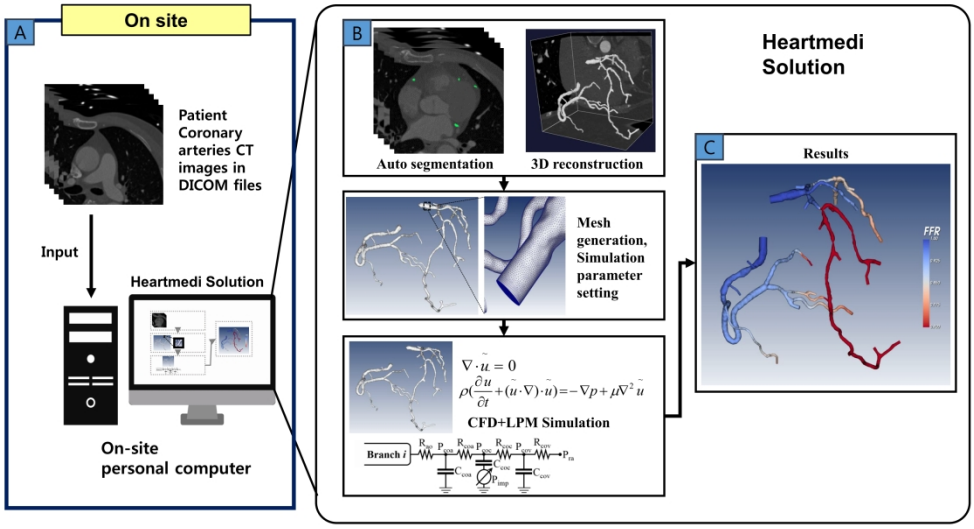

Figure 1. Process of computational FFR calculation.

338x190mm (300 x 300 DPI)

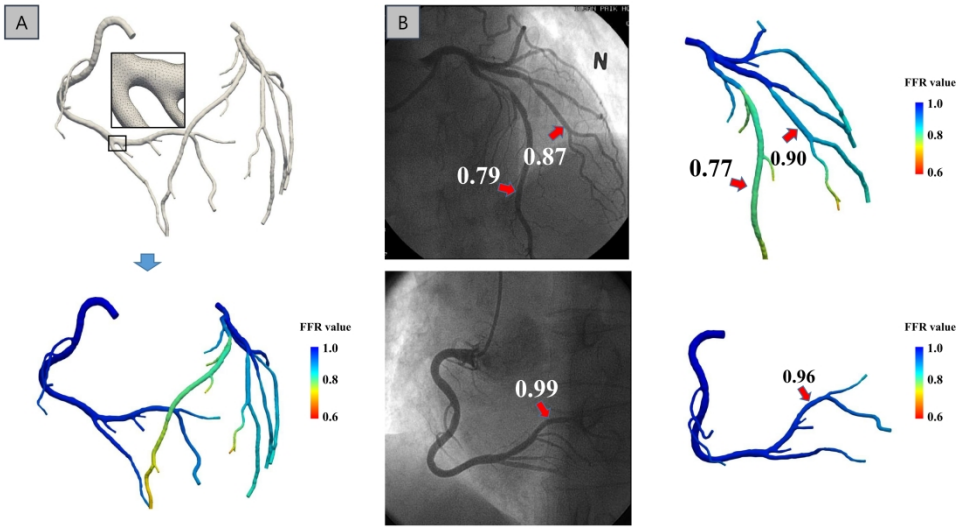

Figure 2. An example case of computed and invasive FFR.

338x190mm (300 x 300 DPI)

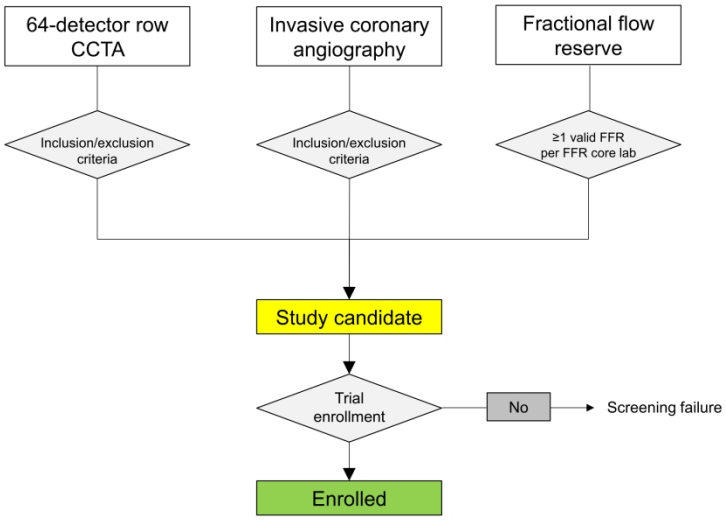

Figure 3. Study flow.

