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Diagnostic Accuracy of CCTA-derived versus Angiography-derived Quantitative Flow Ratio (CAREER) Study: Rationale and Design

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Title: Diagnostic Accuracy of CCTA-derived versus Angiography-derived Quantitative Flow Ratio (CAREER) Study: Rationale and Design

Running title: Diagnostic Accuracy of CAREER Study: Rationale and Design

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Abstract

Introduction: Coronary computed tomography angiography (CCTA)-derived quantitative flow ratio (CT-QFR) is a novel non-invasive technology to assess the physiological significance of coronary stenoses, which enables fast and on site computation of fractional flow reserve (FFR) from CCTA images. The objective of this investigator-initiated, prospective, single-center clinical trial is to evaluate the diagnostic performance of CT-QFR with respect to angiography-derived QFR, using FFR as the reference standard.

Methods and analysis: A total of 216 patients who have at least 1 lesion with a diameter stenosis of30% to 90% in an artery with≥2.0mm reference diameter will be enrolled in the study. FFR will be measured during invasive coronary angiography. CT-QFR, and QFR will be assessed in two independent core laboratories in blinded fashion. The primary endpoint is the diagnostic accuracy of CT-QFR in identifying hemodynamically significant coronary stenosis with FFR as the reference standard. Major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions.

Ethic and Dissemination: This study will be the first study to prospectively validate the diagnostic accuracy of CT-QFR compared with QFR, using FFR as the reference standard.

Article summary

Strengths and limitations of this study:

- This study will lay the foundation for future studies to look at the potential

value of CT-QFR technology in patients management. Through CT-QFR measurement, outpatients can receive coronary artery functional evaluation while undergoing CCTA Examination.

- It will greatly reduce unnecessary invasive coronary angiography and coronary interventions if the study achieves the expected objectives.
- Unfortunately, due to the tight schedule and insufficient funding, a multi-center study cannot be conducted.

Key words: Coronary computed tomography angiography- derived quantitative flow ratio （CT-QFR）； Angiography-derived quantitative flow ratio （QFR）； Diagnostic accuracy；Non-inferiority

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Introduction

Coronary computed tomography angiography (CCTA) is a noninvasive test that enables visualization of coronary anatomy and the characteristics of arterial plaques with high sensitivity and negative predictive value [1]. However, conventional CCTA does not allow for physiological assessment of coronary stenosis[2].Fractional flow reserve (FFR) is the current gold standard for evaluating the physiological significance of coronary stenosis in the catheterization laboratory [3]. An FFR-guided revascularization strategy was validated with improved clinical outcomes and cost-effectiveness compared to a traditional invasive coronary angiography-guided strategy [4-7]. The use of FFR is supported by both European guidelines (Class I, Level of Evidence: A) and American guidelines (Class IIa, Level of Evidence: A) in assessing coronary stenosis and to guide revascularization[8].However, the adoption of FFR was limited due to prolonged procedural time, increased cost, patient discomfort, and operator's confidence in visual assessment from coronary angiograms.

Several computational FFR methods were developed to overcome the above limitations. Quantitative flow ratio (QFR), a new method for fast computation of FFR based on invasive coronary angiography (ICA) and empirical fluid dynamic equations was recently developed[9]. The overall diagnostic concordance between QFR and FFR was reported as 87% in a recent meta-analysis of prospective clinical studies[13].

More recently, CCTA-derived QFR, namely CT-QFR, has been developed as a method for fast computation of FFR from CCTA images based on previously validated QFR algorithm. A recent retrospective and observational study

demonstrated a good diagnostic concordance of 87% [14].In addition, it's analysis time has been reduced to less than 5 minutes per patient on an off-the-shelf work station. The diagnostic accuracy of this CT-QFR software version for on-site evaluation of coronary stenosis severity remains unknown. Furthermore, the difference in the diagnostic performance of QFR when applied to noninvasive CCTA images and to ICA has not been studies. We are therefore planning to prospectively validate the diagnostic performance of on-site CT-QFR analysis compared with QFR, using FFR as the reference standard.

Methods and analysis

Study design

This study is an investigator-initiated, prospective, single-center clinical trial to validate the diagnostic performance of on-site CT-QFR using FFR as the reference standard. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Before the study starts, written informed consent form will be obtained from patients willing to participate in the study and approved by the institutional review board/independent ethics committee of Huadong Hospital Affiliated to Fudan University (2020K192). The protocol of the trial has been registered at http://clinicaltrials.gov (NCT04665817).

Study objectives

The primary endpoint of the study is the patient-level diagnostic accuracy of on-site CT-QFR in identifying physiologically significant coronary artery stenosis, using FFR as the reference standard. Major secondary end point is the non-inferiority of CT-QFR compared with QFR in the vessels without extensively calcified lesions defined by the combination of a cross-sectional calcium arc >90° and a thickness >1.5 mm. Other secondary objectives of the study will include the following. (1) Other common measures of diagnostic performance of CT-QFR, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at the patient level compared with FFR as the reference standard. (2) Correlation between CT-QFR and FFR. （3） The comparison of the discrimination ability between CT-QFR, CCTA-derived percent diameter stenosis (CTA-DS%), and QCA-derived DS% for identifying physiologically significant stenosis with FFR as the reference standard.

Patient population

Patients with stable or unstable angina pectoris or non-acute phase of myocardial infarction who are undergoing CCTA examination and scheduled for coronary angiography within 30 days will be screened. Inclusion criteria are: (1) at least 1 lesion with DS% between 30% and 90% in a coronary artery with a ≥2.0mm reference vessel diameter by visual estimation; (2) invasive coronary angiography performed less than 30 days after CCTA; (3) age over 35 years but less than or equal to 85 years. Exclusion criteria are: (1) prior percutaneous coronary intervention (PCI)

or coronary artery bypass graft (CABG) of the interrogated lesion; (2) myocardial bridge involved in the interrogated vessel; (3) presence of collateral flow; (4) severe heart failure (NYHA ≥III); (5) known severe renal failure (eGFR<30 ml/min/1.73m^2); (6) contraindicated to use contrast agents, beta blockers, nitrates or adenosine drugs; (7) Recent prior myocardial infarction within 1 month of CCTA; (8) low image quality CCTA or coronary angiography to be assessed such as motion artifacts, poor filling of contrast agent, etc.; (9) any factors that affect the image quality of CCTA and coronary angiography, such as frequent premature contractions, atrial fibrillation, etc.

Statistical hypotheses and Sample Size Calculation

The primary endpoint is the diagnostic accuracy of CT-QFR≤0.8 to identify hemodynamically significant coronary stenosis with FFR≤0.8as the reference standard. The trial is powered for testing significance of the primary endpoint. The primary null and alternative hypotheses to be tested are H0, diagnostic accuracy of CT-QFR≤0.72, and H1, diagnostic accuracy of CT-QFR > 0.72. Estimates for the sample size calculation are based on the results from the retrospective study of CT-QFR[14], where an accuracy of 87% at patient level was found. In this prospective study, the accuracy is conservatively estimated as 82% for consecutively enrolled patient population, and with a target value set as 72%, which is chosen to be higher than the one in the DeFACTO study[15].The sample size is analysed for paired proportions using the following formula:

$$N = \frac{\left[Z_{1-\alpha/2}\sqrt{P_0(1-P_0)} + Z_{1-\beta}\sqrt{P_T(1-P_T)}\right]^2}{(P_T - P_0)^2}$$

With power = 0.90, two-tailed alpha = 0.05, a total of 188 patients with paired CT-QFR and FFR are required to reject the null hypothesis for diagnostic accuracy. To account for incomplete CT-QFR/CT-DS%/FFR/QFR/QCA data of 15% at most, a total of 216 patients need to be enrolled.

The major secondary endpoint is to validate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions. Analyzed by the enrollment of 216 patients, about 158 patients will be calculated according to the proportion, 26.9%, of extensively calcified lesions from the retrospective study[14]. It will be tested for the capability in achieving the major secondary endpoint. The accuracy of 89.5% for CT-QFR in non-severe calcified lesions[14] and the accuracy of 92.7% for QFR[10] are used to calculate the sample size. We set the non-inferiority threshold as 15%. It will be analyzed by the following formula:

$$N_T = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2[P_C(1-P_C) + P_T(1-P_T)]}{(D-\Delta)^2}$$

With power = 0.90, two-tailed alpha = 0.05, a total of 122 patients are required to validate the non-inferiority. To account for incomplete CT-QFR/CTA-DS%/FFR/QFR/QCA data of 15% at most, 141 patients need to be enrolled. Therefore, 158 patients without extensively calcified lesions meet the sample size of the major secondary endpoint. Therefore, the sample size is set as 216 patients to satisfy the requirements for validating both primary and major secondary endpoints.

CCTA and CTA-DS% Analysis

Coronary computed tomographic angiography is performed on a dual-source CT system (SOMATOM Drive; Siemens Healthineers, Erlangen, Germany) or a 256 detector row scanners CT system (Revolution CT; GE Healthcare) with prospective or retrospective electrocardiographic gating in accordance with Society of Cardiovascular Computed Tomography guidelines[16].Image interpretation of CCTA is conducted in blinded fashion by an experienced investigator. Images with coronary artery stenosis detected visually will be further analyzed (CtaPlus; version 1.0, Pulse Medical Imaging Technology, Shanghai, China). Coronary stenosis will be quantified by using the following parameters: (i) the minimal lumen area (MLA) and the minimal lumen diameter (MLD), and (ii) the percentage diameter stenosis (DS%) and the percentage area stenosis (AS%).

CT- QFR Computation

CT-QFR computation is performed by experienced analysts using a recently developed software package (CtaPlus, version 1.0; Pulse Medical Imaging Technology, Shanghai, China), blinded to both QFR and FFR data. Detailed methodologies for CT-QFR computation have been published previously[14]. A recent upgrade in the CT-QFR algorithm integrated deep learning technique into coronary segmentation method to improve the computation efficiency. Manual corrections are allowed if the automated delineation lumen contour is sub-optimal, particularly at the

segment with calcified plaques. All coronary artery segments with reference lumen diameter ≥1.5 mm are analyzed. Subsequently, all the delineated coronary branches are automatically merged for reconstruction of entire coronary tree, based on which the healthy reference lumen is also reconstructed. Finally, CT-QFR value at each position of the coronary tree is computed using the previous validated QFR algorithm[9, 17].

Coronary Angiography

Coronary angiography is performed by using a 5- or 6-F catheter with a transfemoral or transradial approach. All patients will receive intravenous injection of heparin 100 IU/kg before angiography. Contrast media (Omnipaque 350 injection, GE Healthcare, Shanghai, China) is injected manually with a forceful and stable injection. Coronary angiograms are obtained from standard series of 6 to 8 projections for the left coronary artery and 2 or 3 projections for the right coronary artery by using a monoplane or biplane radiographic system (AXIOM Artis FC and Artis zee Biplane MN, Siemens) at 15 frames/s. All images are digitally stored for analysis.

FFR Measurement

Intracoronary pressure is measured by using a RadiAnalyzer Xpress instrument and Certus pressure wire (St. Jude Medical, Plymouth, Minnesota). The pressure guidewire is introduced into the coronary artery and positioned distal to the coronary stenosis. The position of the sensor of the pressure guide wire is recorded on cine

fluorography. Hyperemia is induced by adenosine-5'-triphosphate (ATP) infusion (160 lg/kg/minute) through an antecubital vein over a minimum of 2 minutes. During steady-state hyperemia, mean proximal aortic pressure, mean intracoronary pressure distal to the target stenosis are measured. Subsequently, the pressure guide wire is slowly pulled back from the most distal to the proximal part of the artery by manual procedure during steady-state maximal hyperemia. If the pressures are not equalized at the end of the pullback (i.e. the pressure drift |Pa-Pd| >3 mmHg), the whole FFR measurements should be repeated from the beginning.

QCA Analysis and QFR Computation

Quantitative coronary angiographic (QCA) analysis and QFR computation are performed in blinded fashion by using the recently developed QFR analysis system (AngioPlus Core; Pulse Medical Imaging Technology, Shanghai, China). The computational methods were previously described[9, 17]. Same as CT-DS% analysis, QCA analysis includes following parameters: (i) MLA and MLD, and (ii) DS% and AS%. It will be analyzed by well-trained technicians who have successfully completed QFR training. Before QFR analysis, the technicians will be informed about the location where the operators measured FFR so that QFR could be measured at the same vessel site. The QFR measure will be performed on the system placed in the control room. The investigators are blinded to the FFR results.

Study flowchart

A study flowchart is shown in Figure 1.

Statistical Analysis

Continuous variables are presented as mean±SD, and categorical variables are presented as counts and percentages. Sensitivity, specificity to predict functionally significant stenosis (FFR≤0.80). The performance of QFR≤0.80 and CT-QFR≤0.80 for predicting FFR≤0.80 will be assessed by using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic accuracy, together with their 95% confidence intervals (CIs). Pearson correlation or spearman's correlation will be used to quantify the correlations between QFR, CT-QFR, and FFR. Agreements between QFR, CT-QFR, and FFR will be assessed by Bland-Altman plot. The Bland-Altman plot depicts the differences of each pair of measurements versus their mean values with reference lines for the mean difference of all paired measurements. The limits of agreement are defined as mean±1.96 SD of absolute difference. The ROC curve analysis will be performed to assess area under the curve (AUC) of CT-QFR, QFR, CT-derived %DS and QCA derived %DS for predicting FFR≤0.80. The ROC curves will be compared by using the DeLong method. A two-side p value <0.05 is considered to indicate statistical significance.

