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

Soo-Hyun Kim,[1] Si-Hyuck Kang,[1] Woo-Young Chung,[2] Chang-Hwan Yoon,[1] Sang-Don Park,[3] Chang-Wook Nam,[4] Ki-Hwan Kwon,[5] Joon-Hyung Doh,[6] Young-Sup Byun,[7] Jang-Whan Bae,[8] Tae-Jin Youn ,[1] In-Ho Chae [1]

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So-HK and Si-HK contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Tae-Jin Youn;
ytjmd@snubh.org

ABSTRACT

Introduction Coronary CT angiography (CCTA) is widely used for non-invasive coronary artery evaluation, but it is limited in identifying the nature of functional characteristics that cause ischaemia. Recent computational fluid dynamic (CFD) techniques applied to CCTA images permit non-invasive computation of fractional flow reserve (FFR), a measure of lesion-specific ischaemia. 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, multicentre, comparative and confirmatory trial designed to evaluate the diagnostic performance of HeartMedi V.1.0, a novel CT-derived FFR measurement for the detection of haemodynamically significant coronary artery stenoses identified by CCTA, based on invasive FFR as a reference standard. The invasive FFR values ≤0.80 will be considered haemodynamically significant. The study will enrol 184 patients who underwent CCTA, invasive coronary angiography and invasive FFR. Computational FFR (c-FFR) will be analysed 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 non-invasively detect the presence of haemodynamically 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 number KCT0002725; Pre-results.

Strengths and limitations of this study

- The non-invasive measurement of fractional flow reserve (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 multicentre, 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 generalisation potential of computed FFR for the overall patients with coronary artery disease is unknown.

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 CT and computational fluid dynamics (CFD) have enabled estimation of FFR with routine CT angiography acquired at rest. Haemodynamics 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