275x190mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor	#5b	Name and contact information for the trial sponsor	18

contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n/a
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	n/a
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will	n/a

		be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	4
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a

Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Validation of the diagnostic performance of 'HeartMedi 1.0', a novel CT-derived fractional flow reserve measurement, for patients with coronary artery disease: a study protocol.

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Validation of the diagnostic performance of 'HeartMedi 1.0', a novel CT-derived fractional flow reserve measurement, for patients with coronary artery disease: a study protocol.

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Running title: a novel CT-derived FFR measurement

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Abstract

Introduction: Coronary computed tomographic angiography (CCTA) is widely used for noninvasive coronary artery evaluation, but it is limited in identifying the nature of functional characteristics that cause ischemia. Recent computational fluid dynamic (CFD) techniques applied to CCTA images permit noninvasive computation of fractional flow reserve (FFR), a measure of lesion-specific ischemia. However, this technology has limitations, such as long computational time and the need for expensive equipment, which hinder widespread use.

Methods and analysis: This study is a prospective, multicenter, comparative, and confirmatory trial designed to evaluate the diagnostic performance of Heartmedi 1.0, a novel CT-derived FFR measurement for the detection of hemodynamically significant coronary artery stenoses identified by CCTA, based on invasive FFR as a reference standard. The invasive FFR values ≤ 0.80 will be considered hemodynamically significant. The study will enroll 184 patients who underwent CCTA, invasive coronary angiography, and invasive FFR. Computational FFR (c-FFR) will be analyzed by CFD techniques using a lumped parameter model based on vessel length method. Blinded core laboratory interpretation will be performed for CCTA, invasive coronary angiography, invasive FFR, and c-FFR. The primary objective of the study is to compare the area under the receiver-operator characteristic curve between c-FFR and CCTA to noninvasively detect the presence of hemodynamically significant coronary stenosis. The secondary endpoints include diagnostic accuracy, sensitivity, specificity, positive predictive value, negative predictive value, and correlation of c-FFR with invasive FFR.

Ethics and dissemination

The study has ethic approval from the ethics committee of Seoul National University Bundang Hospital (E-1709/420-001) and informed consent will be obtained for all enrolled patients. The result will be published in a peer-reviewed journal.

Trial Registration: Clinical Research Information Service [Internet]; Osong (Chungcheongbuk-do): Korea Centers for Disease Control and Prevention, Ministry of Health and Welfare (Republic of Korea), 2010: KCT0002725; Pre-results.

Available from: https://cris.nih.go.kr/cris/search/search_result_st01.jsp?seq=15286

Strengths and limitations of this study

The non-invasive measurement of FFR can improve diagnostic performance for the severity of coronary disease and enhance the quality of patient outcomes.

The novel simulating method for predicting FFR in the study allows shorter time and easier access using an on-site personal computer.

The study aims to reduce the biases associated with selection and referrals through a multicenter, prospective study design.

The study excludes patients with acute myocardial infarction, previous percutaneous coronary intervention, or coronary artery bypass graft, so there is a limitation that the generalization potential of computed FFR for the overall patients with coronary artery disease is unknown.

Keywords

Computed tomography, Coronary CT angiography, Fractional flow reserve, Computational fluid dynamics, Coronary artery disease

Introduction

Fractional flow reserve (FFR) has become the standard of care for functional assessment of the extent and severity of coronary disease.[1 2] Recent advances in computed tomography (CT) and computational fluid dynamics (CFD) have enabled estimation of FFR with routine CT angiography acquired at rest. Hemodynamics of the aorta and coronary arteries calculated using CFD are coupled with parameter models of the cardiovascular system. The current technology has shown acceptable diagnostic accuracy compared with invasive FFR.[3-5] However, there are several limitations with it, such as prolonged time for calculation and the need for high-performance computational power; these hamper its widespread use in clinical practice.

