The Effect of On-site CT-derived Fractional Flow Reserve on the Management Making for the Patients With Stable Chest Pain (TARGET Trial)

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STUDY PROTOCOL

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Background

Coronary computed tomographic angiography (CCTA) has become an excellent rule-out test for suspect coronary artery disease (CAD). The recommendation for CCTA was even expanded by one national guideline as a first-line test to patients with intermediate and high likelihood of CAD based on their cost-effectiveness analysis suggesting that this would be a lower-cost strategy. However, the relative low specificity of CCTA in the diagnosis of functional myocardial ischemia makes it difficult to act as a real gate- keeper for the patients to be referred to invasive coronary angiography (ICA). In developing countries like China, for the patients with prior CCTA test who are subject to downstream ICA, over 30% of them were found to have no obstructive CAD. Even more, the invasive procedure seems to be much more frequent when CCTA was introduced to clinical practice in some pragmatic clinical trials.

Recently, CT-FFR, a kind of novel functional assessment derived from CCTA, dramatically increases the specificity of diagnosis on flow-limiting coronary stenosis, enabling CCTA to become a more robust non-invasive strategy. It showed a great potential in detecting functional myocardial ischemia related to coronary-specific lesion (in Discovery-Flow, DEFACTO, and NXT trials). Moreover, clinical care guided by CT-FFR could provide benefits with equivalent clinical outcomes and lower expenditure, compared with routine clinical care over 1-year follow-up (Platform trial). In addition, ADVANCE study revealed that CT-FFR modified the treatment recommendation which might reduce unnecessary ICA, predict revascularization, and further identify subjects at low risk of adverse events through 90 days.

However, these studies were not randomized designed and selection bias still existed. Also, the cost-effectiveness of CT-FFR in clinical practice remains to be determined, especially in developing countries. The purpose of this present study will be to evaluate whether CCTA/CT-FFR outperforms the usual care in ruling out patients without significantly obstructive CAD before invasive catheterization and improving clinical prognosis during follow-up in a randomized design.

Method/design

Study aim

TARGET trial is a multicenter, prospective, open-label, and pragmatic randomized controlled trial evaluating the effect of a CCTA/CT-FFR strategy (group A) on management decision making versus usual care (group B) in intermediate-to-high risk patients with suspected CAD who undergo clinically indicated diagnostic evaluation. Recruitment commenced in August 2019. The schedule of enrollment and assessments follows the SPIRIT Figure. The study protocol (Version 3.0/201812) and other relevant documentations have been approved by the institutional human research ethic committee of Chinese PLA

General Hospital and the relevant national ethics committees as well as registered on ClinicalTrials.gov identifier: NCT03901326.

Setting

This multicenter randomized controlled clinical trial will be carried out in 6 tertiary hospitals across China, all of which has the volume of over 200 patients in outpatient area of cardiology division each working day. Participating subjects will be enrolled and subsequently assigned to either usual care group or CT-FFR care group via computer-generated random numbers (1:1 ratio) (Figure 1). The trial accords with the SPIRIT guidelines. The treatments (both intervention and control) will be delivered by licensed clinicians in the participating sites. Central telephone is used for allocation of sequence. Participants will be randomized to the CT-FFR examination group or usual care group using a randomization procedure. The cardiologist will be aware of patients' group allocation because they will provide the trial intervention, but they will not be involved in the analysis. Participants are not blind to their group allocation, nor are their physicians who are informed of screening results of their patients (if the patient consents) and give the recommendation by outpatient or telephone. There will be no special criteria for discontinuing or modifying allocated interventions.

