

Rationale and design of the Prospective Longitudinal Trial of FFR_{CT}: Outcome and Resource IMPacts study

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Background Fractional flow reserve (FFR) measured by coronary computed tomography angiography (FFR_{CT}) has been validated against invasive FFR. However, there are no data on how the use of FFR_{CT} affects patient care and outcomes. The aim of this study is to compare standard practice guided by usual care testing to FFR_{CT}-guided management in symptomatic subjects with suspected coronary artery disease (CAD).

Methods In this prospective nonrandomized trial, symptomatic patients with suspected CAD will be enrolled in 2 consecutive cohorts: a usual care-guided pathway (cohort 1) and an FFR_{CT}-guided pathway (cohort 2). Each cohort is divided into 2 groups according to whether noninvasive or invasive diagnostic testing was planned before enrollment. In all subjects, the patient's clinical team will review all diagnostic test results and determine a treatment strategy. A total sample size of 580 subjects will be enrolled and followed up for 12 months.

Results The primary end point is the comparison of the percentage of patients with planned invasive testing who have a catheterization (invasive coronary angiography) within 90 days from initial assessment, which does not show a significant stenosis (defined as coronary artery stenosis >50% or invasive FFR ≤0.80). Secondary end points include the rate of invasive coronary angiography without obstructive CAD in those with planned noninvasive testing and, in all groups, noninferiority of resource use, quality of life, medical radiation exposure, and major adverse cardiac events up to 365 days of follow-up.

Conclusions The study compares clinical and economic outcomes based on diagnostic evaluation using FFR_{CT} with that based on standard diagnostic strategies (Am Heart J 2015;0:1-9.e44.)

Noninvasive tests are commonly used to assess risk of coronary artery disease (CAD) and to identify patients for invasive coronary angiography (ICA). Despite the routine

use of these tests, only a minority of patients with suspected CAD referred for elective ICA have obstructive CAD.¹ The low diagnostic yield of elective ICA may be due to the limited accuracy of noninvasive functional stress tests. Coronary computed tomography angiography (cCTA) is a highly sensitive method to rule out the presence of CAD² with low radiation exposure,³ which also improves prognostic assessment.^{4,5} Despite its high negative predictive value, the positive predictive value may be limited, and it could be responsible for overestimation of CAD⁶ with poor correlation with invasive fractional flow reserve (FFR).⁷ Therefore, an optimal noninvasive test would characterize both the anatomy and functional significance of coronary lesions. A noninvasive method to determine FFR that computes the hemodynamics of coronary stenoses from subject-specific cCTA data (FFR measured by cCTA [FFR_{CT}]) (HeartFlow, Inc, Redwood City, CA) has recently been developed.⁸ Fractional flow reserve measured by cCTA has been validated using invasively measured FFR,⁹⁻¹¹ but

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there are no data on the clinical utility of this new method and how its use affects patient care and clinical outcomes. The present study was designed to compare subjects with suspected CAD receiving standard practice evaluation and treatment versus subjects receiving FFR_{CT}-guided management in terms of rate of finding no obstructive CAD at invasive ICA, resource utilization, medical radiation exposure, quality of life (QOL), and clinical outcomes.

Methods

Overall study design

The PLATFORM study is a postmarket, multicenter, longitudinal, prospective, consecutive cohort study (registration no. NCT01943903). The target population is symptomatic subjects suspected of having CAD with an intermediate likelihood (between 20% and 80%) of obstructive CAD based on updated Diamond-Forrester risk model score¹² referred for nonemergent, clinically indicated coronary testing. Exclusion criteria include (a) acute coronary syndrome; (b) previously documented CAD; (c) history of previous revascularization; (d) absolute or relative contraindications for cCTA or FFR_{CT}; (e) need for emergent procedure within 48 hours of presentation; (f) evidence of active clinical instability; (g) any active, serious, life-threatening disease with a life expectancy of <2 years; (h) inability to comply with study follow-up requirements; (i) current participation in any other clinical trial involving an investigational device or dictating care pathways at the time of enrolment; and (j) the performance of any noninvasive diagnostic testing within 90 days before enrolment or of ICA at any time in the past.