Recently, a novel simulating method for predicting FFR with coronary CT angiography (CCTA) has been developed.[6 7] It represents a simple simulation method using a personal computer to estimate FFR values. CT images of coronary arteries and basal physiological data of patients are the only requirements for patient-specific simulation model.[6] For the construction of a patient-specific CFD model, a fast segmentation system of CT images is used, which enables the on-site solution of computational FFR (c-FFR). The lumped parameter model used to reflect the effect of microvasculature and veins adopts only the coronary circulation rather than using the entire cardiovascular system (Figure 1, 2). Potential advantages include shorter computational time and no need for supercomputers.

A recent retrospective analysis demonstrated acceptable diagnostic performance of the simulation method.[8] In this study, we will prospectively perform a trial to confirm the diagnostic performance of c-FFR. c-FFR estimated using the routine CCTA images will be compared with anatomical assessment alone with invasive FFR as the reference standard.

Methods

Study Aim

This study will be a prospective, multicenter, comparative, and confirmatory trial. The primary objective of the trial is to assess the diagnostic performance of c-FFR based on routinely acquired CCTA (HeartMedi 1.0, SiliconSapiens, Korea) in patients with coronary artery disease. The invasive FFR acquired during invasive coronary angiography (ICA) will be the reference standard, and non-invasive CCTA will be the comparator diagnostic method. The primary endpoint is to test the superiority of c-FFR compared to CCTA alone in terms of identification of significant hemodynamic stenosis validated by invasive FFR with ICA.

Study Population

Patients with coronary artery disease undergoing non-emergent ICA and invasive FFR will be eligible for inclusion in the trial. All study subjects will provide written informed consent. CCTA with ≥64 multidetector slices needs to be taken within 90 days before enrollment. ICA and invasive FFR will be performed with a clinical indication that will be left on physicians' discretion. Patients will be enrolled after completion of ICA and invasive FFR if he/she provides informed consent (Figure 3). The key inclusion criteria include the presence of CCTA within 90 days, available ICA, and invasive FFR measurements. Key exclusion criteria include resting anginal symptom, chronic kidney disease, tachycardia, hypotension, and high coronary artery calcium score. The inclusion and exclusion criteria are detailed in Table 1. The study subjects will be enrolled from 12 medical centers in Korea.

Table 1. Inclusion and Exclusion criteria

Inclusion criteria	Exclusion criteria
1. Men and women age ≥ 19 2. Voluntary agreement to a written consent 3. 64 Multidetector row CCTA taken within 90 days of coronary angiography 4. Subjects who needs a preliminary test for FFR during coronary angiography	1. Needs for emergency procedures 2. Difficult cooperating with medical staff for reasons such as cognitive impairment 3. Experienced acute myocardial infarction within the last 30 days 4. Complains of chest pain during rest (CCS Class IV) 5. Impaired chronic renal function (Serum creatinine > 2.0 mg/dL) 6. Heart rate ≥100 beats/m 7. Systolic BP ≤90 mmHg 8. CAC ≥1000 9. Pregnancy 10. Body mass index > 35 kg/m2 11. Prior PCI or CABG in the subject blood vessel 12. Previous valvular surgery 13. Complicated congenital heart disease 14. Acute pulmonary edema 15. Unstable hemodynamics including cardiogenic shock, abrupt chest pain 16. Pacemaker, or internal defibrillator leads implanted 17. Known hypersensitivity or contraindication to β-blocker, nitroglycerin, adenosine 18. History of contrast dye allergy 19. Significant arrhythmia including Complete AV block, Ventricular arrhythmia 20. Subjects who are currently participating in other clinical trials or have participated in other clinical trials within 30 days before screening 21. Others who is inappropriate subject judged by clinician

FFR, fractional flow reserve; CCTA, coronary CT angiography; CCS, Canadian Cardiovascular Society; BP, blood pressure; CAC, Coronary artery calcium

Study Process

Study images such as CCTA, ICA, and invasive FFR will be transferred to blinded independent core laboratories where study images of CCTA and invasive FFR will be interpreted independently. CCTA images will be anonymized and sent to the vendor (c-FFR core laboratory), where measurements of c-FFR will be performed. All study processes will be blinded, and measurements will be conducted independently. All measurement data will be recorded in electronic case report forms, which will be blinded to other participants of the study. Specifically, the c-FFR core laboratory of SiliconSapiens will be completely blinded to the findings of the CCTA, quantitative coronary angiography, and invasive FFR core laboratories. The independent statistical core laboratory will collect the data after completion of the trial.