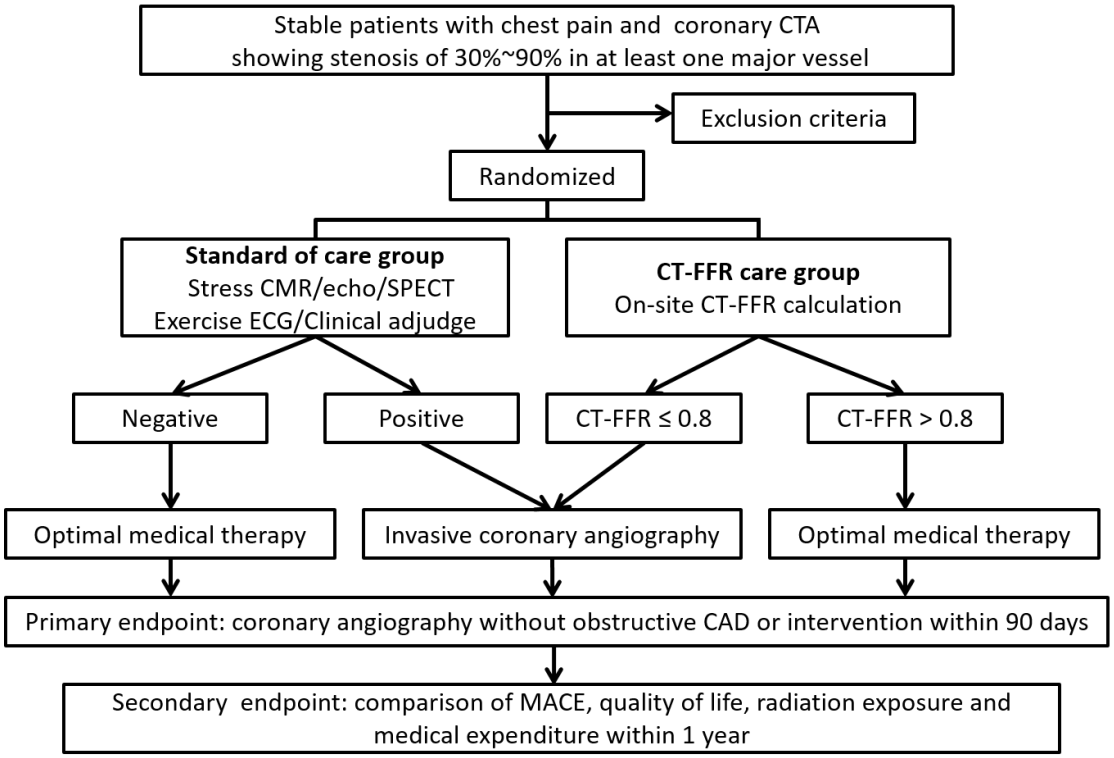

Figure 1: The flow chart of TARGET trial.

Eligibility criteria

Inclusion criteria

Consecutive patients with new-onset chest pain suspicious for CAD will be included. Subjects with

intermediate-to-high pretest probability of CAD will be recruited based on the CAD Consortium basic pretest probability score. Another major inclusion criterion is the CCTA result which showed that the diameter stenosis is between 30 and 90% in at least one major coronary artery (coronary artery diameter ≥ 2.5 mm).

The typicality of the chest pain was determined by three characteristics of chest pain, including central chest discomfort lasting below 15min, provoked by exertion or emotional stress, and relieved by rest or nitrates. This definition is similar with the NICE guideline update (2016). Non-anginal pain was defined as the presence or absence of only one characteristic of chest pain. Atypical angina was defined as the presence of two characteristics. Agreement to participate in this trial will be necessary and informed consents will be obtained from all subjects before recruiting.

Exclusion criteria

a. Diagnosed or suspected acute coronary syndrome requiring hospitalization or emergent testing;
b. Hemodynamically or clinically unstable condition systolic blood pressure < 90 mmHg or serious atrial or ventricular arrhythmias;
c. Known CAD with prior myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or any angiographic evidence of ≥ 50% stenosis in any major coronary artery;
d. Patients with left main branch stenosis ≥ 50% or one major coronary stenosis > 90% by CCTA;
e. Known severe congenital, valvular (moderate and above), or cardiomyopathy process (hypertrophic cardiomyopathy or reduced systolic left ventricular function ≤ 40%) which could explain cardiac symptoms;
f. Unable to provide written informed consent or participate in long-term follow-up.

Measurement

CCTA image is obtained before the patient's first visit and assessment. When subjects are randomized to the CT-FFR arm, on-site FFR based on the CCTA imaging (DEEPVESSEL FFR, Beijing CuraCloud Technology Co., Ltd., Beijing, China) will be measured. DEEPVESSEL FFR workstation is very dedicated software utilizing the original CCTA imaging to meter simulated FFR values based on a machine learning algorithm, which has been introduced in previous articles. The calculation process could be summarized as follows: the first step is to extract a 3D coronary artery model and generate coronary centerlines which are similar to the routine reconstruction of CCTA. A modified 3D U-Net like model is employed to generate a major coronary artery tree followed by a graph cut to refine the boundary of the arteries. The center-lines are extracted using a minimal path extraction filter. Then, a novel path-based deep learning model, referred to DEEPVESSEL FFR, is used to predict the simulated FFR values on the vascular center-lines. Deep learning algorithm is used to establish characteristic sample database of coronary hemodynamic characteristic parameters. When the deep training model is proved to be valid, it is