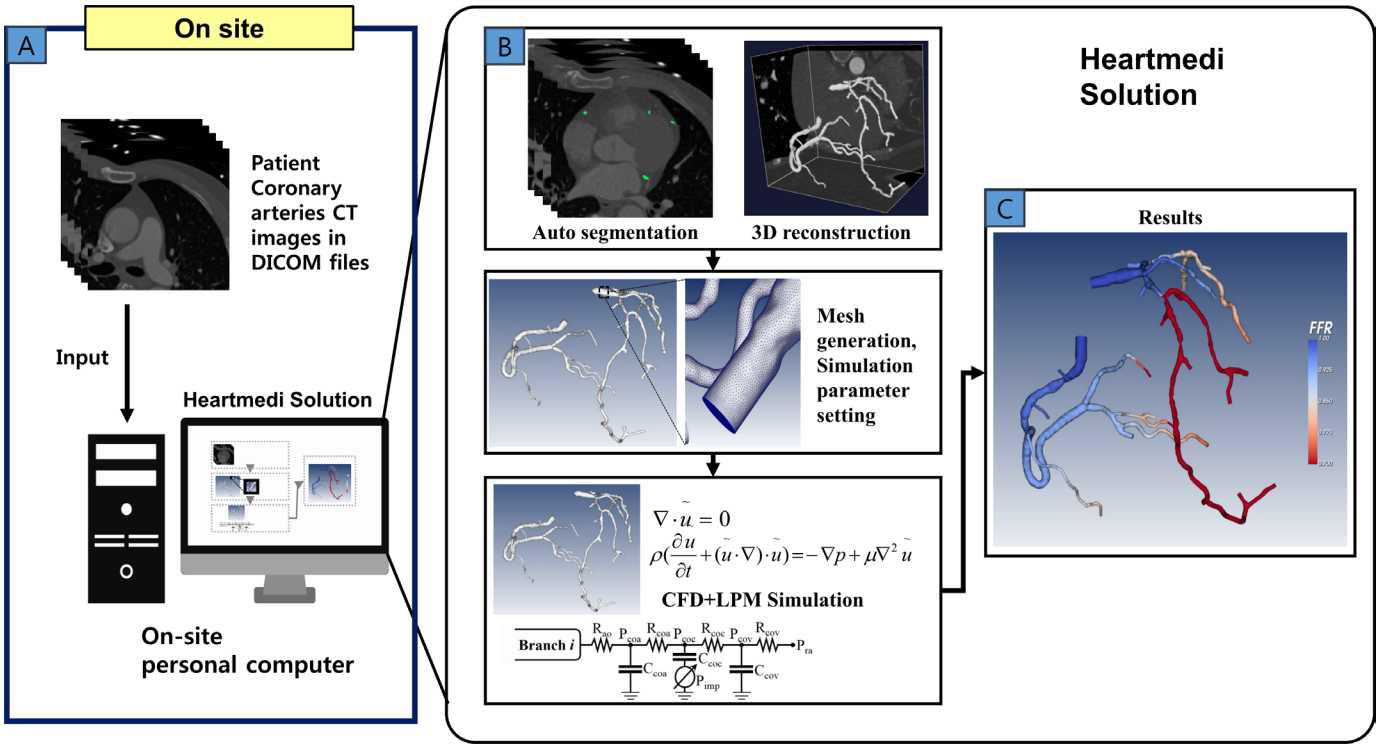

Figure 1 Process of computational fractional flow reserve (FFR) calculation. (A) Digital imaging and communications in medicine (DICOM) data sets from segmented coronary CT angiography image and physiological data required for haemodynamic calculations. (B) FFR is calculated through computational fluid dynamic (CFD) technique and three-dimensional (3D) vascular modelling. Blood flow is calculated using coronary artery length instead of the volume of myocardium based on lumped parameter model (LPM) resistance. (C) Visualised results are derived based on the computed FFR.

(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

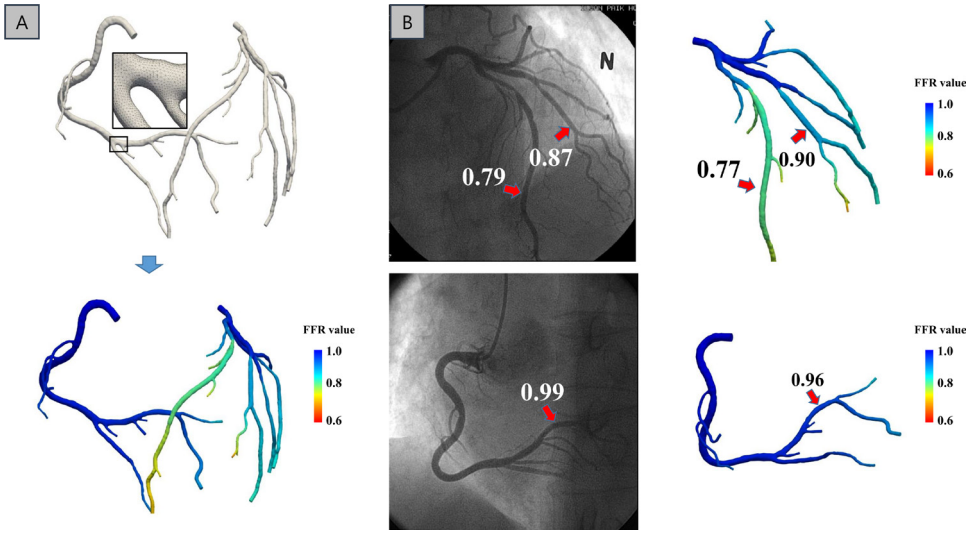

Figure 2 An example case of computed and invasive FFR. (A) 3D model reconstruction derived from CCTA image segmentation and FFR simulated using the novel methods. (B) Coronary angiography shows significant stenosis at the proximal LAD, an intermediate lesion at the distal LCX and an insignificant lesion 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.

using the entire cardiovascular system (figures 1 and 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, multicentre, 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 V.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 with CCTA alone in terms of identification of significant haemodynamic 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 enrolment. 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 centres in Korea.