Consecutive patients who meet the inclusion criteria will be enrolled as cohort 1 and will receive the diagnostic evaluation planned at the time of enrollment, with care guided by this testing. Once the enrollment in cohort 1 has finished, each site will start to enroll consecutive patients in cohort 2, who will receive the intervention of a cCTA/FFR_{CT}-guided diagnostic evaluation instead of the planned noninvasive or invasive testing, with care guided by cCTA/FFR_{CT} (Figure 1). The timing of enrollment between cohort 1 and cohort 2 will be consecutive to avoid any potential inclusion bias related to intention to diagnose. The study population will be further divided, as follows:

Group 1A: Subjects for whom initial noninvasive testing is planned will be evaluated according to institutional standard practice. Based on the noninvasive testing results, the subjects may be referred for additional noninvasive tests or ICA and treated with medical therapy, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG).¹³

Group 1B: Subjects for whom nonemergent, clinically indicated ICA is planned will be studied by ICA with or without the addition of intravascular ultrasound, optical coherence tomography, or invasive FFR according to the standard practice. After ICA, the patients may be treated with medical therapy, PCI, or CABG following standard practice.¹³

Group 2A: Subjects enrolled in this group will have the same inclusion criteria as group 1A. However, instead of receiving the planned noninvasive test, they will be evaluated by cCTA plus FFR_{CT} (if a $\geq 30\%$ diameter stenosis in a vessel ≥ 2 mm in diameter according to cCTA is found). Fractional flow reserve measured by cCTA will be determined by HeartFlow, and results will be provided to the investigator within 48 hours. Subjects with cCTA image quality unacceptable for FFR_{CT} analysis will remain in the group and followed up in an “intention-to-diagnose” basis as will patients in whom no stenosis $\geq 30\%$ is found on cCTA. The institution's clinical team will review the results of all available diagnostic tests, including cCTA and FFR_{CT} and will recommend a treatment strategy accordingly.¹³