applied to a new lesion-specific measurement. DEEPVESSEL FFR system consists of a multi-layer perceptron network (MLP) and a bidirectional multi-layer recursive neural network (BRNN). The whole model can process variable-length input, and each point of the input sequence is transferred separately corresponding to MLP; the output of the MLP is transferred into the BRNN to optimize the sequence model. In comparison with the previous technology, the major advantage of DEEPVESSEL FFR model is more accurate because of the incorporation of context information on target FFR along the vessel path. More specifically, DEEPVESSEL FFR workstation includes the neural networks set on each point of the vascular path. Structural and functional features of each point on the vascular centerlines are considered as input, while calculating FFR of each point as output. Therefore, DEEPVESSEL FFR is on the coronary tree simultaneously at a quick time at post-processing **(Figure 2)**. Lesion-specific CT-FFR is defined as simulated FFR value at distance of 20mm away from the lesion of interest.

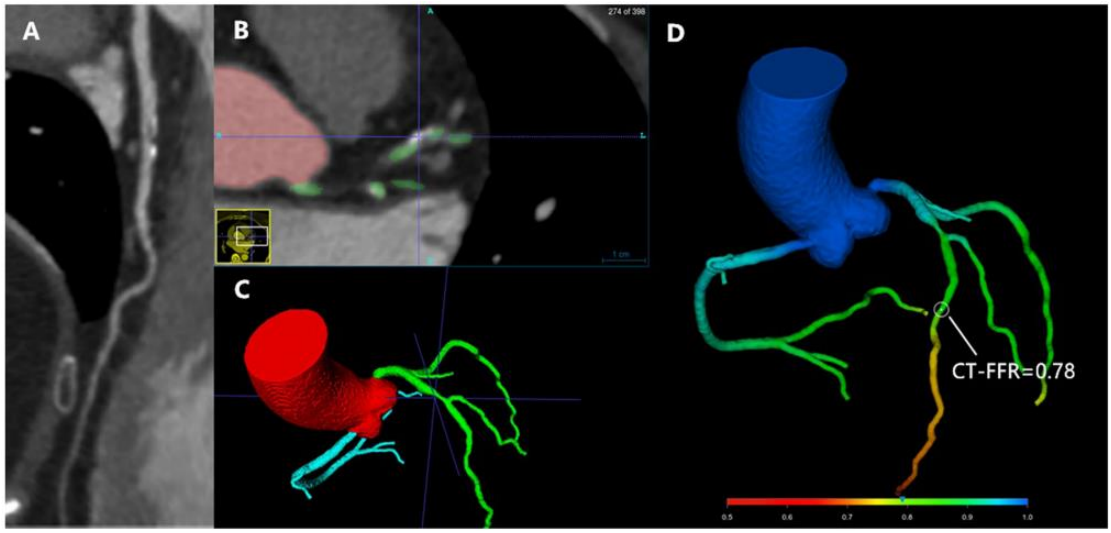

Figure 2: Schematic presentation of DEEPVESSEL FFR measurement on coronary artery stenosis

If the subjects are randomly allocated to CT-FFR arm, they will be examined by DEEPVESSEL FFR for three major epicardial arteries. If the result of CT-FFR calculation is less than or equal to 0.8 in one or more major，coronary arteries, the patient will be referred to ICA directly; if the result of CT-FFR value is more than 0.8, optimal medical therapy will be recommended. The decision on the mode of revascularization is left to the treating cardiologists and depends on local practice standard.

Correspondingly, if the subjects are randomized to usual care arm, attending physicians will decide the next step of diagnosis and treatment, such as exercise ECG, stress cardiac echo, cardiac MR, and SPECT. According to the results of examination combined with risk factors assessment and clinical manifestations, physicians should provide recommendation whether the subjects would undergo ICA or not. The evaluation criteria of functional examination include but not all:

a. The exercise ECG criterion for a positive test is greater ≥ 1 mm of horizontal or down sloping ST segment deviation (depression or elevation) in any lead except aVR for at least 60 to 80 ms after the end

of the QRS complex, either during or after exercise;