Coronary CT angiography

Patients who underwent CCTA as part of routine clinical care will be enrolled in the study. The minimum requirement for CCTA includes ≥64 multidetector slices and a row width of ≤0.75 mm. CT angiography scanning protocols in the participating centers are consistent with the quality standards by the Society of Cardiac Computed Tomography.[9] The quality of CCTA images of each participating center has been confirmed by the core laboratory before the trial initiation. Study CCTA images will be transmitted to the core laboratory, where the characteristics and severity of coronary atherosclerotic lesions will be quantified by two independent, blinded radiologists. Any disagreement between the two radiologists will be resolved by discussion. The coronary system will be divided into the left anterior descending artery (LAD), left circumflex artery (LCX) and right coronary artery (RCA), and then further into 15 segments according to the American Heart Association (AHA) classification guidelines.[10] [11] Using a semi-automated dedicated three-

dimensional workstation (Intellispace Portal, Philips Healthcare, Cleveland, OH), curved multiplanar reformatted images will be reconstructed for assessment. The degree of stenosis of the vessels will be measured around the narrowest area at a rate based on the average of the normal coronary arteries above and below the stenosis site. Quantitative analysis of stenosis grade will be classified as normal (0%), minimal (1-24%), mild (26-49%), moderate (50-69%), severe (70-99%), and occlusion (100%) according to Society of Cardiovascular Computed Tomography (SCCT) guidelines.[9]

Coronary angiography

ICA and invasive FFR procedures will be performed according to the American College of Cardiology/American Heart Association for guidelines for coronary angiography and intervention.[12] Intracoronary nitroglycerine (100–200 mg) will be administered in the coronary arteries before initial cine angiograms unless contraindicated. Coronary arterial images will be obtained with selective catheterization of the left and right coronary arteries. The coronary angiography images will be analyzed using an automated edge-detection system (Cardiovascular Angiography Analysis Systems, Maastricht, the Netherlands) at the core laboratory by an experienced technician who is blinded to the study. After calibration with the outer diameter of the coronary catheter, the minimal lumen diameter, reference vessel diameter, % diameter stenosis, will be measured. If there are two or more stenosed vessels over 2.0 mm, the most severe lesion will be chosen as the index lesion.

Invasive FFR

The invasive FFR measurements performed in the coronary arteries with a diameter of ≥2 mm

will be included in the study. The invasive FFR should be measured using a sensor-tipped 0.014-inch guidewire (PressureWire; St. Jude Medical, St. Paul, MN or Verrata wire; Philips, Eindhoven, the Netherlands) through a 5- to 7-Fr guiding catheter. Pressure calibration should be confirmed as zero at the ascending aorta or proximal segment of the coronary arteries. The location of the pressure wire distal to the index lesion should be recorded on a coronary angiographic image. Maximal myocardial hyperemia should be induced by continuous intravenous adenosine infusion via a central or peripheral vein with an infusion rate of 140 mg/kg per minute. The invasive FFR will be calculated as the mean distal coronary pressure divided by the mean aortic pressure during hyperemia. A pullback recording should be performed and recorded. The absence of pressure signal drift (0.97–1.03) needs to be confirmed at the distal end of the guiding catheter. The raw data of the invasive FFR measurements will be sent to the invasive FFR core laboratory, where potential bias such as maximum hyperemia and pressure drift will be confirmed, and the measurements will be validated. The validated invasive FFR values will be transmitted to the statistical core laboratory.

Computational FFR

The vendor (c-FFR core laboratory) will receive the segmented CCTA images from the CCTA core laboratory. The invasive FFR core laboratory will demarcate the location of invasive FFR measurement on the reconstructed CCTA, which will be transmitted to SiliconSapiens via the study coordinator. SiliconSapiens will analyze c-FFR according to the method of using medical devices for clinical trials. The simulations use a three-dimensional model of epicardial coronary arteries derived from CCTA image segmentation, and the estimation is based on vessel lengths but not on myocardial volume. The parameters will be assigned by physiological data customized to

each individual patient-specific model. Coronary blood flow will be simulated under conditions that mimic maximal hyperemia. For suboccluded or chronically occluded arteries by coronary CTA (i.e., stenosis >90%) default c-FFR values of 0.50 will be assigned to that vessel.