Current status

The study has been approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Five analysts have successfully completed the International Course on Coronary Image Analysis and Computational Physiology which covers FFR, QFR and CT-QFR. All of them have obtained qualification

certificates for relevant analysis. Recruitment is ongoing at Huadong Hospital Affiliated to Fudan University, Shanghai, China. At present, 35 participants have been recruited to the study.

Ethics and dissemination

The CAREER study will for the first time prospectively evaluate the diagnostic accuracy of on-site CT-QFR analysis in identifying patients with physiologically significant coronary stenosis. In addition, diagnostic performance of CCTA-based versus angiography-based QFR in vessels without significantly calcified lesions will be compared. The study findings will provide pivotal data to support the clinical applications of CT-QFR in management of CAD patients.

The previously presented FFR computation method derived from computed tomography (FFR_{CT}), a non-invasive technology, is a computational fluid dynamics modeling technique that enables the calculation of FFR from a coronary computed tomographic angiographic dataset[19]. The diagnostic performance of FFR_{CT} has been validated in several multi-center prospective clinical trials [20-22]. The application of FFR_{CT} can reduce unnecessary invasive coronary angiography [23, 24]. However, it heavily relies on the quality of the underlying computational models and sophisticated boundary conditions and required a few hours for computation[22]. Moreover, severe calcified lesions might affect the calculation results of FFR_{CT} [25].

Recently, a novel technique for the rapid computation of FFR from radiographic coronary angiography, named QFR, was accomplished by estimating the pressure

drop due to coronary stenosis according to coronary lumen morphology and virtual hyperemic flow derived from contrast frame count without use of pressure wire and drug-induced hyperemia[9]. The diagnostic performance of this minimally invasive technique has been validated by several studies[9-12].More recently, the novel QFR algorithm has been applied to CCTA-images, and CCTA-derived QFR (namely CT-QFR), has been derived as anon-invasive technology to assess the physiological significance of coronary stenoses[13].The patient-specific virtual hyperemic flow was used to compute CT-QFR value at every position of the reconstructed coronary tree. A recent retrospective and observational study with 156 vessels from 134 patients demonstrated good correlation ($r = 0.79$; $p < 0.001$) and agreement (0.00 ± 0.06; $p = 0.823$) between CT-QFR and wire-based FFR, with a vessel-level diagnostic concordance of 87% [14]. The average analysis time for CT-QFR was reported as less than 20 minutes, with CT-QFR pullback curve computed in less than 20 seconds [14].

A recent upgrade in the CT-QFR algorithm integrated deep learning technique into coronary segmentation method thus improving the accuracy of automatic lumen delineation and reducing the analysis time to less than 5 minutes per patient on an off-the-shelf workstation. The incorporation of deep learning technique in CT-QFR algorithm had the potential to improve the calculation efficiency significantly. Large-scale studies have shown that the application of CT-FFR can reduce unnecessary invasive coronary angiography. At the same time, it brings higher health and economic benefits[23, 26]. The one-year follow-up of the ADVANCE study showed that the MACE of patients with a CT-FFR value ≤ 0.8 was significantly higher than

that of patients with a CT-FFR value> 0.8[27]. Therefore, a kind of strategy pertaining more to a rapid diagnosis， reduced invasive strategy, and lower costs is particularly important. This study will prospectively validate the diagnostic efficacy of such a faster computational approach to derive FFR from coronary CT angiography with can be onsite for the first time.

Furthermore, severe calcification will affect the diagnosis of lesions on CT images. It was proved that the presence of extensively calcified lesions influenced the diagnostic accuracy and analysis variability[14]. Therefore, we intend to avoid the effects of severe calcification so as to define whether CT-QFR is equivalent to QFR. It's also the first time to compare the diagnostic performance of CCTA-derived QFR with angiography-derived QFR. Therefore, the major secondary endpoint was intended to investigate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions.

This study will lay the foundation for future studies to look at the potential value of CT-QFR technology in patients management. If the study achieves the expected objectives, outpatients can receive coronary artery functional evaluation while undergoing CCTA Examination. It can greatly reduce unnecessary invasive coronary angiography and coronary interventions.

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Author Contributions

Xinkai Qu and Shenxian Tu participated in study design, statistical hypotheses and sample size calculation. Tingwen Weng and Qian Gan participated in manuscript preparation, sample size calculation and writing the protocol ofFFR measurement. Zehang Li was involved in manuscript preparation, writing the protocol of QFR computation and CT-QFR computation. XinrongZhai was involved in writing the protocol of FFR measurement. Ming Li, Lin Qi and Cheng Li participated in writing the protocol of CCTA Analysis. Shaofeng Guan, Wenzheng Han, Yang Chen, Liang Zhang, Xifeng Chang was involved in writing the protocol of coronary angiography.

Compliance with ethical standards

This research will not increase the risk and economic burden of patients; the patients' rights will be fully protected. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University.

Conflict of interest

The authors declare that they have no conflict of interest.

Data Availability Statement

The data will be available from the corresponding author upon the reasonable request.

Patient and Public Involvement

Patients or the public will be involved in the design, or conduct, or reporting, or dissemination plans of our research.

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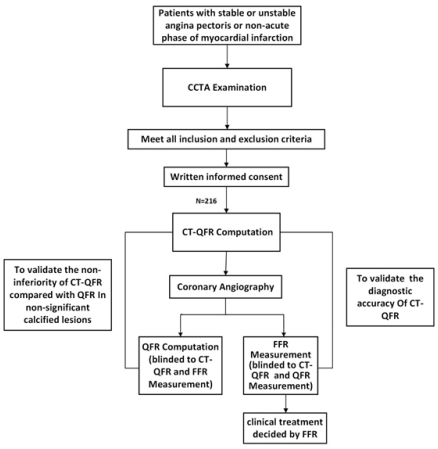
Figure legend:

Figure 1. Study flowchart. CCTA, Coronary computed tomography angiography; FFR, fractional flow reserve; QFR, Quantitative flow ratio; CT-QFR, CCTA-derived Quantitative Flow Ratio.



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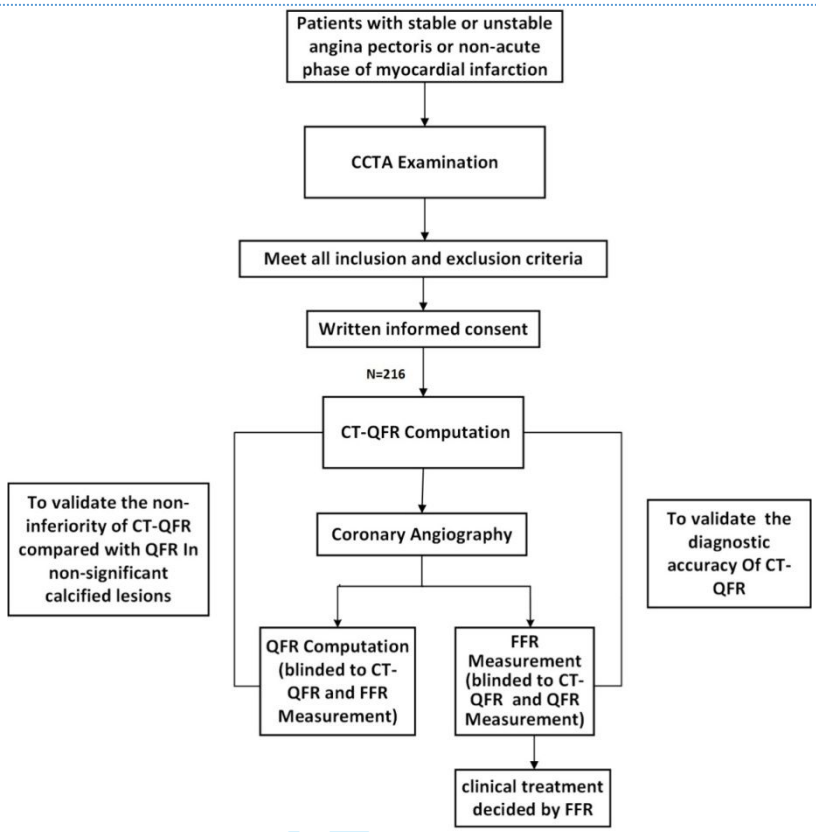
	2	Structured summary of study design, methods, results, and conclusions : Background: Coronary computed tomography angiography (CCTA)- derived quantitative flow ratio (CT-QFR) is a novel non-invasive technology to assess the physiological significance of coronary stenoses, which enables fast and onsite computation of fractional flow reserve (FFR) from CCTA images. The objective of this investigator-initiated, prospective, single-center clinical trial is to evaluate the diagnostic performance of CT-QFR with respect to angiography-derived QFR, using FFR as the reference standard. Methods: A total of 216 patients who have at least 1 lesion with a diameter stenosis of 30% to 90% in an artery with ≥2.0 mm reference diameter will be enrolled in the study. FFR will be measured during invasive coronary angiography. CT-QFR, and QFR will be assessed in two independent core laboratories in blinded fashion. The primary endpoint is the diagnostic accuracy of CT-QFR in identifying hemodynamically significant coronary stenosis with FFR as the reference standard. Major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions. Discussion: This study will be the first study to prospectively validate the diagnostic accuracy of CT-QFR compared with QFR, using FFR as the reference standard.	Page 3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test : Coronary computed tomography angiography (CCTA) is a non−invasive test that enables visualization of coronary anatomy and the characteristics of arterial plaques with high sensitivity and negative predictive value. However, conventional CCTA does not allow for physiological assessment of coronary stenosis. Fractional flow reserve (FFR) is the current gold standard for evaluating the physiological significance of coronary stenosis in the catheterization laboratory. An FFR-guided revascularization strategy was validated with improved clinical outcomes and cost-effectiveness compared to a traditional invasive coronary angiography-guided strategy. The use of FFR is supported by both European guidelines (Class I, Level of Evidence: A) and American guidelines (Class IIa, Level of Evidence: A) in assessing coronary stenosis and to guide revascularization. However, the adoption of FFR was limited due to prolonged procedural time, increased cost, patient discomfort, and operator's confidence in visual assessment from coronary angiograms. Several computational FFR methods were developed to overcome the above limitations. Quantitative flow ratio (QFR), a new method for fast computation of FFR based on invasive coronary angiography (ICA) and empirical fluid dynamic equations was recently developed. The overall diagnostic concordance between QFR and FFR was reported as 87% in a recent meta-analysis of prospective clinical studies. More recently, CCTA-derived QFR, namely CT-QFR, has been developed as a method for fast computation of FFR from CCTA images based on previously validated QFR algorithm. A recent retrospective and observational study demonstrated a good diagnostic concordance of 87%. In addition, it's analysis time has been reduced to less than 5 minutes per patient on an off-the-shelf workstation. The diagnostic accuracy of this CT-QFR software version for on-site evaluation of coronary stenosis severity remains unknown. Furthermore, the difference in the diagnostic performance of QFR when applied to non−invasive CCTA images and to ICA has not been studies. We are therefore planning to prospectively validate the diagnostic performance of on-site CT-QFR analysis compared with QFR, using FFR as the reference standard.	Page 4, 5
	4	Study objectives and hypotheses： The primary endpoint of the study is the patient-level diagnostic accuracy of on-site CT-QFR in identifying physiologically significant coronary artery stenosis, using FFR as the reference standard. Major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the vessels without extensively calcified lesions defined by the combination of a cross-sectional calcium arc >90° and a thickness >1.5 mm. Other secondary objectives of the study will include the following. (1) Other common measures of diagnostic performance of CT-QFR, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at the patient level compared with FFR as the reference standard. (2) Correlation between CT-QFR and FFR. (3) The comparison of the discrimination ability between CT-QFR, CCTA-derived percent	Page 5,6

		diameter stenosis (CTA-DS%), and QCA-derived DS% for identifying physiologically significant stenosis with FFR as the reference standard.	
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study): This study is an investigator-initiated, prospective, single-center clinical trial to validate the diagnostic performance of on-site CT-QFR using FFR as the reference standard. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Before the study starts, written informed consent form will be obtained from patients willing to participate in the study and approved by the institutional review board/independent ethics committee of Huadong Hospital Affiliated to Fudan University.	Page 5
Participants	**6**	Eligibility criteria : Inclusion criteria are: (1) at least 1 lesion with DS% between 30% and 90% in a coronary artery with a ≥2.0mm reference vessel diameter by visual estimation; (2) invasive coronary angiography performed less than 30 days after CCTA; (3) age over 35 years but less than or equal to 85 years. Exclusion criteria are: (1) prior percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) of the interrogated lesion; (2) myocardial bridge involved in the interrogated vessel; (3) presence of collateral flow; (4) severe heart failure (NYHA ≥III); (5) known severe renal failure (eGFR<30 ml/min/1.73m2); (6) contraindicated to use contrast agents, beta blockers, nitrates or adenosine drugs; (7) Recent prior myocardial infarction within 1 month of CCTA; (8) low image quality CCTA or coronary angiography to be assessed such as motion artifacts, poor filling of contrast agent, etc.; (9) any factors that affect the image quality of CCTA and coronary angiography, such as frequent premature contractions, atrial fibrillation, etc.	Page 5, 6
	7	Potentially eligible participants will be identified on their symptoms and results from previous tests.	Page 5
	8	Where and when potentially eligible participants were identified (setting, location and dates): Recruitment has been ongoing at Huadong Hospital Affiliated to Fudan University, Shanghai, China since December 2020.	Page 5,6
	9	Participants formed a consecutive, convenience series.	Page 5
Test methods	**10a**	Index test: Coronary computed tomography angiography - derived quantitative flow ratio (CT-QFR); Angiography-derived quantitative flow ratio（QFR）	Page 4, 5
	10b	Reference standard: Fractional flow reserve (FFR).	Page 4, 5
	11	Rationale for choosing the reference standard: Fractional flow reserve (FFR) is the current gold standard for evaluating the physiological significance of coronary stenosis in the catheterization laboratory. An FFR-guided revascularization strategy was validated with improved clinical outcomes and cost-effectiveness compared to a traditional invasive coronary angiography-guided strategy.	Page 4
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory : The performances of QFR≤0.80 and CT-QFR≤0.80 predict hemodynamically significant coronary stenosis.	Page11
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory: The performance of FFR≤0.80 predicts hemodynamically significant coronary stenosis.	Page11
	13a	Clinical information and reference standard results will not be available to the performers/readers of the index test.	Page 7-10
	13b	Clinical information and index test results will not be available to the assessors of the reference standard.	Page 7-10
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy : The performance of QFR≤0.80 and CT-QFR≤0.80 for predicting FFR≤0.80 will be assessed by using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic accuracy, together with their 95% confidence intervals (CIs). The ROC curve analysis will be performed to assess area under the curve (AUC) of CT-QFR, QFR, CT-derived %DS and QCA-derived %DS for predicting	Page 7-10