b. The nuclear cardiology criterion for a positive result is evaluated as follows: perfusion is graded using a 5-point scale (0 to 4) in each of 20 myocardial segments. Summed rest scores, summed stress scores, and summed difference scores (SDS) are recorded. Reversible defects are graded as small if SDS was 2 to 4, moderate if SDS was 5 to 8, or large if SDS was > 8. Subjects are categorized as having ischemia if more than 1 of the following criteria was present: SDS was ≥ 2 and/or there was an ungated stress-and-rest volume (transitory ischemic dilation) ratio of > 1.19;

c. The stress cardiac echo criterion for a positive result is evaluated as follows: abnormal findings include those with fixed wall-motion abnormalities or new or worsening abnormalities indicative of ischemia. A segment with resting dysfunction may show either a sustained improvement during stress indicating a non-jeopardized myocardium (stunned) or improve during early stress with subsequent deterioration at peak (biphasic response). The biphasic response is suggestive of viability and ischemia, with jeopardized myocardium fed by a critically coronary stenosis. Resting wall motion abnormalities, unchanged with stress, are classified as "fixed" and most often represent regions of prior infarction.

The DICOM imaging data will be transferred to on-site workstation to complete DEEPVESSEL FFR measurement and the on-site lab will provide the report to the referral physician within 24 h for decision making.

On the consent form, participants will be asked if they agree to use of their data should they choose to withdraw from the trial. Participants will also be asked for permission for the research team to share relevant data with people from the hospital taking part in the research, where relevant. This trial does not involve collecting biological specimens for storage.

Downstream decision making

The results of the index test will be provided to the reference cardiologist of the patients' institution who will make clinical decisions based on the integrated evaluation of patient clinical assessment and index test findings. Optional use of invasive FFR or intravascular imaging (IVUS or OCT) and the decision on the mode of revascularization are left to the interventional cardiologists and depends on local practice standard.

At baseline, 6 months, and 12 months, recommendations for therapy are made in line with guidelines published. The goal of anti-hypertensive therapy is to achieve a blood pressure of less than 140/90 mmHg. The choice of anti-hypertensive therapy will be left to the treating physician. The aim of anti-lipid therapy is to achieve levels of LDL < 1.9mmol/l. In the first instance, statin therapy will be initiated and then increased with the addition of a second agent if necessary. In the case of diabetics with a raised blood sugar, the primary health care physician is asked to measure HbA1c and to ensure that the patients' subsequent therapy is tailored to achieve a HbA1c of less than 6.5mg/dl. Smokers are referred to the

smoking cessation clinic.

Follow-up

Subjects will be contacted regularly by trained interviewers at 90 days, 3 months, 6 months, and 12 months post-enrollment for follow-up assessment until death, withdrawal, or end of the trial **(Figure 3)**. All subjects are followed for a minimum of 12 months. An independent clinical event adjudication committee (CEC) reviewed all primary endpoint event and secondary endpoints in a blinded fashion. The decisions of CEC will be used to implement the final statistical analysis.

	STUDY PERIOD					
Time point	**Enrollment visit**	**Allocation**	**Intervention**	**3months± 7days**	**6months ± 7days**	**1 year ± 7days**
Eligibility screen	×					
Informed consent	×					
Demographic data	×					
Allocation		×				
Diagnosis			×			
Conventional Coronary Angiography			×	×		
Coronary revascularization			×	×	×	×
MACE				×	×	×
AE				×	×	×
Medical cost				×	×	×
Quality of life				×	×	×
Radiation exposure				×	×	×

Figure 3: Chronology of the research (Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Figure)

The data were collected, coded, and entered by the trial investigators, and the paper-based CRF form is sent to the trial office by investigators to ensure that the data would not be tampered. The researchers used double data entry and range checks for data value method to ensure the accuracy of the data. A clinical research organization (CRO) has been contracted to oversee the monitoring of all sites, establishing the eCRF and checking the completeness and consistency of the trial data. Adherence to this trial will be monitored via hospital information system. The follow-up examination results should be sent to the research site, and the examination results of the grade 3 hospital can be accepted to maintain the credibility.

Endpoint of the study

The primary endpoint of the present trial is comparison between the two arms in the rate of planned ICA without significant obstructive CAD or interventions within 90 days. Significant obstructive CAD is defined as more than or equal to 70% of diameter stenosis by quantitative coronary analysis in core lab or invasive FFR $\leq$ 0.8 if available during procedure. Interventions includes stent implantation, balloon dilation and bypass surgery.

The secondary endpoint will be the comparison between the two treatment arms in terms of MACE, quality of life, cumulative effect dose of radiation exposure, and overall cardiac medical cost during the follow-up at 1 year.