Primary efficacy analysis

The primary measure of performance will be the area under the receiver-operator characteristic curve (AUC) to detect hemodynamically significant stenosis. The gold standard for significant stenosis will be defined as invasive FFR ≤ 0.80. The measurements will be % stenosis for CCTA and simulated FFR based on CT for c-FFR. Sensitivity will be plotted against (1-Specificity) for different cut-off points of the study measurements. The AUC, standard error, and 95% confidence intervals will be presented. Delong's test will be used to compare two correlated C-statistics.[13]

Secondary efficacy analysis

Diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and correlation will be presented as secondary analyses. The cutoff for significant obstruction of CCTA will be defined as a diameter stenosis of $\geq 50\%$. The cutoff for c-FFR will the simulated c-FFR measured by the software HeartMedi 1.0 of ≤ 0.8. Each value will be calculated as shown below.

$$\text{Predictive accuracy} = \frac{TP + TN}{TP + FP + FN + TN}$$

$$\text{Sensitivity} = \frac{TP}{TP + FN}$$

$$\text{Specificity} = \frac{TN}{TN + FP}$$

$$\text{Positive predictive value} = \frac{TP}{TP + FP}$$

$$\text{Negative predictive value} = \frac{TN}{TN + FN}$$

Each value and 95% confidence interval will be presented. The performance will be compared using McNemar's test. Correlation will be assessed with the use of Pearson or Spearman Correlation, whereby coefficient (r) and p-values will be determined.

Statistical hypotheses and sample size calculation

The study hypothesis is that the AUC of c-FFR would be greater than that of CCTA. The NXT trial previously reported the AUC of FFRct (HeartFlow) and CCTA to be 0.90 and 0.81, respectively.[3 14] The NOVEL-FLOW study also showed similar discriminatory functions (AUC, 0.93 for CT-FFR and 0.74 for CCTA).[8] In the present study, the AUC of c-FFR and CCTA were assumed to be 0.90 and 0.81, respectively. We expected the prevalence of hemodynamically significant stenosis to be 31.5% based on the previous studies.[3 15-17] The assumptions included 0.6 of the correlation coefficient of AUCs between c-FFR and CCTA and the attrition rate of 15%. With these assumptions, 184 study participants would be required to achieve a one-sided significance level of 0.025 and power of 80%.

Patient and public involvement statements

There was no patient or public involvement in the design of the present study, and there is no planned patient or public involvement to recruit and conduct the study.

Discussion

FFR-guided coronary revascularization has shown clinical benefits over angiography guidance alone.[18 19] CCTA is currently the most widely used imaging modality for non-invasive coronary evaluation.[20 21] Recent advances in CT imaging enabled high diagnostic accuracy for detecting obstructive coronary artery disease.[22 23] The combination of high image quality of CCTA and functional assessment of FFR has the potential to improve diagnostic performance and enhance the quality of patient outcomes. It allows the functional assessment of coronary stenosis without invasive catheterization, which inevitably is associated with complications.

Previous studies have proven the benefit of such approaches, including FFR_{CT} developed by HeartFlow.[24-26] The limitations of this technology include the need for high-performance computing power, long computation time, and potential simulation errors. The novel simulation method tested in this study (CT-FFR, HeartMedi 1.0) has several advantages over the previous methods. The previous methods use computational fluid dynamics that require myocardial mass estimation based on the whole cardiac anatomy coupled with lumped parameter models (volume-based method).[3 4 27] In contrast, computational fluid dynamics used in the novel c-FFR technology calculates vessel length and three-dimensional coronary artery geometry, which is combined with coronary circulation of lumped parameter models (length-based method). A previous study demonstrated no significant difference in hemodynamic simulation between the two estimation methods.[7] The feature is translated into less need for computational power. Functional assessment can be performed on-site with a personal computer environment without transferring large volume CT images to central laboratories. In addition, this method excludes the possibility of errors due to the segmentation of LV muscle.