		FFR≤0.80. The ROC curves will be compared by using the DeLong method. A two-side p value <0.05 is considered to indicate statistical significance.	
	15	How indeterminate index test or reference standard results were handled: When calculating the sample size, the data that could not be completed was included as the dropout rate, which accounted for 15%.	Page 7,8
	16	How missing data on the index test and reference standard were handled: When calculating the sample size, the data that could not be completed was included as the dropout rate, which accounted for 15%.	Page 7,8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory: Agreements between QFR, CT-QFR, and FFR will be assessed by Bland-Altman plot. The Bland-Altman plot depicts the differences of each pair of measurements versus their mean values with reference lines for the mean difference of all paired measurements. The limits of agreement are defined as mean±1.96 SD of absolute difference	Page 11,12
	18	Intended sample size and how it was determined: The primary endpoint is the diagnostic accuracy of CT-QFR≤0.8 to identify hemodynamically significant coronary stenosis with FFR≤0.8 as the reference standard. The trial is powered for testing significance of the primary endpoint. The primary null and alternative hypotheses to be tested are H0, diagnostic accuracy of CT-QFR≤0.72, and H1, diagnostic accuracy of CT-QFR＞0.72. Estimates for the sample size calculation are based on the results from the retrospective study of CT-QFR[14], where an accuracy of 87% at patient level was found. In this prospective study, the accuracy is conservatively estimated as 82% for consecutively enrolled patient population, and with a target value set as 72%, which is chosen to be higher than the one in the DeFACTO study[15].The sample size is analysed for paired proportions using the following formula: $$N = \frac{\left[Z_{1-\alpha/2}\sqrt{P_0(1-P_0)} + Z_{1-\beta}\sqrt{P_T(1-P_T)}\right]^2}{(P_T - P_0)^2}$$ With power = 0.90, two-tailed alpha = 0.05, a total of 188 patients with paired CT-QFR and FFR are required to reject the null hypothesis for diagnostic accuracy. To account for incomplete CT-QFR/CT-DS%/FFR/QFR/QCA data of 15% at most, a total of 216 patients need to be enrolled. The major secondary endpoint is to validate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions. Analyzed by the enrollment of 216 patients, about 158 patients will be calculated according to the proportion, 26.9%, of extensively calcified lesions from the retrospective study[14]. It will be tested for the capability in achieving the major secondary endpoint. The accuracy of 89.5% for CT-QFR in non-severe calcified lesions[14] and the accuracy of 92.7% for QFR[10] are used to calculate the sample size. We set the non-inferiority threshold as 15%. It will be analyzed by the following formula: $$N_T = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2[P_C(1-P_C) + P_T(1-P_T)]}{(D-\Delta)^2}$$ With power = 0.90, two-tailed alpha = 0.05, a total of 122 patients are required to validate the non-inferiority. To account for incomplete CT-QFR/CTA-DS%/FFR/QFR/QCA data of 15% at most , 141 patients need to be enrolled. Therefore, 158 patients without extensively calcified lesions meet the sample size of the major secondary endpoint. Therefore, the sample size is set as 216 patients to satisfy the requirements for validating both primary and major secondary endpoints.	Page 7,8
RESULTS			
Participants	**19**	Flow of participants, using a diagram:	Page 11



	20	Baseline demographic and clinical characteristics of participants: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	21a	Distribution of severity of disease in those with the target condition: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	21b	Distribution of alternative diagnoses in those without the target condition: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	22	Time interval and any clinical interventions between index test and reference standard: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals): This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	25	Any adverse events from performing the index test or the reference standard: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	27	Implications for practice, including the intended use and clinical role of the index test: This study will prospectively validate the diagnostic efficacy of a fast computational approach to derive FFR from coronary CT angiography with can be onsite for the first time. Furthermore, severe calcification will affect the diagnosis of lesions on CT images. It was proved that the presence of extensively calcified lesions influenced the diagnostic accuracy and analysis	Page 12-15

		variability. Therefore, we intend to avoid the effects of severe calcification so as to define whether CT-QFR is equivalent to QFR. It's also the first time to compare the diagnostic performance of CCTA-derived QFR with angiography-derived QFR. This study will lay the foundation for future studies to look at the potential value of CT-QFR technology in patients management. If the study achieves the expected objectives, outpatients can receive coronary artery functional evaluation while undergoing CCTA Examination. It can greatly reduce unnecessary invasive coronary angiography and coronary interventions.	
OTHER INFORMATION			
	28	Registration number and name of registry: ClinicalTrials.gov Identifier: NCT04665817	Page 5
	29	Where the full study protocol can be accessed: This is the protocol manuscript.	
	30	Sources of funding and other support; role of funders: CAREER Study is an investigator-initiated clinical trial with external funding from Clinical Research Plan of SHDC（No. SHDC2020CR3024B）issued by Shanghai Hospital Development Center, Research Fund of Huadong Hospital (No. 2019lc015) and a Center of Geratic Coronary Artery Disease.	Page 15

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the abilityof one or more medical tests to correctly classify study participants as having a**target condition.**This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**.The reference standardisthe best available method for establishing the presence or absence ofthe target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against thoseof the reference standardcan be used to estimate the**sensitivity** of the index test(the proportion of participants *with* the target conditionwho have a positive index test), and its **specificity** (the proportion *without* the target conditionwho have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test.Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiveroperatingcharacteristic(ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage testis used before an existing test; an add-on test is used after an existing test.

Besides diagnosticaccuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis.The STARD list was not explicitly developed for these other outcomes, statistics, and studytypes, although mostSTARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

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Diagnostic Accuracy of CCTA-derived versus Angiography-derived Quantitative Flow Ratio (CAREER) Study: A prospective study protocol

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diagnostics
Keywords:	Adult cardiology < CARDIOLOGY, Coronary heart disease < CARDIOLOGY, Coronary intervention < CARDIOLOGY, Cardiomyopathy < CARDIOLOGY, Ischaemic heart disease < CARDIOLOGY

Title: Diagnostic Accuracy of CCTA-derived versus Angiography-derived Quantitative Flow Ratio (CAREER) Study: A prospective study protocol

Running title: The research protocol of the CAREER study

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Abstract

Introduction: Coronary computed tomography angiography (CCTA)-derived quantitative flow ratio (CT-QFR) is a novel non-invasive technology to assess the physiological significance of coronary stenoses, which enables fast and on site computation of fractional flow reserve (FFR) from CCTA images. The objective of this investigator-initiated, prospective, single-center clinical trial is to evaluate the diagnostic performance of CT-QFR with respect to angiography-derived QFR, using FFR as the reference standard.

Methods and analysis: A total of 216 patients who have at least 1 lesion with a diameter stenosis of30% to 90% in an artery with≥2.0mm reference diameter will be enrolled in the study. FFR will be measured during invasive coronary angiography. CT-QFR, and QFR will be assessed in two independent core laboratories in blinded fashion. The primary endpoint is the diagnostic accuracy of CT-QFR in identifying hemodynamically significant coronary stenosis with FFR as the reference standard. Major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions.

Ethic and Dissemination: The study was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University (2020K192). Outcomes will be disseminated through publications in peer-reviewed journals and presentations at scientific conferences.

Article summary

Strengths and limitations of this study:

- This study is the first prospective clinical trial to validate the diagnostic performance of on-site CT-QFR using FFR as the reference standard.
- This study will lay the foundation for future studies to look at the potential value of CT-QFR technology in patients management.
- It's the first time to explore the difference in the diagnostic performance of QFR technology when applied to noninvasive CCTA images and to ICA.
- CT-QFR and QFR will be computed in blinded fashion and compared with FFR.
- Unfortunately, due to the tight schedule and insufficient funding, a multi-center study cannot be conducted.

Key words: Coronary computed tomography angiography- derived quantitative flow ratio （CT-QFR）; Angiography-derived quantitative flow ratio （QFR）; Diagnostic accuracy；Non-inferiority

Trial registration: ClinicalTrials.gov Identifier: NCT04665817

Introduction

Coronary computed tomography angiography (CCTA) is a noninvasive test that enables visualization of coronary anatomy and the characteristics of arterial plaques with high sensitivity and negative predictive value [1]. However, conventional CCTA does not allow for physiological assessment of coronary stenosis[2].Fractional flow reserve (FFR) is the current gold standard for evaluating the physiological significance of coronary stenosis in the catheterization laboratory [3]. An FFR-guided revascularization strategy was validated with improved clinical outcomes and cost-effectiveness compared to a traditional invasive coronary angiography-guided strategy [4-7]. The use of FFR is supported by both European guidelines (Class I, Level of Evidence: A) and American guidelines (Class IIa, Level of Evidence: A) in assessing coronary stenosis and to guide revascularization[8].However, the adoption of FFR was limited due to prolonged procedural time, increased cost, patient discomfort, and operator's confidence in visual assessment from coronary angiograms.

Several computational FFR methods were developed to overcome the above limitations. Quantitative flow ratio (QFR), a new method for fast computation of FFR based on invasive coronary angiography (ICA) and empirical fluid dynamic equations was recently developed[9]. The overall diagnostic concordance between QFR and FFR was reported as 87% in a recent meta-analysis of prospective clinical studies[10].

More recently, CCTA-derived QFR, namely CT-QFR, has been developed as a method for fast computation of FFR from CCTA images based on previously validated QFR algorithm. A recent retrospective and observational study demonstrated a good diagnostic concordance of 87% [11].In addition, it's analysis time has been reduced to

less than 5 minutes per patient on an off-the-shelf work station. The diagnostic accuracy of this CT-QFR software version for on-site evaluation of coronary stenosis severity remains unknown. Furthermore, the differences in the diagnostic performance of QFR when applied to noninvasive CCTA images and to ICA have not been studied. We are therefore planning to prospectively validate the diagnostic performance of on-site CT-QFR analysis compared with QFR, using FFR as the reference standard.

Methods and analysis

Study design

This study is an investigator-initiated, prospective, single-center clinical trial to validate the diagnostic performance of on-site CT-QFR using FFR as the reference standard. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Before the study starts, written informed consent form will be obtained from patients willing to participate in the study and approved by the institutional review board/independent ethics committee of Huadong Hospital Affiliated to Fudan University (2020K192). The protocol of the trial has been registered at http://clinicaltrials.gov (NCT04665817).

Study objectives

The primary endpoint of the study is the patient-level diagnostic accuracy of on-site CT-QFR in identifying physiologically significant coronary artery stenosis, using

FFR as the reference standard. Major secondary end point is the non-inferiority of CT-QFR compared with QFR in the vessels without extensively calcified lesions defined by the combination of a cross-sectional calcium arc >90° and a thickness >1.5 mm. Other secondary objectives of the study will include the following. (1) Other common measures of diagnostic performance of CT-QFR, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at the patient level compared with FFR as the reference standard. (2) Correlation between CT-QFR and FFR. （3） The comparison of the discrimination ability between CT-QFR, CCTA-derived percent diameter stenosis (CTA-DS%), and QCA-derived DS% for identifying physiologically significant stenosis with FFR as the reference standard.

Patient population

Patients with stable or unstable angina pectoris or non-acute phase of myocardial infarction who are undergoing CCTA examination and scheduled for coronary angiography within 30 days will be screened. Inclusion criteria are: (1) at least 1 lesion with DS% between 30% and 90% in a coronary artery with a ≥2.0mm reference vessel diameter by visual estimation; (2) invasive coronary angiography performed less than 30 days after CCTA; (3) age over 35 years but less than or equal to 85 years. Exclusion criteria are: (1) prior percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) of the interrogated lesion; (2) myocardial bridge involved in the interrogated vessel; (3) presence of collateral flow; (4) severe heart failure (NYHA ≥III); (5) known severe renal failure (eGFR<30 ml/min/1.73m^2); (6) contraindicated to use

contrast agents, beta blockers, nitrates or adenosine drugs; (7) Recent prior myocardial infarction within 1 month of CCTA; (8) low image quality CCTA or coronary angiography to be assessed such as motion artifacts, poor filling of contrast agent, etc.; (9) any factors that affect the image quality of CCTA and coronary angiography, such as frequent premature contractions, atrial fibrillation, etc.