The Seattle Angina Questionnaire (SAQ-7) was used to assess the clinical effect and quality of life (QOL). We will also measure the cumulative radiation exposure dose (ED) over the entire study period by assessing the original average dose for each test performed during the follow-up. In case the ED for each test is not known, we will use the standard ED available for each test in the literature.

Major adverse cardiovascular events (MACE) will be defined as a combined endpoint of (a) hospitalization for unstable angina, (b) revascularization by PCI or CABG after 90 days, (c) non-fatal MI, and (d) cardiac death: any death because of immediate cardiac cause (e.g., MI, low- output failure, fatal arrhythmia) or vascular cause (e.g., cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause). Unwitnessed death and death of unknown cause will be classified as cardiovascular death. An independent clinical event adjudication committee will review the agreement between all events and the provided definitions.

Adverse event (AE) monitoring will begin when a participant has been randomized and will continue for 1 year. We will record AEs which are defined as serious or which are potentially related to the intervention according to CT-FFR result independently. Since we defined MACE as a secondary endpoint, the SAEs (including death, cardiac events, hospitalization for unstable angina pectoris) are parts of the study. There is no anticipated harm and compensation for trial participation.

Date management and organization

In order to ensure and monitor the progress of TARGET registry trial, a Trial Steering Committee (TSC) has been established including the authors of this study. As the principal investigators, YC and JY are responsible for co-leading the study. They will ensure the integrity and standardization of the study by managing and supervising the study activities and report of the finding as a whole. They will facilitate closely with the sub-center, by initiating and maintaining communication among the study staff of six sub-center, meeting with the faculty investigators every month, and providing continuous supervision and support. DS, ZW, MD, XM, XH, and HZ, as the investigators of sub-center, are mainly responsible for identifying potential recruitment and taking consensus. One data collector will be based at each sub-center and will be responsible for recruiting participants and obtaining data through regular interviews. The data management team, led by JY, will be responsible for the storage, analysis, and interpretation of quantitative data. The team will clean up the data and code measures at each point in time to ensure that the data is valid and easy to be interpreted. The sponsor played no part in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Data collected during the course of the research will be kept strictly confidential and only accessed by members of the trial team (or individuals from the sponsor organization or center sites where relevant to the trial). On the consent form, participants will be asked if they agree to use of their data should they choose to withdraw from the trial. Participants will also be asked for permission for the research team to

share relevant data with people from the hospital taking part in the research, where relevant. This trial does not involve collecting biological specimens for storage. At present, there is no plan to share the data with other teams or organizations. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Results will be disseminated via a peer-reviewed report to the sponsor, which will be freely available, and through open access journal articles and conference presentations. Standard journal authorship criteria will apply; there will be no use of professional writers.

Informed consent forms are available from the corresponding author on request. If it is necessary to amend protocol, we will notify the sponsor and funder first then the primary investigator will notify the centers, and a copy of the revised protocol will be sent to the primary investigator to add to the Investigator Site File. Any deviations from the protocol will be fully documented using a breach report form, and the amendment of protocol will be updated in the clinical trial registry.

Ethics statement

The study protocol is complied with the World Medical Association Declaration of Helsinki. Ethical clearance for the TARGET trial has been obtained from the ethical committee of Chinese PLA general hospital.

Ethics approval and consent to participate

The study protocol has been approved by the ethics committee of Chinese PLA general hospital and other 5 participating sites, including Qilu Hospital of Shandong University, Anzhen Hospital Capital Medical University, First Affiliated Hospital of Xinjiang Medical University, Second Affiliated Hospital School of Medicine Zhejiang University and Tongji Hospital Tongji Medical College Huazhong University of Science and Technology. We will obtain written informed consent from each patient before they are randomized. Participants may withdraw from the trial at any time for any reason.

Sample size calculation

The sample size is defined based on the rate of planned ICA without significant obstructive CAD within 90 days. Based on previous data and assuming the prevalence of non-obstructive CAD or intervention during ICA in usual care group is about 30%. The frequency of reduction in the primary endpoint is expected to be 30% for a≥90% power. Considering a drop-off up to 10%, the final overall population should be of 1216 patients.