One previous study retrospectively analyzed 218 vessels from 117 patients to validate the c-

FFR method compared with invasively measured FFR.[8] The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of c-FFR were shown to be 85.8%, 86.2%, 85.5%, 79.8%, and 90.3%, respectively. The diagnostic performance measured by the area under the receiver operating characteristic curve was significantly higher for c-FFR than those for CCTA. c-FFR showed a slight underestimation of the functional severity of the lesions. The present study is designed to prospectively validate the performance of the novel simulation method. Eligible subjects who have coronary artery disease with CCTA and invasive FFR available will be prospectively enrolled. The sample size is planned based on statistical power calculation.

In conclusion, the present study will prospectively assess the diagnostic performance of c-FFR. The values will be compared with that of CCTA with invasive FFR as the gold standard.

Limitations

Since this study excludes patients with acute myocardial infarction, previous percutaneous coronary intervention, or coronary artery bypass graft, there is a limitation that the generalization potential of computed FFR for the overall patients with coronary artery disease is unknown. However, the novel method in this study can be easily applied to these cases, and further study will attempt to include them.

Another limitation of the present study is that, although prospective, we are recruiting patients following the performance of CCTA and invasive FFR. This may lead to selection bias. Finally, while the technology was developed for on-site usage, the measurements will be performed in a core laboratory. This was included in the study design to ensure adequate blinding of investigators to the reference values and hence, to minimize study bias.

Protocol amendments

All changes in the study protocol were reviewed by the ethics committee of Seoul National University Bundang Hospital and reported to the sponsor and funder. Significant protocol changes were recorded in Clinical Research Information Service (KCT0002725).

Ethics and dissemination

This study was approved by the institutional review board of Seoul National University Bundang Hospital (E-1709/420-001). Written informed consent will be obtained for all enrolled patients. The result will be published in a peer-reviewed journal.

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Footnotes

Authors' contributions: SH Kang and TJY conceived and designed the study. SH Kim and SH Kang wrote the draft of the paper. WYC, CHY, SDP, CWN, KHK, JHD, YSB, and JWB will conduct screening and data collection. Analysis will be performed by SH Kang, SH Kim and TJY. TJY and IHC were involved in critical revision of the study for important intellectual content. All authors contributed to revision and approved the final version of the manuscript.

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Competing interests: None declared.

Figures

Figure 1. Process of computational FFR calculation. (A) DICOM data sets from segmented CCTA image and physiological data required for hemodynamic calculations. (B) FFR is calculated through computational fluid dynamic (CFD) technique and three-dimensional vascular modeling. Blood flow is calculated using coronary artery length instead of the volume of myocardium based on lumped parameter model (LPM) resistance. (C) Visualized results are derived based on the computed FFR.

DICOM, digital imaging and communications in medicine; FFR, fractional flow reserve.

Figure 2. An example case of computed and invasive FFR. (A) 3D model reconstruction derived from CCTA image segmentation and FFR simulated using the novel methods. (B) Coronary angiography shows significant stenosis at the proximal LAD, an intermediate lesion at the distal LCX, and an insignificant lesion at the mid-RCA. The arrow indicates the position of the pressure sensor when measuring FFR. The measured FFR was 0.79 for LAD, 0.87 for LCX, and 0.99 for RCA, respectively. (C) The computed FFR at the corresponding point was 0.77, 0.90, and 0.96.

3D, three-dimensional; CCTA, coronary CT angiogram; FFR, fractional flow reserve; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

Figure 3. Study flow. CCTA, coronary CT angiography; FFR, fractional flow reserve.