Statistical hypotheses and Sample Size Calculation

The primary endpoint is the diagnostic accuracy of CT-QFR≤0.8 to identify hemodynamically significant coronary stenosis with FFR≤0.8as the reference standard. The trial is powered for testing significance of the primary endpoint. The primary null and alternative hypotheses to be tested are H0, diagnostic accuracy of CT-QFR≤0.72, and H1, diagnostic accuracy of CT-QFR $>$ 0.72. Estimates for the sample size calculation are based on the results from the retrospective study of CT-QFR[11], where an accuracy of 87% at patient level was found. In this prospective study, the accuracy is conservatively estimated as 82% for consecutively enrolled patient population, and with a target value set as 72%, which is chosen to be higher than the one in the DeFACTO study[12].The sample size is analysed for paired proportions using the following formula:

$$N = \frac{\left[Z_{1-\alpha/2}\sqrt{P_0(1-P_0)} + Z_{1-\beta}\sqrt{P_T(1-P_T)}\right]^2}{(P_T - P_0)^2}$$

With power = 0.90, two-tailed alpha = 0.05, a total of 188 patients with paired CT-QFR and FFR are required to reject the null hypothesis for diagnostic accuracy. To account for incomplete CT-QFR/CT-DS%/FFR/QFR/QCA data of 15% at most, a total of 216

patients need to be enrolled.

The major secondary endpoint is to validate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions. Analyzed by the enrollment of 216 patients, about 158 patients will be calculated according to the proportion, 26.9%, of extensively calcified lesions from the retrospective study[11]. It will be tested for the capability in achieving the major secondary endpoint. The accuracy of 89.5% for CT-QFR in non-severe calcified lesions[11] and the accuracy of 92.7% for QFR[13] are used to calculate the sample size. We set the non-inferiority threshold as 15%. It will be analyzed by the following formula:

$$N_T = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2[P_C(1-P_C) + P_T(1-P_T)]}{(D-\Delta)^2}$$

With power = 0.90, two-tailed alpha = 0.05, a total of 122 patients are required to validate the non-inferiority. To account for incomplete CT-QFR/CTA-DS%/FFR/QFR/QCA data of 15% at most, 141 patients need to be enrolled. Therefore, 158 patients without extensively calcified lesions meet the sample size of the major secondary endpoint. Therefore, the sample size is set as 216 patients to satisfy the requirements for validating both primary and major secondary endpoints.

CCTA and CTA-DS% Analysis

Coronary computed tomography angiography will be performed on a dual-source CT system (SOMATOM Drive; Siemens Healthineers, Erlangen, Germany) or a 256 detector row scanners CT system (Revolution CT; GE Healthcare) with prospective or retrospective electrocardiographic gating in accordance with Society of Cardiovascular

Computed Tomography guidelines[14].Image interpretation of CCTA will be conducted in blinded fashion by an experienced investigator. Images with coronary artery stenosis detected visually will be further analyzed (CtaPlus; version 1.0, Pulse Medical Imaging Technology, Shanghai, China). Coronary stenosis will be quantified by using the following parameters: (i) the minimal lumen area (MLA) and the minimal lumen diameter (MLD), and (ii) the percentage diameter stenosis (DS%) and the percentage area stenosis (AS%).

CT- QFR Computation

CT-QFR computation will be performed by experienced analysts using a recently developed software package (CtaPlus, version 1.0; Pulse Medical Imaging Technology, Shanghai, China), blinded to both QFR and FFR data. Detailed methodologies for CT-QFR computation have been published previously[11]. A recent upgrade in the CT-QFR algorithm integrated deep learning technique into coronary segmentation method to improve the computation efficiency. Manual corrections are allowed if the automated delineation lumen contour is sub-optimal, particularly at the segment with calcified plaques. All coronary artery segments with reference lumen diameter ≥1.5 mm are analyzed. Subsequently, all the delineated coronary branches are automatically merged for reconstruction of entire coronary tree, based on which the healthy reference lumen is also reconstructed. Finally, CT-QFR value at each position of the coronary tree is computed using the previous validated QFR algorithm[9, 15].

Coronary Angiography

Coronary angiography will be performed by using a 5- or 6-F catheter with a transfemoral or transradial approach. All patients will receive intravenous injection of heparin 100 IU/kg before angiography. Contrast media (Omnipaque 350 injection, GE Healthcare, Shanghai, China) will be injected manually with a forceful and stable injection. Coronary angiograms will be obtained from standard series of 6 to 8 projections for the left coronary artery and 2 or 3 projections for the right coronary artery by using a monoplane or biplane radiographic system (AXIOM Artis FC and Artis zee Biplane MN, Siemens) at 15 frames/s. All images will be digitally stored for analysis.

FFR Measurement

Intracoronary pressure will be measured by using a RadiAnalyzer Xpress instrument and Certus pressure wire (St. Jude Medical, Plymouth, Minnesota). The pressure guidewire will be introduced into the coronary artery and positioned distal to the coronary stenosis. The position of the sensor of the pressure guide wire will be recorded on cine fluorography. Hyperemia will be induced by adenosine-5'-triphosphate (ATP) infusion (160 lg/kg/minute) through an antecubital vein over a minimum of 2 minutes. During steady-state hyperemia, mean proximal aortic pressure, mean intracoronary pressure distal to the target stenosis will be measured. Subsequently, the pressure guide wire will be slowly pulled back from the most distal to the proximal part of the artery by manual procedure during steady-state maximal hyperemia. If the

pressures are not equalized at the end of the pullback (i.e. the pressure drift |Pa-Pd| >3 mmHg), the whole FFR measurements should be repeated from the beginning.

QCA Analysis and QFR Computation

Quantitative coronary angiographic (QCA) analysis and QFR computation will be performed in blinded fashion by using the recently developed QFR analysis system (AngioPlus Core; Pulse Medical Imaging Technology, Shanghai, China). The computational methods were previously described[9, 15]. Same as CT-DS% analysis, QCA analysis includes following parameters: (i) MLA and MLD, and (ii) DS% and AS%. It will be analyzed by well-trained technicians who have successfully completed QFR training. Before QFR analysis, the technicians will be informed about the location where the operators measured FFR so that QFR could be measured at the same vessel site. The QFR measure will be performed on the system placed in the control room. The investigators will be blinded to the FFR results.

Study flowchart

A study flowchart is shown in Figure 1.

Statistical Analysis

Continuous variables are presented as mean±SD, and categorical variables will be presented as counts and percentages. Sensitivity, specificity to predict functionally significant stenosis (FFR≤0.80). The performance of QFR≤0.80 and CT-QFR≤0.80 for predicting FFR≤0.80 will be assessed by using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio

(+LR), negative likelihood ratio (-LR), and diagnostic accuracy, together with their 95% confidence intervals (CIs). Pearson correlation or spearman's correlation will be used to quantify the correlations between QFR, CT-QFR, and FFR. Agreements between QFR, CT-QFR, and FFR will be assessed by Bland-Altman plot. The Bland-Altman plot depicts the differences of each pair of measurements versus their mean values with reference lines for the mean difference of all paired measurements. The limits of agreement will be defined as mean±1.96 SD of absolute difference. The ROC curve analysis will be performed to assess area under the curve (AUC) of CT-QFR, QFR, CT-derived %DS and QCA derived %DS for predicting FFR≤0.80. The ROC curves will be compared by using the DeLong method. A two-side p value <0.05 will be considered to indicate statistical significance.

Current status

The study has been approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Five analysts have successfully completed the International Course on Coronary Image Analysis and Computational Physiology which covers FFR, QFR and CT-QFR. All of them have obtained qualification certificates for relevant analysis. Recruitment is ongoing at Huadong Hospital Affiliated to Fudan University, Shanghai, China. At the time of submission of this manuscript, 35 participants have been recruited to the study.

Discussion

The CAREER study will for the first time prospectively evaluate the diagnostic

accuracy of on-site CT-QFR analysis in identifying patients with physiologically significant coronary stenosis. In addition, diagnostic performance of CCTA-based versus angiography-based QFR in vessels without significantly calcified lesions will be compared. The study findings will provide pivotal data to support the clinical applications of CT-QFR in management of CAD patients.

The previously presented FFR computation method derived from computed tomography (FFR_{CT}), a non-invasive technology, is a computational fluid dynamics modeling technique that enables the calculation of FFR from a coronary computed tomographic angiographic dataset[16]. The diagnostic performance of FFR_{CT} has been validated in several multi-center prospective clinical trials [17-19]. The application of FFR_{CT} can reduce unnecessary invasive coronary angiography [20, 21]. However, it heavily relies on the quality of the underlying computational models and sophisticated boundary conditions and required a few hours for computation[19]. Moreover, severe calcified lesions might affect the calculation results of FFR_{CT} [22].

Recently, a novel technique for the rapid computation of FFR from radiographic coronary angiography, named QFR, was accomplished by estimating the pressure drop due to coronary stenosis according to coronary lumen morphology and virtual hyperemic flow derived from contrast frame count without use of pressure wire and drug-induced hyperemia[9]. The diagnostic performance of this minimally invasive technique has been validated by several studies[9, 13, 23, 24].More recently, the novel QFR algorithm has been applied to CCTA-images, and CCTA-derived QFR (namely CT-QFR), has been derived as anon-invasive technology to assess the physiological

significance of coronary stenoses[10].The patient-specific virtual hyperemic flow was used to compute CT-QFR value at every position of the reconstructed coronary tree. A recent retrospective and observational study with 156 vessels from 134 patients demonstrated good correlation ($r = 0.79$; $p < 0.001$) and agreement (0.00 ± 0.06; $p = 0.823$) between CT-QFR and wire-based FFR, with a vessel-level diagnostic concordance of 87% [11]. The average analysis time for CT-QFR was reported as less than 20 minutes, with CT-QFR pullback curve computed in less than 20 seconds [11].

A recent upgrade in the CT-QFR algorithm integrated deep learning technique into coronary segmentation method thus improving the accuracy of automatic lumen delineation and reducing the analysis time to less than 5 minutes per patient on an off-the-shelf workstation. The incorporation of deep learning technique in CT-QFR algorithm had the potential to improve the calculation efficiency significantly. Large-scale studies have shown that the application of CT-FFR can reduce unnecessary invasive coronary angiography. At the same time, it brings higher health and economic benefits[20, 25]. The one-year follow-up of the ADVANCE study showed that the MACE of patients with a CT-FFR value ≤ 0.8 was significantly higher than that of patients with a CT-FFR value> 0.8[26]. Therefore, a kind of strategy pertaining more to a rapid diagnosis， reduced invasive strategy, and lower costs is particularly important. This study will prospectively validate the diagnostic efficacy of such a faster computational approach to derive FFR from coronary CT angiography with can be onsite for the first time.

Furthermore, severe calcification will affect the diagnosis of lesions on CT images.

It was proved that the presence of extensively calcified lesions influenced the diagnostic accuracy and analysis variability[11]. Therefore, we intend to avoid the effects of severe calcification so as to define whether CT-QFR is equivalent to QFR. It's also the first time to compare the diagnostic performance of CCTA-derived QFR with angiography-derived QFR. Therefore, the major secondary endpoint was intended to investigate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions.

This study will lay the foundation for future studies to look at the potential value of CT-QFR technology in patients management. If the study achieves the expected objectives, outpatients can receive coronary artery functional evaluation while undergoing CCTA Examination. It can greatly reduce unnecessary invasive coronary angiography and coronary interventions.

Ethics and dissemination

This research will not increase the risk and economic burden of patients and the patients' rights will be fully protected. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University (ref. number 2020K192). All patients will provide written informed consent. Results of this study are to be published in respected, peer-reviewed journals and findings presented at scientific conferences in the field of Cardiology.

Acknowledgements

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Author Contributions

Xinkai Qu and Shenxian Tu participated in study design, statistical hypotheses and sample size calculation. Tingwen Weng and Qian Gan participated in manuscript preparation, sample size calculation and writing the protocol of FFR measurement. Zehang Li was involved in manuscript preparation, writing the protocol of QFR computation and CT-QFR computation. XinrongZhai was involved in writing the protocol of FFR measurement. Ming Li, Lin Qi and Cheng Li participated in writing the protocol of CCTA Analysis. Shaofeng Guan, Wenzheng Han, Yang Chen, Liang Zhang, Xifeng Chang was involved in writing the protocol of coronary angiography.

Conflict of interest

The authors declare that they have no conflict of interest.

Data Availability Statement

The data will be available from the corresponding author upon the reasonable request.

Patient and Public Involvement

Patients or the public will be involved in the design, or conduct, or reporting, or dissemination plans of our research.