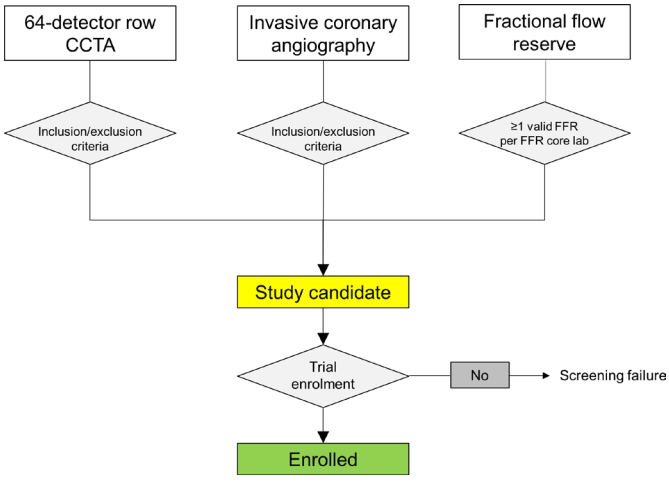

Figure 3 Study flow. CCTA, coronary CT angiography; FFR, fractional flow reserve.

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 anonymised 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 centres are consistent with the quality standards by the Society of Cardiac Computed Tomography.[9] The quality of CCTA images of each participating centre 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, left circumflex artery and right coronary artery (RCA) and then further into 15 segments according to the American Heart Association (AHA) classification guidelines.[10 11] Using a semiautomated dedicated three-dimensional workstation (Intellispace Portal, Philips Healthcare, Cleveland, Ohio, USA), 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 guidelines.[9]

Coronary angiography

ICA and invasive FFR procedures will be performed according to the American College of Cardiology/AHA for guidelines for coronary angiography and

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 need 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. Report of chest pain during rest (CCS class IV) 5. Impaired chronic renal function (serum creatinine >2.0 mg/dL) 6. Heart rate ≥100 beats/min 7. Systolic BP ≤90 mm Hg 8. CAC ≥1000 9. Pregnancy 10. Body mass index >35 kg/m^2 11. Prior PCI or CABG in the subject blood vessel 12. Previous valvular surgery 13. Complicated congenital heart disease 14. Acute pulmonary oedema 15. Unstable haemodynamics 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 are inappropriate subject judged by clinician

AV, atrioventricular; BP, blood pressure; CABG, coronary artery bypass graft; CAC, coronary artery calcium; CCS, Canadian Cardiovascular Society; CCTA, coronary CT angiography; FFR, fractional flow reserve; PCI, Percutaneous coronary intervention.

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 catheterisation of the left coronary artery and RCA. The coronary angiography images will be analysed 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, Minnesota, USA or Verrata Wire; Philips, Eindhoven, the Netherlands) through a 5–7 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 hyperaemia should be induced by continuous intravenous adenosine infusion via a central or peripheral vein with an infusion rate of 140 mg/kg/min. The invasive FFR will be calculated as the mean distal coronary pressure divided by the mean aortic pressure during hyperaemia. A pull-back 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 hyperaemia 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 analyse 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 customised to each individual patient-specific model. Coronary blood flow will be simulated under conditions that mimic maximal hyperaemia. For subocclude or chronically occluded arteries by CCTA (ie, 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 haemodynamically 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, SE and 95% CIs 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 cut-off for significant obstruction of CCTA will be defined as a diameter stenosis of ≥50%. The cut-off for c-FFR will the simulated c-FFR measured by the software HeartMedi V.1.0 of ≤0.8. Each value will be calculated as shown below.

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

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

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

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

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

(TP, True positive; TN, True negative; FP, False positive; FN, False negative.)