Statistical analysis plan

Baseline characteristics will be presented. Continuous variables were described as mean ± Standard deviation (SD) or median (interquartile range), and compared between the groups using either Student's 2 sample t- test for paired or nonparametric Wilcoxon rank sum test. Categorical variables were summarized as counts (percentages) and compared using the Pearson chi-square test or Fisher exact test if cell frequencies

were insufficient. Kaplan-Meier survival curves and Cox-regression modelling will be used for time to event outcomes. The patient reported outcomes, such as Seattle Angina Questionnaire, will be compared between the two groups using 2 sample t-test. The total cardiac costs will be compared using nonparametric Wilcoxon rank-sum test) or a 2 sample t-test based on means of log transformed costs between the two groups, because of the expected skew in cost data. The hazard ratio (HR) is presented as 95% confidence intervals (CI). $P < 0.05$ is considered as significance in statistics. Because there are no anticipated problems that are detrimental to the participants, interim analyses and formal stopping procedure are not necessary for this trial. Missing values will be managed by using multiple imputation. If there is any non-adherence with the trial protocol and intervention plan, investigators will record it truthfully. Intention-to-treat analysis will be applied for patients who do not adhere to the intervention. In addition, all efficacy analyses were performed on a per-protocol set that excluded patients with major protocol deviations. Based on the data of the current study, further subgroup analysis will be conducted for the additional purpose in the future.

Analysis and reporting Plan

1. Disposition of the study population

A clear account of all patients who entered the trial will be produced. Withdrawal information including the primary reasons of discontinuation will be summarised and presented by group.

2. Protocol deviations

A listing of all Major or Potential/Serious Breach (Major protocol deviations with potential to affect patient safety/data) and Potential/Serious Breach (Major, Potential or Serious Breach of GCP guidelines or consistent non-compliance by site) will be produced (by patient and site where applicable).

3. Baseline and demographic characteristics and Treatment information (ITT population)

Summary statistics will be produced and presented by group for demographic and baseline characteristics, comparisons will be undertaken to investigate clinical importance of any imbalance.

4. Primary outcome (ITT population)

The primary endpoint of the present trial is comparison between the two arms in the rate of ICA without significant obstructive CAD or intervention within 90 days. The significant obstructive CAD is defined as more than or equal to 70% DS by quantitative coronary analysis or invasive FFR ≤ 0.8, if available during the procedure. Intervention includes stent implantation, balloon dilation and bypass surgery. This result will be showed by a Figure.

5. Secondary outcome: clinical outcomes (ITT population and PP population)

For the comparison of clinical outcomes between the two groups at 1 year. The number and proportion of experiencing at least one event, including: (a) hospitalization for unstable angina, (b) revascularization by PCI or CABG after 90 days, (c) non-fatal MI, and (d) cardiac death: any death because of immediate cardiac cause) will be reported and presented by group. Time to the first clinical event will be described using Kaplan Meier plots, presented by arm, and analysed using Cox regression

modelling.

6. Secondary outcome: medical cost outcomes (ITT population)

Total medical costs over 12 months of follow-up will be measured for each patient by sum of the numbers of key medical resources used between study entry and the 12 months follow-up point. The CT-FFR assessment is free during the trial, but the cost of CT-FFR will be add in the analysis based on a uniform market price once obtained. The total cardiac medical costs over follow-up will be compared between the two arms in an intention-to-treat fashion. The mean and median cost should be presented and compared in the two randomly assigned groups. The total cardiac cost was compared using a two-sample t-test after a log transformation if skew distribution of the data was found. If the distribution remains right-skewed after log transformation, a non-parametric Mann-Whitney tests will be needed to test the hypotheses that nine month costs differ between groups.

7. Secondary outcome: patient reporting outcome (ITT population)

For the questionnaire patient reported endpoints (Seattle Angina questionnaire-7) at 12 months, change scores from baseline to 12 months will be presented and mean (or median) change from baseline to 9 months will be compared between groups using t-tests (or the Wilcoxon rank-sum test), where appropriate.

8. Secondary outcome: radiation exposure outcome (ITT population)

The cumulative radiation exposure dose (ED) over the entire study period will be reported by assessing the original average dose for each test performed during the follow-up. In case the ED for each test is not known, we will use the standard ED available for each test in the literature.

9. Safety reporting (ITT population and PP population)

CCTA related serious adverse events will be recorded and summarized if any. A listing of serious adverse events will be provided for all related/unrelated SAEs.

10. Other analyses (ITT population and PP population)

If differences on the primary outcome are observed between groups, exploratory analyses into revascularization rate to determine what the drivers are will be carried out. Some results of diagnostic Strategy during initial management, as well as invasive coronary angiography, will be showed by tables and.