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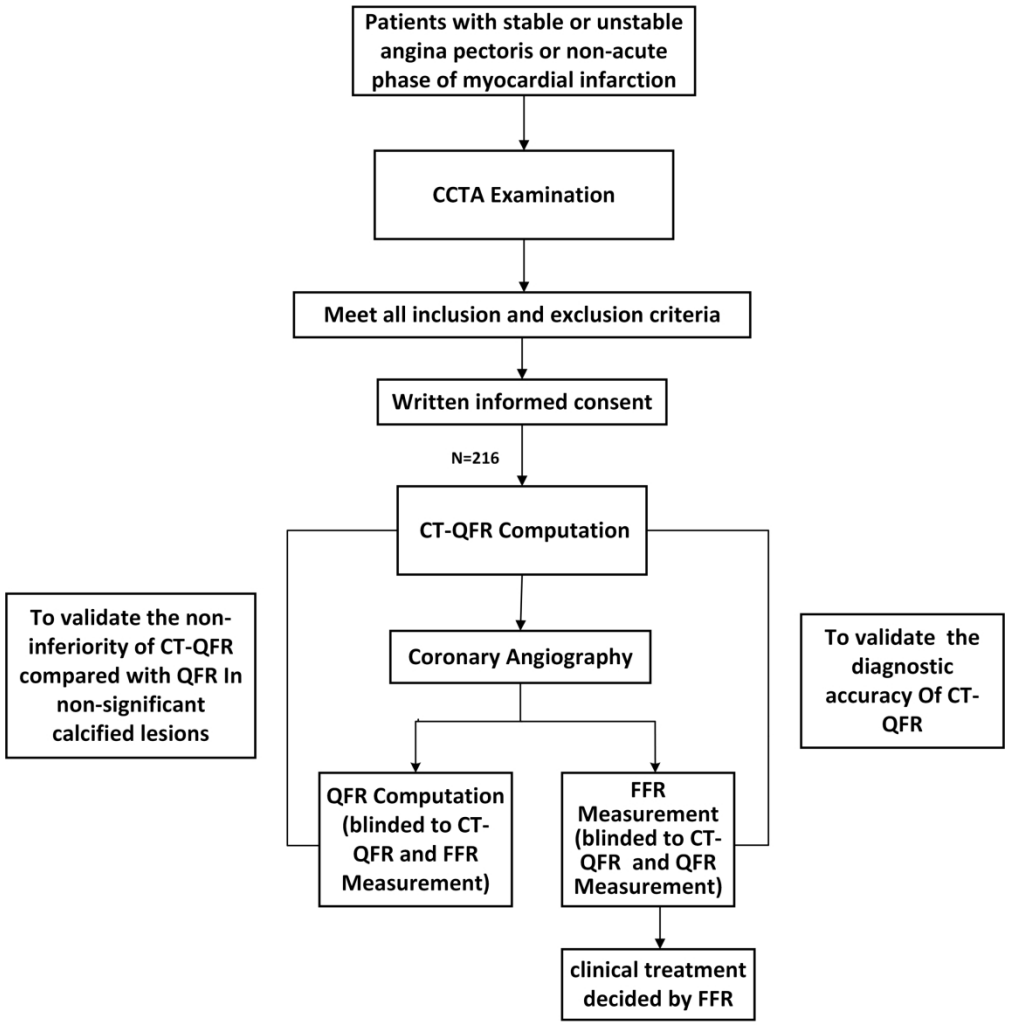
Figure legend:

Figure 1. Study flowchart. CCTA, Coronary computed tomography angiography; FFR, fractional flow reserve; QFR, Quantitative flow ratio; CT-QFR, CCTA-derived Quantitative Flow Ratio.



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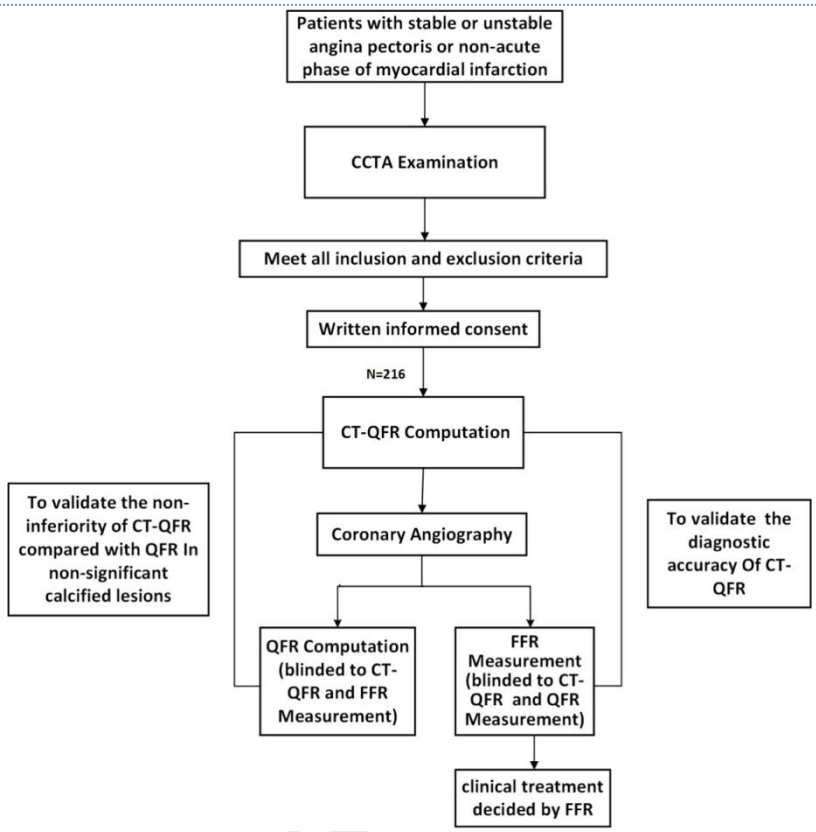
Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy: Diagnostic Accuracy of CCTA-derived versus AngiogRaphy-dErived QuantitativE Flow Ratio (CAREER) Study: Rationale and Design	Page 1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions : Background: Coronary computed tomography angiography (CCTA)- derived quantitative flow ratio (CT-QFR) is a novel non-invasive technology to assess the physiological significance of coronary stenoses, which enables fast and onsite computation of fractional flow reserve (FFR) from CCTA images. The objective of this investigator-initiated, prospective, single-center clinical trial is to evaluate the diagnostic performance of CT-QFR with respect to angiography-derived QFR, using FFR as the reference standard. Methods: A total of 216 patients who have at least 1 lesion with a diameter stenosis of 30% to 90% in an artery with ≥2.0 mm reference diameter will be enrolled in the study. FFR will be measured during invasive coronary angiography. CT-QFR, and QFR will be assessed in two independent core laboratories in blinded fashion. The primary endpoint is the diagnostic accuracy of CT-QFR in identifying hemodynamically significant coronary stenosis with FFR as the reference standard. Major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions. Discussion: This study will be the first study to prospectively validate the diagnostic accuracy of CT-QFR compared with QFR, using FFR as the reference standard.	Page 3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test : Coronary computed tomography angiography (CCTA) is a non−invasive test that enables visualization of coronary anatomy and the characteristics of arterial plaques with high sensitivity and negative predictive value. However, conventional CCTA does not allow for physiological assessment of coronary stenosis. Fractional flow reserve (FFR) is the current gold standard for evaluating the physiological significance of coronary stenosis in the catheterization laboratory. An FFR-guided revascularization strategy was validated with improved clinical outcomes and cost-effectiveness compared to a traditional invasive coronary angiography-guided strategy. The use of FFR is supported by both European guidelines (Class I, Level of Evidence: A) and American guidelines (Class IIa, Level of Evidence: A) in assessing coronary stenosis and to guide revascularization. However, the adoption of FFR was limited due to prolonged procedural time, increased cost, patient discomfort, and operator's confidence in visual assessment from coronary angiograms. Several computational FFR methods were developed to overcome the above limitations. Quantitative flow ratio (QFR), a new method for fast computation of FFR based on invasive coronary angiography (ICA) and empirical fluid dynamic equations was recently developed. The overall diagnostic concordance between QFR and FFR was reported as 87% in a recent meta-analysis of prospective clinical studies. More recently, CCTA-derived QFR, namely CT-QFR, has been developed as a method for fast computation of FFR from CCTA images based on previously validated QFR algorithm. A recent retrospective and observational study demonstrated a good diagnostic concordance of 87%. In addition, it's analysis time has been reduced to less than 5 minutes per patient on an off-the-shelf workstation. The diagnostic accuracy of this CT-QFR software version for on-site evaluation of coronary stenosis severity remains unknown. Furthermore, the difference in the diagnostic performance of QFR when applied to non−invasive CCTA images and to ICA has not been studies. We are therefore planning to prospectively validate the diagnostic performance of on-site CT-QFR analysis compared with QFR, using FFR as the reference standard.	Page 4, 5
	4	Study objectives and hypotheses： The primary endpoint of the study is the patient-level diagnostic accuracy of on-site CT-QFR in identifying physiologically significant coronary artery stenosis, using FFR as the reference standard. Major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the vessels without extensively calcified lesions defined by the combination of a cross-sectional calcium arc >90° and a thickness >1.5 mm. Other secondary objectives of the study will include the following. (1) Other common measures of diagnostic performance of CT-QFR, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at the patient level compared with FFR as the reference standard. (2) Correlation between CT-QFR and FFR. (3) The comparison of the discrimination ability between CT-QFR, CCTA-derived percent	Page 5,6

		diameter stenosis (CTA-DS%), and QCA-derived DS% for identifying physiologically significant stenosis with FFR as the reference standard.	
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study): This study is an investigator-initiated, prospective, single-center clinical trial to validate the diagnostic performance of on-site CT-QFR using FFR as the reference standard. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Before the study starts, written informed consent form will be obtained from patients willing to participate in the study and approved by the institutional review board/independent ethics committee of Huadong Hospital Affiliated to Fudan University.	Page 5
Participants	**6**	Eligibility criteria : Inclusion criteria are: (1) at least 1 lesion with DS% between 30% and 90% in a coronary artery with a ≥2.0mm reference vessel diameter by visual estimation; (2) invasive coronary angiography performed less than 30 days after CCTA; (3) age over 35 years but less than or equal to 85 years. Exclusion criteria are: (1) prior percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) of the interrogated lesion; (2) myocardial bridge involved in the interrogated vessel; (3) presence of collateral flow; (4) severe heart failure (NYHA ≥III); (5) known severe renal failure (eGFR<30 ml/min/1.73m2); (6) contraindicated to use contrast agents, beta blockers, nitrates or adenosine drugs; (7) Recent prior myocardial infarction within 1 month of CCTA; (8) low image quality CCTA or coronary angiography to be assessed such as motion artifacts, poor filling of contrast agent, etc.; (9) any factors that affect the image quality of CCTA and coronary angiography, such as frequent premature contractions, atrial fibrillation, etc.	Page 5, 6
	7	Potentially eligible participants will be identified on their symptoms and results from previous tests.	Page 5
	8	Where and when potentially eligible participants were identified (setting, location and dates): Recruitment has been ongoing at Huadong Hospital Affiliated to Fudan University, Shanghai, China since December 2020.	Page 5,6
	9	Participants formed a consecutive, convenience series.	Page 5
Test methods	**10a**	Index test: Coronary computed tomography angiography - derived quantitative flow ratio (CT-QFR); Angiography-derived quantitative flow ratio（QFR）	Page 4, 5
	10b	Reference standard: Fractional flow reserve (FFR).	Page 4, 5
	11	Rationale for choosing the reference standard: Fractional flow reserve (FFR) is the current gold standard for evaluating the physiological significance of coronary stenosis in the catheterization laboratory. An FFR-guided revascularization strategy was validated with improved clinical outcomes and cost-effectiveness compared to a traditional invasive coronary angiography-guided strategy.	Page 4
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory : The performances of QFR≤0.80 and CT-QFR≤0.80 predict hemodynamically significant coronary stenosis.	Page11
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory: The performance of FFR≤0.80 predicts hemodynamically significant coronary stenosis.	Page11
	13a	Clinical information and reference standard results will not be available to the performers/readers of the index test.	Page 7-10
	13b	Clinical information and index test results will not be available to the assessors of the reference standard.	Page 7-10
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy : The performance of QFR≤0.80 and CT-QFR≤0.80 for predicting FFR≤0.80 will be assessed by using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic accuracy, together with their 95% confidence intervals (CIs). The ROC curve analysis will be performed to assess area under the curve (AUC) of CT-QFR, QFR, CT-derived %DS and QCA-derived %DS for predicting	Page 7-10

		FFR≤0.80. The ROC curves will be compared by using the DeLong method. A two-side p value <0.05 is considered to indicate statistical significance.	
	15	How indeterminate index test or reference standard results were handled: When calculating the sample size, the data that could not be completed was included as the dropout rate, which accounted for 15%.	Page 7,8
	16	How missing data on the index test and reference standard were handled: When calculating the sample size, the data that could not be completed was included as the dropout rate, which accounted for 15%.	Page 7,8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory: Agreements between QFR, CT-QFR, and FFR will be assessed by Bland-Altman plot. The Bland-Altman plot depicts the differences of each pair of measurements versus their mean values with reference lines for the mean difference of all paired measurements. The limits of agreement are defined as mean±1.96 SD of absolute difference	Page 11,12
	18	Intended sample size and how it was determined: The primary endpoint is the diagnostic accuracy of CT-QFR≤0.8 to identify hemodynamically significant coronary stenosis with FFR≤0.8 as the reference standard. The trial is powered for testing significance of the primary endpoint. The primary null and alternative hypotheses to be tested are H0, diagnostic accuracy of CT-QFR≤0.72, and H1, diagnostic accuracy of CT-QFR＞0.72. Estimates for the sample size calculation are based on the results from the retrospective study of CT-QFR[14], where an accuracy of 87% at patient level was found. In this prospective study, the accuracy is conservatively estimated as 82% for consecutively enrolled patient population, and with a target value set as 72%, which is chosen to be higher than the one in the DeFACTO study[15].The sample size is analysed for paired proportions using the following formula: $$N = \frac{\left[Z_{1-\alpha/2}\sqrt{P_0(1-P_0)} + Z_{1-\beta}\sqrt{P_T(1-P_T)}\right]^2}{(P_T - P_0)^2}$$ With power = 0.90, two-tailed alpha = 0.05, a total of 188 patients with paired CT-QFR and FFR are required to reject the null hypothesis for diagnostic accuracy. To account for incomplete CT-QFR/CT-DS%/FFR/QFR/QCA data of 15% at most, a total of 216 patients need to be enrolled. The major secondary endpoint is to validate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions. Analyzed by the enrollment of 216 patients, about 158 patients will be calculated according to the proportion, 26.9%, of extensively calcified lesions from the retrospective study[14]. It will be tested for the capability in achieving the major secondary endpoint. The accuracy of 89.5% for CT-QFR in non-severe calcified lesions[14] and the accuracy of 92.7% for QFR[10] are used to calculate the sample size. We set the non-inferiority threshold as 15%. It will be analyzed by the following formula: $$N_T = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2[P_C(1-P_C) + P_T(1-P_T)]}{(D-\Delta)^2}$$ With power = 0.90, two-tailed alpha = 0.05, a total of 122 patients are required to validate the non-inferiority. To account for incomplete CT-QFR/CTA-DS%/FFR/QFR/QCA data of 15% at most , 141 patients need to be enrolled. Therefore, 158 patients without extensively calcified lesions meet the sample size of the major secondary endpoint. Therefore, the sample size is set as 216 patients to satisfy the requirements for validating both primary and major secondary endpoints.	Page 7,8
RESULTS			
Participants	**19**	Flow of participants, using a diagram:	Page 11