Each value and 95% CI 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 (HeartFlow analysis of coronary blood flow using CT angiography: NeXt sTeps) trial previously reported the AUC of FFR_{CT} (HeartFlow) and CCTA to be 0.90 and 0.81, respectively.[3 14] The NOVEL-FLOW (Diagnostic Performance of a Novel Method for Fractional Flow Reserve Computed From Noninvasive Computed Tomography Angiography) 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 was assumed to be 0.90 and 0.81, respectively. We expected the prevalence of haemodynamically 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

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 revascularisation 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 catheterisation, 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 V.1.0) has several advantages over the previous methods. The previous methods use CFD that requires myocardial mass estimation based on the whole cardiac anatomy coupled with lumped parameter models (volume-based method).[3 4 27] In contrast, CFD 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 haemodynamic 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 left ventricular muscle.

One previous study retrospectively analysed 218 vessels from 117 patients to validate the c-FFR method compared with invasively measured FFR.[8] The accuracy, sensitivity, specificity, PPV and NPV 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 AUC 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 the 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 generalisation 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 minimise the 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.

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.

Author affiliations
[1]Division of Cardiology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, The Republic of Korea
[2]Department of Internal Medicine, Seoul Metropolitan Boramae Hospital, Dongjak-gu, Seoul, The Republic of Korea
[3]Division of Cardiology, Department of Internal Medicine, Inha University Hospital, Incheon, The Republic of Korea
[4]Department of Medicine, Keimyung University Dongsan Medical Center, Daegu, The Republic of Korea
[5]Division of Cardiology, Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, The Republic of Korea
[6]Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang-si, Gyeonggi-do, The Republic of Korea
[7]Division of Cardiology, Department of Internal Medicine, Inje University Sanggye Paik Hospital, Seoul, The Republic of Korea
[8]Department of Internal Medicine, College of Medicine, Chungbuk National University, Cheongju, The Republic of Korea

Contributors Si-HK and T-JY conceived and designed the study. So-HK and Si-HK wrote the draft of the paper. W-YC, C-HY, S-DP, C-WN, K-HK, J-HD, Y-SB and J-WB will conduct screening and data collection. Analysis will be performed by Si-HK, So-HK and T-JY. T-JY and I-HC 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.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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ORCID iDs
Tae-Jin Youn http://orcid.org/0000-0001-9957-4204
In-Ho Chae http://orcid.org/0000-0003-1644-2105

REFERENCES

1 Neumann F-J, Sousa-Uva M, Ahlsson A, *et al*. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87–165.
2 Levine GN, Bates ER, Blankenship JC, *et al*. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of cardiology Foundation/American heart association Task force on practice guidelines and the Society for cardiovascular angiography and interventions. *Circulation* 2011;124:e574–651.
3 Nørgaard BL, Leipsic J, Gaur S, *et al*. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (analysis of coronary blood flow using CT angiography: next steps). *J Am Coll Cardiol* 2014;63:1145–55.
4 Koo B-K, Erglis A, Doh J-H, *et al*. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. results from the prospective multicenter DISCOVER-FLOW (diagnosis of Ischemia-Causing stenoses obtained via noninvasive fractional flow reserve) study. *J Am Coll Cardiol* 2011;58:1989–97.
5 Min JK, Leipsic J, Pencina MJ, *et al*. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. *JAMA* 2012;308:1237–45.
6 Kwon S-S, Chung E-C, Park J-S, *et al*. A novel patient-specific model to compute coronary fractional flow reserve. *Prog Biophys Mol Biol* 2014;116:48–55.
7 Lee KE, Kwon S-S, Ji YC, *et al*. Estimation of the flow resistances exerted in coronary arteries using a vessel length-based method. *Pflugers Arch* 2016;468:1449–58.
8 Chung J-H, Lee KE, Nam C-W, *et al*. Diagnostic performance of a novel method for fractional flow reserve computed from noninvasive computed tomography angiography (NOVEL-FLOW study). *Am J Cardiol* 2017;120:362–8.
9 Leipsic J, Abbara S, Achenbach S, *et al*. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of cardiovascular computed tomography guidelines Committee. *J Cardiovasc Comput Tomogr* 2014;8:342–58.
10 Austen WG, Edwards JE, Frye RL, *et al*. A reporting system on patients evaluated for coronary artery disease. Report of the AD hoc Committee for grading of coronary artery disease, Council on cardiovascular surgery, American heart association. *Circulation* 1975;51:5–40.