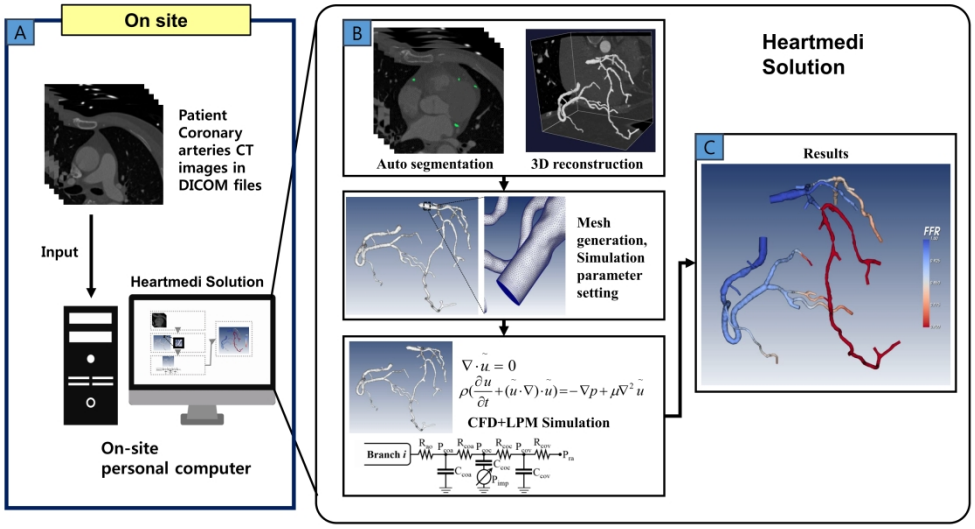

Figure 1. Process of computational FFR calculation.

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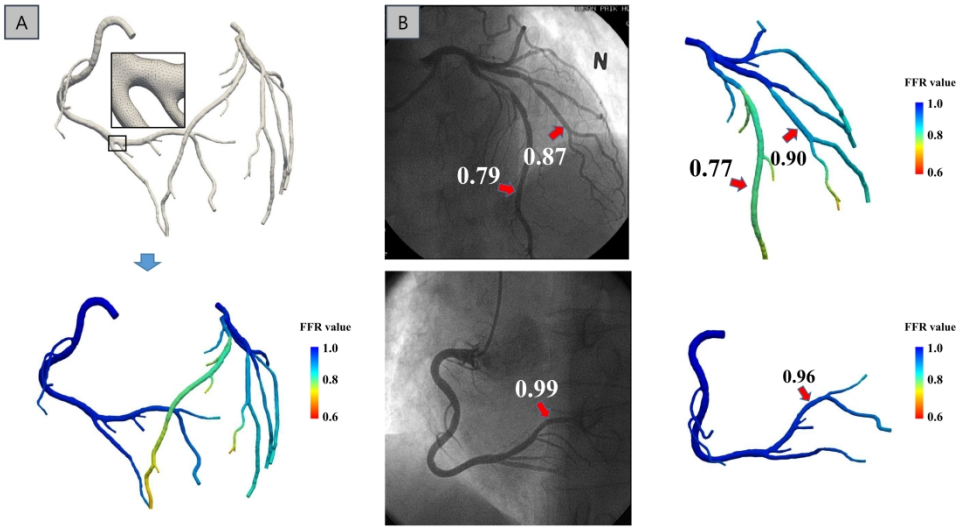

Figure 2. An example case of computed and invasive FFR.

338x190mm (300 x 300 DPI)

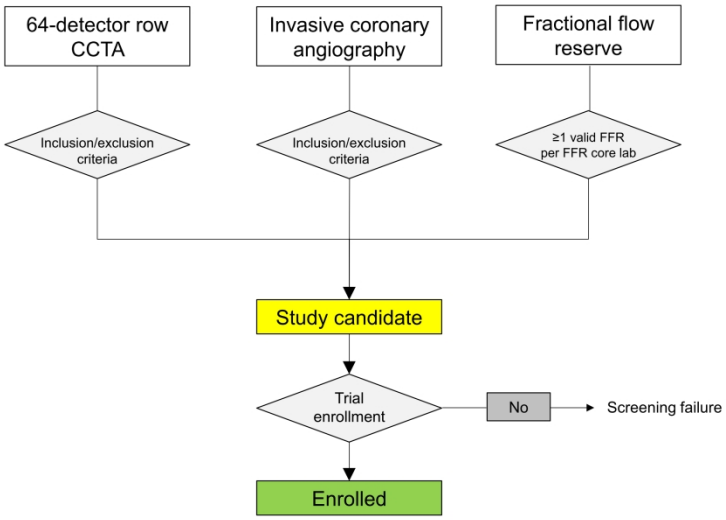

Figure 3. Study flow.

275x190mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	18
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team,	18

		and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	n/a
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data	6

		will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical	10

		relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their	9

		reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	n/a
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	n/a
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	n/a
Methods: Monitoring			

Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	4

Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	16
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a

Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	n/a
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary files
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a