	20	Baseline demographic and clinical characteristics of participants: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	21a	Distribution of severity of disease in those with the target condition: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	21b	Distribution of alternative diagnoses in those without the target condition: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	22	Time interval and any clinical interventions between index test and reference standard: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals): This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	25	Any adverse events from performing the index test or the reference standard: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	27	Implications for practice, including the intended use and clinical role of the index test: This study will prospectively validate the diagnostic efficacy of a fast computational approach to derive FFR from coronary CT angiography with can be onsite for the first time. Furthermore, severe calcification will affect the diagnosis of lesions on CT images. It was proved that the presence of extensively calcified lesions influenced the diagnostic accuracy and analysis	Page 12-15

		variability. Therefore, we intend to avoid the effects of severe calcification so as to define whether CT-QFR is equivalent to QFR. It's also the first time to compare the diagnostic performance of CCTA-derived QFR with angiography-derived QFR. This study will lay the foundation for future studies to look at the potential value of CT-QFR technology in patients management. If the study achieves the expected objectives, outpatients can receive coronary artery functional evaluation while undergoing CCTA Examination. It can greatly reduce unnecessary invasive coronary angiography and coronary interventions.	
OTHER INFORMATION			
	28	Registration number and name of registry: ClinicalTrials.gov Identifier: NCT04665817	Page 5
	29	Where the full study protocol can be accessed: This is the protocol manuscript.	
	30	Sources of funding and other support; role of funders: CAREER Study is an investigator-initiated clinical trial with external funding from Clinical Research Plan of SHDC（No. SHDC2020CR3024B）issued by Shanghai Hospital Development Center, Research Fund of Huadong Hospital (No. 2019lc015) and a Center of Geratic Coronary Artery Disease.	Page 15

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the abilityof one or more medical tests to correctly classify study participants as having a**target condition.**This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**.The reference standardisthe best available method for establishing the presence or absence ofthe target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against thoseof the reference standardcan be used to estimate the**sensitivity** of the index test(the proportion of participants *with* the target conditionwho have a positive index test), and its **specificity** (the proportion *without* the target conditionwho have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test.Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiveroperatingcharacteristic(ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage testis used before an existing test; an add-on test is used after an existing test.

Besides diagnosticaccuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis.The STARD list was not explicitly developed for these other outcomes, statistics, and studytypes, although mostSTARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

Diagnostic Accuracy of CCTA-derived versus Angiography-derived Quantitative Flow Ratio (CAREER) Study: A prospective study protocol

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Title: Diagnostic Accuracy of CCTA-derived versus Angiography-derived Quantitative Flow Ratio (CAREER) Study: A prospective study protocol

Running title: The research protocol of the CAREER study

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Abstract

Introduction: Coronary computed tomography angiography (CCTA)-derived quantitative flow ratio (CT-QFR) is a novel non-invasive technology to assess the physiological significance of coronary stenoses, which enables fast and on-site computation of fractional flow reserve (FFR) from CCTA images. The objective of this investigator-initiated, prospective, single-center clinical trial is to evaluate the diagnostic performance of CT-QFR with respect to angiography-derived QFR, using FFR as the reference standard.

Methods and analysis: A total of 216 patients who have at least 1 lesion with a diameter stenosis of 30% to 90% in an artery with ≥ 2.0mm reference diameter will be enrolled in the study. FFR will be measured during invasive coronary angiography. CT-QFR and QFR will be assessed in two independent core laboratories in a blinded fashion. The primary endpoint is the diagnostic accuracy of CT-QFR in identifying hemodynamically significant coronary stenosis with FFR as the reference standard. The major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions.

Ethics and Dissemination: The study was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University (2020K192). Outcomes will be disseminated through publications in peer-reviewed journals and presentations at scientific conferences.

Article summary

Strengths and limitations of this study:

- The Diagnostic Accuracy of CCTA-derived versus Angiography-derived Quantitative Flow Ratio (CAREER) Study is a prospective and observational study initiated by investigator.
- This is a non-inferiority study comparing CT-QFR to QFR.
- CT-QFR and QFR will be computed in a blinded fashion and compared with FFR.
- Differences in cultural, economic, and social factors that affect patients' willingness to participate in the study will limit the inclusivity of the population.
- Due to the tight schedule and insufficient funding, a multi-center study cannot be conducted at this time.

Keywords: Coronary computed tomography angiography-derived quantitative flow ratio (CT-QFR) ; Angiography-derived quantitative flow ratio (QFR) ; Diagnostic accuracy; Non-inferiority

Trial registration: ClinicalTrials.gov Identifier: NCT04665817

Introduction

Coronary computed tomography angiography (CCTA) is a noninvasive test that enables visualization of coronary anatomy and the characteristics of arterial plaques with high sensitivity and negative predictive value [1]. However, conventional CCTA does not allow for physiological assessment of coronary stenosis[2]. Fractional flow reserve (FFR) is the current gold standard for evaluating the physiological significance of coronary stenosis in the catheterization laboratory[3]. An FFR-guided revascularization strategy was validated with improved clinical outcomes and cost-effectiveness compared to a traditional invasive coronary angiography-guided strategy [4-7]. The use of FFR is supported by both European guidelines (Class I, Level of Evidence: A) and American guidelines (Class IIa, Level of Evidence: A) in assessing coronary stenosis and guiding revascularization[8]. However, the adoption of FFR was limited due to prolonged procedural time, increased cost, patient discomfort, and operator's confidence in visual assessment from coronary angiograms.

Several computational FFR methods were developed to overcome the above limitations. Quantitative flow ratio (QFR), a new method for fast computation of FFR based on invasive coronary angiography (ICA) and empirical fluid dynamic equations was recently developed[9]. The overall diagnostic concordance between QFR and FFR was reported as 87% in a recent meta-analysis of prospective clinical studies[10].

More recently, CCTA-derived QFR, namely CT-QFR, has been developed as a method for fast computation of FFR from CCTA images based on a previously validated QFR algorithm. A recent retrospective and observational study demonstrated

a good diagnostic concordance of 87% [11]. In addition, its analysis time has been reduced to less than 5 minutes per patient on an off-the-shelf workstation. The diagnostic accuracy of this CT-QFR software version for on-site evaluation of coronary stenosis severity remains unknown. Furthermore, the differences in the diagnostic performance of QFR when applied to noninvasive CCTA images and ICA have not been studied. We are therefore planning to prospectively validate the diagnostic performance of on-site CT-QFR analysis compared with QFR, using FFR as the reference standard.

Methods and analysis

Study design

This study is an investigator-initiated, prospective, single-center clinical trial to validate the diagnostic performance of on-site CT-QFR using FFR as the reference standard. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Before the study starts, a written informed consent form will be obtained from patients willing to participate in the study and approved by the institutional review board/independent ethics committee of Huadong Hospital Affiliated to Fudan University (2020K192). The protocol of the trial has been registered at http://clinicaltrials.gov (NCT04665817).

Study objectives

The primary endpoint of the study is the patient-level diagnostic accuracy of on-site CT-QFR in identifying physiologically significant coronary artery stenosis, using FFR as the reference standard. The major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the vessels without extensively calcified lesions defined by the combination of a cross-sectional calcium arc > 90° and a thickness > 1.5 mm. Other secondary objectives of the study will include the following: (1) Other common measures of diagnostic performance of CT-QFR, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at the patient level compared with FFR as the reference standard. (2) Correlation between CT-QFR and FFR. (3) The comparison of the discrimination ability between CT-QFR, CCTA-derived percent diameter stenosis (CTA-DS%), and QCA-derived DS% for identifying physiologically significant stenosis with FFR as the reference standard.

Patient population

Patients with stable or unstable angina pectoris or non-acute phase of myocardial infarction who are undergoing CCTA examination and scheduled for coronary angiography within 30 days will be screened. We require the interval between ICA and CCTA to be less than 30 days which was in line with previous studies on CCTA-based FFR[12, 13] to avoid a mismatch between CCTA images and invasive coronary angiography images due to the progression of the patient's coronary artery stenosis. Inclusion criteria are: (1) at least 1 lesion with DS% between 30% and 90% in a coronary artery with a ≥ 2.0mm reference vessel diameter by visual estimation; (2)

invasive coronary angiography performed less than 30 days after CCTA; (3) age over 35 years but less than or equal to 85 years. Exclusion criteria are: (1) prior percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) of the interrogated lesion; (2) myocardial bridge involved in the interrogated vessel; (3) presence of collateral flow; (4) severe heart failure (NYHA ≥III); (5) known severe renal failure (eGFR < 30 ml/min/1.73m^2); (6) contraindicated to use contrast agents, beta-blockers, nitrates, or adenosine drugs; (7) recent prior myocardial infarction within 1 month of CCTA; (8) low image quality CCTA or coronary angiography to be assessed such as motion artifacts, poor filling of contrast agent, etc.; (9) any factors that affect the image quality of CCTA and coronary angiography, such as frequent premature contractions, atrial fibrillation, etc. Patients with comorbidities such as diabetes mellitus, hypertension or other chronic diseases, in particular, will not be excluded in this study because the coronary hemodynamics and image quality of CCTA and ICA will not be significantly influenced by these comorbidities.

Statistical hypotheses and Sample Size Calculation

The primary endpoint is the diagnostic accuracy of CT-QFR ≤ 0.8 to identify hemodynamically significant coronary stenosis with FFR ≤ 0.8 as the reference standard. The trial is powered for testing the significance of the primary endpoint. The primary null and alternative hypotheses to be tested are H0, diagnostic accuracy of CT-QFR ≤ 0.72, and H1, diagnostic accuracy of CT-QFR > 0.72. Estimates for the sample size calculation are based on the results from the retrospective study of CT-QFR[11],

where an accuracy of 87% at the patient level was found. In this prospective study, the accuracy is conservatively estimated as 82% for the consecutively enrolled patient population, and with a target value set as 72%, which is chosen to be higher than the one in the DeFACTO study[14]. The sample size is analyzed for paired proportions using the following formula:

$$N = \frac{\left[Z_{1-\alpha/2}\sqrt{P_0(1-P_0)} + Z_{1-\beta}\sqrt{P_T(1-P_T)}\right]^2}{(P_T - P_0)^2}$$

With power = 0.90, two-tailed alpha = 0.05, a total of 188 patients with paired CT-QFR and FFR are required to reject the null hypothesis for diagnostic accuracy. To account for incomplete CT-QFR/CT-DS%/FFR/QFR/QCA data of 15% at most, a total of 216 patients needs to be enrolled.

The major secondary endpoint is to validate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions. Analyzed by the enrollment of 216 patients, about 158 patients will be calculated according to the proportion, 26.9%, of extensively calcified lesions from the retrospective study[11]. It will be tested for the capability of achieving the major secondary endpoint. The accuracy of 89.5% for CT-QFR in non-severe calcified lesions[11] and the accuracy of 92.7% for QFR[15] are used to calculate the sample size. We set the non-inferiority threshold as 15%. It will be analyzed by the following formula:

$$N_T = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2[P_C(1-P_C) + P_T(1-P_T)]}{(D-\Delta)^2}$$

With power = 0.90, two-tailed alpha = 0.05, a total of 122 patients are required to validate the non-inferiority. To account for incomplete CT-QFR/CTA-

DS%/FFR/QFR/QCA data of 15% at most，141 patients need to be enrolled. Therefore, 158 patients without extensively calcified lesions meet the sample size of the major secondary endpoint. Thus, the sample size is set as 216 patients to satisfy the requirements for validating both primary and major secondary endpoints.

CCTA and CTA-DS% Analysis

Coronary computed tomography angiography will be performed on a dual-source CT system (SOMATOM Drive; Siemens Healthineers, Erlangen, Germany) or a 256 detector row scanners CT system (Revolution CT; GE Healthcare) with prospective or retrospective electrocardiographic gating in accordance with Society of Cardiovascular Computed Tomography guidelines[16]. Image interpretation of CCTA will be conducted in a blinded fashion by an experienced investigator. Images with coronary artery stenosis detected visually will be further analyzed (CtaPlus; version 1.0, Pulse Medical Imaging Technology, Shanghai, China). Coronary stenosis will be quantified by using the following parameters: (i) the minimal lumen area (MLA) and the minimal lumen diameter (MLD), and (ii) the percentage diameter stenosis (DS%) and the percentage area stenosis (AS%).

CT- QFR Computation

CT-QFR computation will be performed by experienced analysts using a recently developed software package (CtaPlus, version 1.0; Pulse Medical Imaging Technology, Shanghai, China), blinded to both QFR and FFR data. Detailed methodologies for CT-

QFR computation have been published previously[11]. A recent upgrade in the CT-QFR algorithm integrated deep learning technique into the coronary segmentation method to improve the computation efficiency. Manual corrections are allowed if the automated delineation lumen contour is sub-optimal, particularly at the segment with calcified plaques. All coronary artery segments with reference lumen diameter ≥ 1.5 mm are analyzed. Subsequently, all the delineated coronary branches are automatically merged for the reconstruction of the entire coronary tree, based on which the healthy reference lumen is also reconstructed. Finally, the CT-QFR value at each position of the coronary tree is computed using the previously validated QFR algorithm[9, 17].