11 Hausleiter J, Meyer T, Hadamitzky M, *et al*. Prevalence of noncalcified coronary plaques by 64-slice computed tomography in patients with an intermediate risk for significant coronary artery disease. *J Am Coll Cardiol* 2006;48:312–8.
12 Levine GN, Bates ER, Blankenship JC, *et al*. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of cardiology Foundation/American heart association Task force on practice guidelines and the Society for cardiovascular angiography and interventions. *Catheter Cardiovasc Interv* 2013;82:E266–355.
13 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.
14 Gaur S, Achenbach S, Leipsic J, *et al*. Rationale and design of the HeartFlowNXT (HeartFlow analysis of coronary blood flow using CT angiography: next sTeps) study. *J Cardiovasc Comput Tomogr* 2013;7:279–88.
15 Park S-J, Kang S-J, Ahn J-M, *et al*. Visual-functional mismatch between coronary angiography and fractional flow reserve. *JACC Cardiovasc Interv* 2012;5:1029–36.
16 Tesche C, De Cecco CN, Caruso D, *et al*. Coronary CT angiography derived morphological and functional quantitative plaque markers correlated with invasive fractional flow reserve for detecting hemodynamically significant stenosis. *J Cardiovasc Comput Tomogr* 2016;10:199–206.
17 Wu J, Barton D, Xie F, *et al*. Comparison of fractional flow reserve assessment with demand stress myocardial contrast echocardiography in angiographically intermediate coronary stenoses. *Circulation* 2016;9.
18 Tonino PAL, De Bruyne B, Pijls NHJ, *et al*. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213–24.
19 De Bruyne B, Fearon WF, Pijls NHJ, *et al*. Fractional flow reserve-guided PCI for stable coronary artery disease. *N Engl J Med* 2014;371:1208–17.
20 , Montalescot G, Sechtem U, *et al*, Task Force Members. 2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of cardiology. *Eur Heart J* 2013;34:2949–3003.
21 National Institute for Health and Clinical Excellence: Guidance. *Chest pain of recent onset: assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin*. London: National Institute for Health and Clinical Excellence, 2010.
22 Min JK, Shaw LJ, Berman DS. The present state of coronary computed tomography angiography a process in evolution. *J Am Coll Cardiol* 2010;55:957–65.
23 Budoff MJ, Dowe D, Jollis JG, *et al*. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter accuracy (assessment by coronary computed tomographic angiography of individuals undergoing invasive coronary angiography) trial. *J Am Coll Cardiol* 2008;52:1724–32.
24 Coenen A, Lubbers MM, Kurata A, *et al*. Fractional flow reserve computed from noninvasive CT angiography data: diagnostic performance of an on-site clinician-operated computational fluid dynamics algorithm. *Radiology* 2015;274:674–83.
25 Renker M, Schoepf UJ, Wang R, *et al*. Comparison of diagnostic value of a novel noninvasive coronary computed tomography angiography method versus standard coronary angiography for assessing fractional flow reserve. *Am J Cardiol* 2014;114:1303–8.
26 Kruk M, Wardziak Łukasz, Demkow M, *et al*. Workstation-Based calculation of CTA-Based FFR for intermediate stenosis. *JACC Cardiovasc Imaging* 2016;9:690–9.
27 Thompson AG, Raju R, Blanke P, *et al*. Diagnostic accuracy and discrimination of ischemia by fractional flow reserve CT using a clinical use rule: results from the determination of fractional flow reserve by anatomic computed tomographic angiography study. *J Cardiovasc Comput Tomogr* 2015;9:120–8.