Coronary Angiography

Coronary angiography will be performed by using a 5- or 6-F catheter with a transfemoral or transradial approach. All patients will receive an intravenous injection of heparin 100 IU/kg before angiography. Contrast media (Omnipaque 350 injection, GE Healthcare, Shanghai, China) will be injected manually with a forceful and stable injection. Coronary angiograms will be obtained from standard series of 6 to 8 projections for the left coronary artery and 2 or 3 projections for the right coronary artery by using a monoplane or biplane radiographic system (AXIOM Artis FC and Artis zee Biplane MN, Siemens) at 15 frames/s. All images will be digitally stored for analysis.

FFR Measurement

Intracoronary pressure will be measured by using a RadiAnalyzer Xpress instrument and Certus pressure wire (St. Jude Medical, Plymouth, Minnesota). The pressure guidewire will be introduced into the coronary artery and positioned distal to the coronary stenosis. The position of the sensor of the pressure guidewire will be recorded on cine fluorography. Hyperemia will be induced by adenosine-5'-triphosphate (ATP) infusion (160 μg/kg/minute) through an antecubital vein over a minimum of 2 minutes. During steady-state hyperemia, mean proximal aortic pressure, and mean intracoronary pressure distal to the target stenosis will be measured. Subsequently, the pressure guidewire will be slowly pulled back from the most distal to the proximal part of the artery by manual procedure during steady-state maximal hyperemia. If the pressures are not equalized at the end of the pullback (i.e., the pressure drift |Pa-Pd| > 3 mmHg), the whole FFR measurements should be repeated from the beginning.

QCA Analysis and QFR Computation

Quantitative coronary angiographic (QCA) analysis and QFR computation will be performed in a blinded fashion by using the recently developed QFR analysis system (AngioPlus Core; Pulse Medical Imaging Technology, Shanghai, China). The computational methods were previously described[9, 15]. Same as CT-DS% analysis, QCA analysis includes the following parameters: (i) MLA and MLD, and (ii) DS% and AS%. It will be analyzed by well-trained technicians who have successfully completed QFR training. Before QFR analysis, the technicians will be informed about the location

where the operators measured FFR so that QFR could be measured at the same vessel site. The QFR measure will be performed on the system placed in the control room. The investigators will be blinded to the FFR results.

Study flowchart

A study flowchart is shown in Figure 1.

Statistical Analysis

Continuous variables are presented as mean ± SD, and categorical variables will be presented as counts and percentages. Sensitivity and specificity to predict functionally significant stenosis (FFR ≤ 0.80). The performance of QFR ≤ 0.80 and CT-QFR ≤ 0.80 for predicting FFR ≤ 0.80 will be assessed by using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic accuracy, together with their 95% confidence intervals (CIs). Pearson correlation or spearman's correlation will be used to quantify the correlations between QFR, CT-QFR, and FFR. Agreements between QFR, CT-QFR, and FFR will be assessed by the Bland-Altman plot. The Bland-Altman plot depicts the differences of each pair of measurements versus their mean values with reference lines for the mean difference of all paired measurements. The limits of the agreement will be defined as mean ± 1.96 SD of absolute difference. The ROC curve analysis will be performed to assess the area under the curve (AUC) of CT-QFR, QFR, CT-derived %DS, and QCA-derived %DS for predicting FFR ≤ 0.80. The ROC curves will be compared by using the DeLong method. A two-sided p-value < 0.05 will be considered to indicate statistical significance.

Current status

The study has been approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Five analysts have successfully completed the International Course on Coronary Image Analysis and Computational Physiology which covers FFR, QFR, and CT-QFR. All of them have passed the final exams (with the diagnostic accuracy higher than 85% and the standard deviation of mean difference less than 0.05 between image-based FFR and invasive FFR) and obtained qualification certificates for relevant analysis. Recruitment is ongoing at Huadong Hospital Affiliated to Fudan University, Shanghai, China. At the time of submission of this manuscript, 35 participants have been recruited for the study.

Discussion

The CAREER study will for the first time prospectively evaluate the diagnostic accuracy of on-site CT-QFR analysis in identifying patients with physiologically significant coronary stenosis. In addition, the diagnostic performance of CCTA-based versus angiography-based QFR in vessels without significantly calcified lesions will be compared. The study findings will provide pivotal data to support the clinical applications of CT-QFR in the management of CAD patients.

The previously presented FFR computation method derived from computed tomography (FFR_{CT}), a non-invasive technology, is a computational fluid dynamic modeling technique that enables the calculation of FFR from a coronary computed tomographic angiographic dataset[18]. The diagnostic performance of FFR_{CT} has been

validated in several multi-center prospective clinical trials[12, 19, 20]. The application of FFR_{CT} can reduce unnecessary invasive coronary angiography[21, 22]. However, it heavily relies on the quality of the underlying computational models and sophisticated boundary conditions and required a few hours for computation[20]. Moreover, severely calcified lesions might affect the calculation results of FFR_{CT} [23].

Recently, a novel technique for the rapid computation of FFR from radiographic coronary angiography, named QFR, was accomplished by estimating the pressure drop due to coronary stenosis according to coronary lumen morphology and virtual hyperemic flow derived from contrast frame count without the use of pressure wire and drug-induced hyperemia[9]. The diagnostic performance of this minimally invasive technique has been validated by several studies[9, 15, 24, 25]. More recently, the novel QFR algorithm has been applied to CCTA-images, and CCTA-derived QFR (namely CT-QFR), has been derived as anon-invasive technology to assess the physiological significance of coronary stenoses[10]. The patient-specific virtual hyperemic flow was used to compute the CT-QFR value at every position of the reconstructed coronary tree. A recent retrospective and observational study with 156 vessels from 134 patients demonstrated good correlation ($r = 0.79$; $p < 0.001$) and agreement (0.00 ± 0.06; $p = 0.823$) between CT-QFR and wire-based FFR, with a vessel-level diagnostic concordance of 87%[11]. The average analysis time for CT-QFR was reported as less than 20 minutes, with the CT-QFR pullback curve computed in less than 20 seconds [11].

A recent upgrade in the CT-QFR algorithm integrated deep learning technique into

the coronary segmentation method thus improving the accuracy of automatic lumen delineation and reducing the analysis time to less than 5 minutes per patient on an off-the-shelf workstation. The incorporation of the deep learning techniques in the CT-QFR algorithm had the potential to improve the calculation efficiency significantly. Large-scale studies have shown that the application of CT-FFR can reduce unnecessary invasive coronary angiography. At the same time, it brings higher health and economic benefits[21, 26]. The one-year follow-up of the ADVANCE study showed that the MACE of patients with a CT-FFR value ≤ 0.8 was significantly higher than that of patients with a CT-FFR value > 0.8[27]. Therefore, a kind of strategy pertaining more to a rapid diagnosis, reduced invasive strategy, and lower costs is particularly important. This study will prospectively validate the diagnostic efficacy of such a faster computational approach to derive FFR from coronary CT angiography with can be onsite for the first time.

Furthermore, severe calcification will affect the diagnosis of lesions on CT images. It was proved that the presence of extensively calcified lesions influenced the diagnostic accuracy and analysis variability[11]. Therefore, we intend to avoid the effects of severe calcification so as to define whether CT-QFR is equivalent to QFR. It's also the first time to compare the diagnostic performance of CCTA-derived QFR with angiography-derived QFR. Therefore, the major secondary endpoint was intended to investigate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions.

This study will lay the foundation for future studies to look at the potential value

of CT-QFR technology in patient management. If the study achieves the expected objectives, outpatients can receive coronary artery functional evaluation while undergoing CCTA Examination. It can greatly reduce unnecessary invasive coronary angiography and coronary interventions.

Ethics and dissemination

This research will not increase the risk and economic burden on patients and the patients' rights will be fully protected. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University (ref. number 2020K192). All patients will provide written informed consent. The results of this study are to be published in respected, peer-reviewed journals, and the findings presented at scientific conferences in the field of Cardiology.

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Author Contributions

Xinkai Qu and Shenxian Tu participated in the study design, statistical hypotheses, and

sample size calculation. Tingwen Weng and Qian Gan participated in manuscript preparation, sample size calculation, and writing the protocol of FFR measurement. Zehang Li was involved in manuscript preparation, writing the protocol of QFR computation, and CT-QFR computation. XinrongZhai was involved in writing the protocol of FFR measurement. Ming Li, Lin Qi, and Cheng Li participated in writing the protocol of CCTA Analysis. Shaofeng Guan, Wenzheng Han, Yang Chen, Liang Zhang, and Xifeng Chang were involved in writing the protocol of coronary angiography.

Conflict of interest

The authors declare that they have no conflict of interest.

Data Availability Statement

The data will be available from the corresponding author upon a reasonable request.

Patient and Public Involvement

Patients or the public will be involved in the design, conduct, reporting, or dissemination plans of our research.

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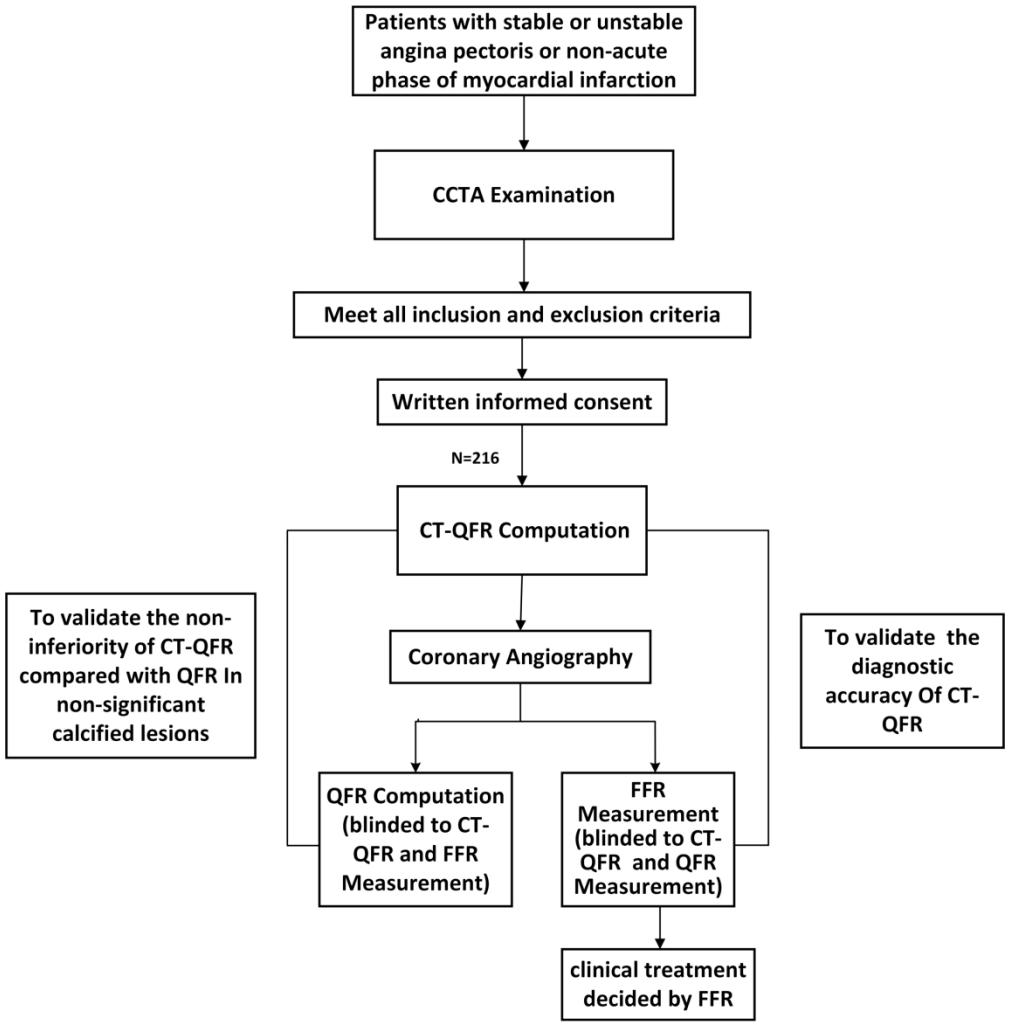
Figure legend:

Figure 1. Study flowchart. CCTA, Coronary computed tomography angiography; FFR, fractional flow reserve; QFR, Quantitative flow ratio; CT-QFR, CCTA-derived Quantitative Flow Ratio.



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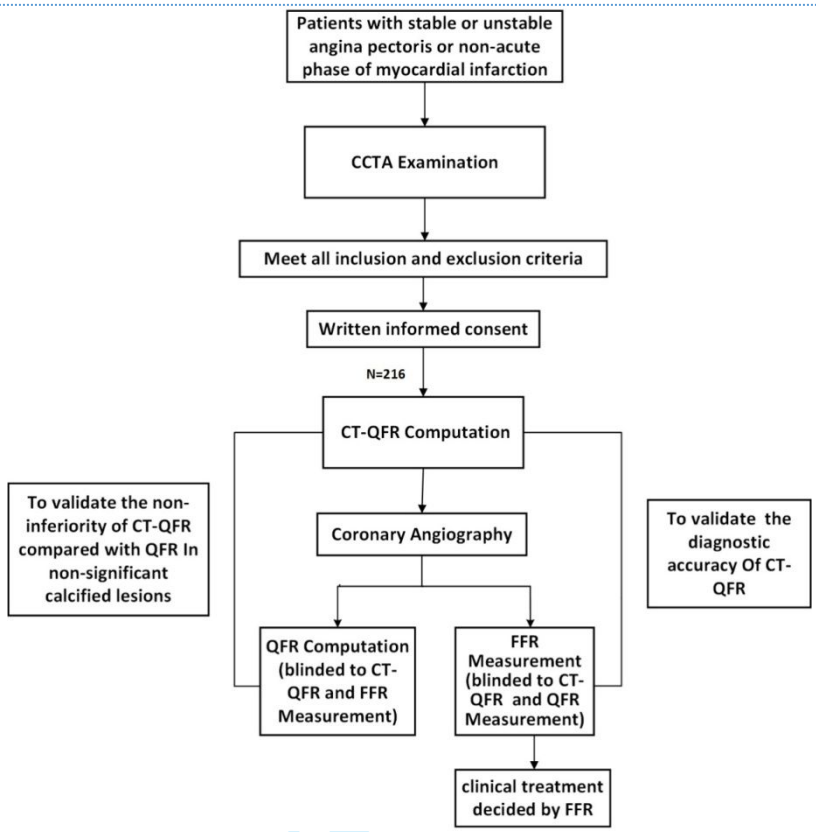
Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy: Diagnostic Accuracy of CCTA-derived versus AngiogRaphy-dErived QuantitativE Flow Ratio (CAREER) Study: Rationale and Design	Page 1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions : Background: Coronary computed tomography angiography (CCTA)- derived quantitative flow ratio (CT-QFR) is a novel non-invasive technology to assess the physiological significance of coronary stenoses, which enables fast and onsite computation of fractional flow reserve (FFR) from CCTA images. The objective of this investigator-initiated, prospective, single-center clinical trial is to evaluate the diagnostic performance of CT-QFR with respect to angiography-derived QFR, using FFR as the reference standard. Methods: A total of 216 patients who have at least 1 lesion with a diameter stenosis of 30% to 90% in an artery with ≥2.0 mm reference diameter will be enrolled in the study. FFR will be measured during invasive coronary angiography. CT-QFR, and QFR will be assessed in two independent core laboratories in blinded fashion. The primary endpoint is the diagnostic accuracy of CT-QFR in identifying hemodynamically significant coronary stenosis with FFR as the reference standard. Major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions. Discussion: This study will be the first study to prospectively validate the diagnostic accuracy of CT-QFR compared with QFR, using FFR as the reference standard.	Page 3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test : Coronary computed tomography angiography (CCTA) is a non−invasive test that enables visualization of coronary anatomy and the characteristics of arterial plaques with high sensitivity and negative predictive value. However, conventional CCTA does not allow for physiological assessment of coronary stenosis. Fractional flow reserve (FFR) is the current gold standard for evaluating the physiological significance of coronary stenosis in the catheterization laboratory. An FFR-guided revascularization strategy was validated with improved clinical outcomes and cost-effectiveness compared to a traditional invasive coronary angiography-guided strategy. The use of FFR is supported by both European guidelines (Class I, Level of Evidence: A) and American guidelines (Class IIa, Level of Evidence: A) in assessing coronary stenosis and to guide revascularization. However, the adoption of FFR was limited due to prolonged procedural time, increased cost, patient discomfort, and operator's confidence in visual assessment from coronary angiograms. Several computational FFR methods were developed to overcome the above limitations. Quantitative flow ratio (QFR), a new method for fast computation of FFR based on invasive coronary angiography (ICA) and empirical fluid dynamic equations was recently developed. The overall diagnostic concordance between QFR and FFR was reported as 87% in a recent meta-analysis of prospective clinical studies. More recently, CCTA-derived QFR, namely CT-QFR, has been developed as a method for fast computation of FFR from CCTA images based on previously validated QFR algorithm. A recent retrospective and observational study demonstrated a good diagnostic concordance of 87%. In addition, it's analysis time has been reduced to less than 5 minutes per patient on an off-the-shelf workstation. The diagnostic accuracy of this CT-QFR software version for on-site evaluation of coronary stenosis severity remains unknown. Furthermore, the difference in the diagnostic performance of QFR when applied to non−invasive CCTA images and to ICA has not been studies. We are therefore planning to prospectively validate the diagnostic performance of on-site CT-QFR analysis compared with QFR, using FFR as the reference standard.	Page 4, 5
	4	Study objectives and hypotheses： The primary endpoint of the study is the patient-level diagnostic accuracy of on-site CT-QFR in identifying physiologically significant coronary artery stenosis, using FFR as the reference standard. Major secondary endpoint is the non-inferiority of CT-QFR compared with QFR in the vessels without extensively calcified lesions defined by the combination of a cross-sectional calcium arc >90° and a thickness >1.5 mm. Other secondary objectives of the study will include the following. (1) Other common measures of diagnostic performance of CT-QFR, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at the patient level compared with FFR as the reference standard. (2) Correlation between CT-QFR and FFR. (3) The comparison of the discrimination ability between CT-QFR, CCTA-derived percent	Page 5,6

		diameter stenosis (CTA-DS%), and QCA-derived DS% for identifying physiologically significant stenosis with FFR as the reference standard.	
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study): This study is an investigator-initiated, prospective, single-center clinical trial to validate the diagnostic performance of on-site CT-QFR using FFR as the reference standard. The study is conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Huadong Hospital Affiliated to Fudan University. Before the study starts, written informed consent form will be obtained from patients willing to participate in the study and approved by the institutional review board/independent ethics committee of Huadong Hospital Affiliated to Fudan University.	Page 5
Participants	**6**	Eligibility criteria : Inclusion criteria are: (1) at least 1 lesion with DS% between 30% and 90% in a coronary artery with a ≥2.0mm reference vessel diameter by visual estimation; (2) invasive coronary angiography performed less than 30 days after CCTA; (3) age over 35 years but less than or equal to 85 years. Exclusion criteria are: (1) prior percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) of the interrogated lesion; (2) myocardial bridge involved in the interrogated vessel; (3) presence of collateral flow; (4) severe heart failure (NYHA ≥III); (5) known severe renal failure (eGFR<30 ml/min/1.73m2); (6) contraindicated to use contrast agents, beta blockers, nitrates or adenosine drugs; (7) Recent prior myocardial infarction within 1 month of CCTA; (8) low image quality CCTA or coronary angiography to be assessed such as motion artifacts, poor filling of contrast agent, etc.; (9) any factors that affect the image quality of CCTA and coronary angiography, such as frequent premature contractions, atrial fibrillation, etc.	Page 5, 6
	7	Potentially eligible participants will be identified on their symptoms and results from previous tests.	Page 5
	8	Where and when potentially eligible participants were identified (setting, location and dates): Recruitment has been ongoing at Huadong Hospital Affiliated to Fudan University, Shanghai, China since December 2020.	Page 5,6
	9	Participants formed a consecutive, convenience series.	Page 5
Test methods	**10a**	Index test: Coronary computed tomography angiography - derived quantitative flow ratio (CT-QFR); Angiography-derived quantitative flow ratio （QFR）	Page 4, 5
	10b	Reference standard: Fractional flow reserve (FFR).	Page 4, 5
	11	Rationale for choosing the reference standard: Fractional flow reserve (FFR) is the current gold standard for evaluating the physiological significance of coronary stenosis in the catheterization laboratory. An FFR-guided revascularization strategy was validated with improved clinical outcomes and cost-effectiveness compared to a traditional invasive coronary angiography-guided strategy.	Page 4
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory : The performances of QFR≤0.80 and CT-QFR≤0.80 predict hemodynamically significant coronary stenosis.	Page11
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory: The performance of FFR≤0.80 predicts hemodynamically significant coronary stenosis.	Page11
	13a	Clinical information and reference standard results will not be available to the performers/readers of the index test.	Page 7-10
	13b	Clinical information and index test results will not be available to the assessors of the reference standard.	Page 7-10
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy : The performance of QFR≤0.80 and CT-QFR≤0.80 for predicting FFR≤0.80 will be assessed by using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and diagnostic accuracy, together with their 95% confidence intervals (CIs). The ROC curve analysis will be performed to assess area under the curve (AUC) of CT-QFR, QFR, CT-derived %DS and QCA-derived %DS for predicting	Page 7-10

		FFR≤0.80. The ROC curves will be compared by using the DeLong method. A two-side p value <0.05 is considered to indicate statistical significance.	
	15	How indeterminate index test or reference standard results were handled: When calculating the sample size, the data that could not be completed was included as the dropout rate, which accounted for 15%.	Page 7,8
	16	How missing data on the index test and reference standard were handled: When calculating the sample size, the data that could not be completed was included as the dropout rate, which accounted for 15%.	Page 7,8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory: Agreements between QFR, CT-QFR, and FFR will be assessed by Bland-Altman plot. The Bland-Altman plot depicts the differences of each pair of measurements versus their mean values with reference lines for the mean difference of all paired measurements. The limits of agreement are defined as mean±1.96 SD of absolute difference	Page 11,12
	18	Intended sample size and how it was determined: The primary endpoint is the diagnostic accuracy of CT-QFR≤0.8 to identify hemodynamically significant coronary stenosis with FFR≤0.8 as the reference standard. The trial is powered for testing significance of the primary endpoint. The primary null and alternative hypotheses to be tested are H0, diagnostic accuracy of CT-QFR≤0.72, and H1, diagnostic accuracy of CT-QFR＞0.72. Estimates for the sample size calculation are based on the results from the retrospective study of CT-QFR[14], where an accuracy of 87% at patient level was found. In this prospective study, the accuracy is conservatively estimated as 82% for consecutively enrolled patient population, and with a target value set as 72%, which is chosen to be higher than the one in the DeFACTO study[15].The sample size is analysed for paired proportions using the following formula: $$N = \frac{\left[Z_{1-\alpha/2}\sqrt{P_0(1-P_0)} + Z_{1-\beta}\sqrt{P_T(1-P_T)}\right]^2}{(P_T - P_0)^2}$$ With power = 0.90, two-tailed alpha = 0.05, a total of 188 patients with paired CT-QFR and FFR are required to reject the null hypothesis for diagnostic accuracy. To account for incomplete CT-QFR/CT-DS%/FFR/QFR/QCA data of 15% at most, a total of 216 patients need to be enrolled. The major secondary endpoint is to validate the non-inferiority of CT-QFR compared with QFR in the patients without extensively calcified lesions. Analyzed by the enrollment of 216 patients, about 158 patients will be calculated according to the proportion, 26.9%, of extensively calcified lesions from the retrospective study[14]. It will be tested for the capability in achieving the major secondary endpoint. The accuracy of 89.5% for CT-QFR in non-severe calcified lesions[14] and the accuracy of 92.7% for QFR[10] are used to calculate the sample size. We set the non-inferiority threshold as 15%. It will be analyzed by the following formula: $$N_T = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2[P_C(1-P_C) + P_T(1-P_T)]}{(D-\Delta)^2}$$ With power = 0.90, two-tailed alpha = 0.05, a total of 122 patients are required to validate the non-inferiority. To account for incomplete CT-QFR/CTA-DS%/FFR/QFR/QCA data of 15% at most , 141 patients need to be enrolled. Therefore, 158 patients without extensively calcified lesions meet the sample size of the major secondary endpoint. Therefore, the sample size is set as 216 patients to satisfy the requirements for validating both primary and major secondary endpoints.	Page 7,8
RESULTS			
Participants	**19**	Flow of participants, using a diagram:	Page 11



	20	Baseline demographic and clinical characteristics of participants: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	21a	Distribution of severity of disease in those with the target condition: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	21b	Distribution of alternative diagnoses in those without the target condition: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	22	Time interval and any clinical interventions between index test and reference standard: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals): This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	25	Any adverse events from performing the index test or the reference standard: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability: This is a protocol manuscript. It reports an ongoing research study. The data collection is incomplete.	
	27	Implications for practice, including the intended use and clinical role of the index test: This study will prospectively validate the diagnostic efficacy of a fast computational approach to derive FFR from coronary CT angiography with can be onsite for the first time. Furthermore, severe calcification will affect the diagnosis of lesions on CT images. It was proved that the presence of extensively calcified lesions influenced the diagnostic accuracy and analysis	Page 12-15

		variability. Therefore, we intend to avoid the effects of severe calcification so as to define whether CT-QFR is equivalent to QFR. It's also the first time to compare the diagnostic performance of CCTA-derived QFR with angiography-derived QFR. This study will lay the foundation for future studies to look at the potential value of CT-QFR technology in patients management. If the study achieves the expected objectives, outpatients can receive coronary artery functional evaluation while undergoing CCTA Examination. It can greatly reduce unnecessary invasive coronary angiography and coronary interventions.	
OTHER INFORMATION			
	28	Registration number and name of registry: ClinicalTrials.gov Identifier: NCT04665817	Page 5
	29	Where the full study protocol can be accessed: This is the protocol manuscript.	
	30	Sources of funding and other support; role of funders: CAREER Study is an investigator-initiated clinical trial with external funding from Clinical Research Plan of SHDC（No. SHDC2020CR3024B）issued by Shanghai Hospital Development Center, Research Fund of Huadong Hospital (No. 2019lc015) and a Center of Geratic Coronary Artery Disease.	Page 15

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the abilityof one or more medical tests to correctly classify study participants as having a**target condition.**This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**.The reference standardisthe best available method for establishing the presence or absence ofthe target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against thoseof the reference standardcan be used to estimate the**sensitivity** of the index test(the proportion of participants *with* the target conditionwho have a positive index test), and its **specificity** (the proportion *without* the target conditionwho have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test.Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiveroperatingcharacteristic(ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage testis used before an existing test; an add-on test is used after an existing test.

Besides diagnosticaccuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis.The STARD list was not explicitly developed for these other outcomes, statistics, and studytypes, although mostSTARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.