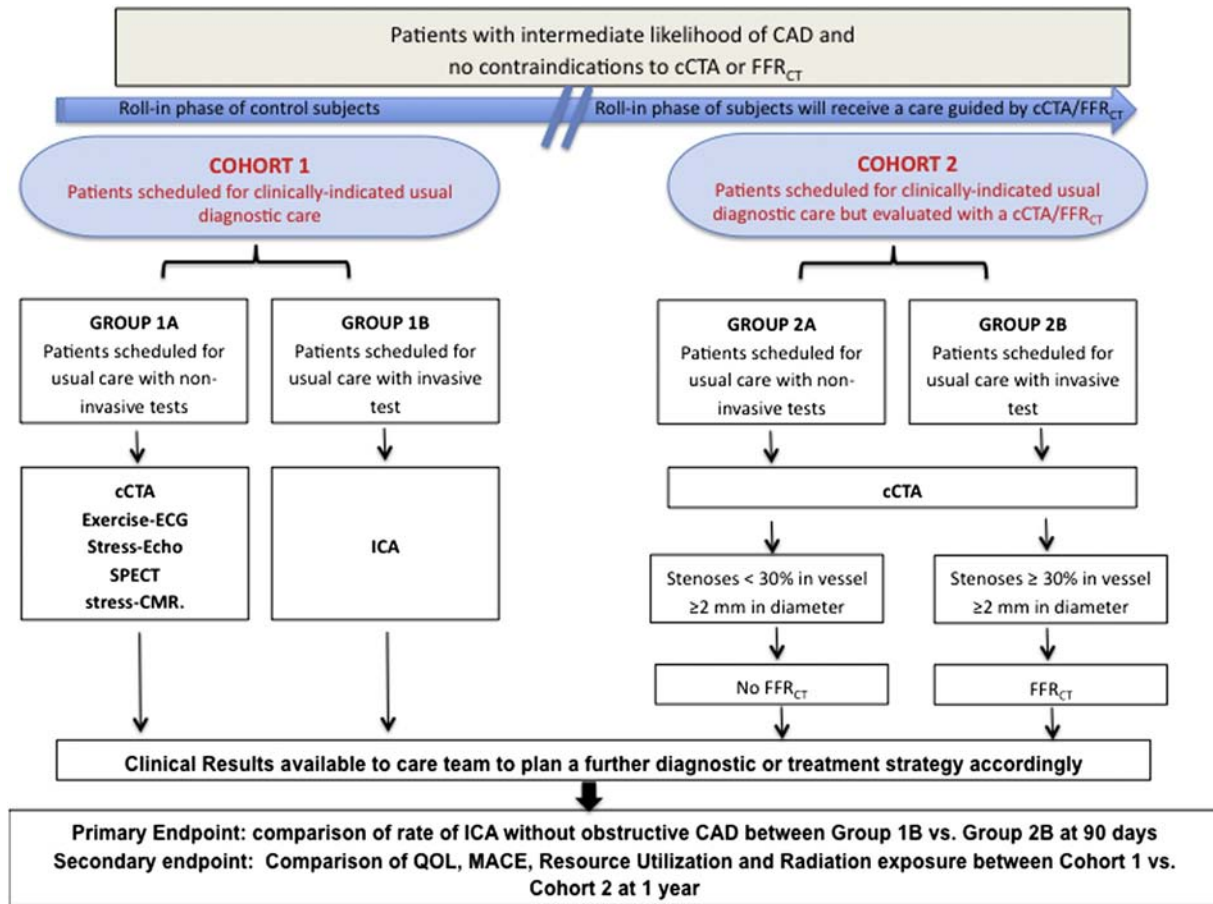
Group 2B: Subjects enrolled in this group will have the same inclusion criteria as group 1B. However, instead of receiving the planned ICA, they will be evaluated by cCTA plus FFR_{CT} (if a $\geq 30\%$ diameter stenosis in a vessel ≥ 2 mm in diameter according to cCTA is found). Similarly to group 2A, FFR_{CT} will be determined by HeartFlow, and results will be provided to the investigator within 48 hours. Subjects with cCTA image quality unacceptable for FFR_{CT} analysis will remain in the group and followed up in an “intention-to-diagnose” basis as will patients in whom no stenosis $\geq 30\%$ is found on cCTA. The institution's clinical team will review the results of all available diagnostic tests, including cCTA and FFR_{CT} and will recommend a treatment strategy accordingly.¹³

In Figures 2 and 3, 2 clinical cases from group 2B are described.

Screening procedure and enrolment

The PLATFORM study will be performed in 11 investigative European sites, and 580 subjects will be enrolled. No institution may enroll >145 subjects. The study protocol will be approved at each participating center by the local institutional review board, and all study subjects will provide written informed consent. Consecutive patients who are referred for nonemergent, clinically indicated coronary

Figure 1



PLATFORM study workflow. CMR, cardiac magnetic resonance; SPECT, single photon emission computed tomography.¹³

testing for suspected CAD will be screened for study eligibility by site personnel to identify symptomatic patients with suspected CAD, an intermediate likelihood of obstructive CAD, and no contraindications for cCTA and FFR_{CT}. Subjects who do not satisfy inclusion and exclusion criteria will be considered screening failures. Subjects meeting all selection criteria will be asked to provide written informed consent. A structured interview will be performed and a clinical history obtained, and the following cardiac risk factors will be assessed before the baseline test: (1) hypertension (blood pressure >140/90 mm Hg or use of antihypertensive agents), (2) smoking (currently or previously), (3) hyperlipidemia (low-density lipoprotein cholesterol >140 mg/dL), (4) diabetes mellitus (fasting glucose level >110 mg/dL or the need for insulin or oral hypoglycemic drugs), (5) family history of CAD in first-degree relatives, (6) home use of cardiovascular drugs (eg, statins, aspirin, and other antiplatelet agents), and (7) symptoms (atypical or typical angina as previously described to estimate the pretest likelihood of CAD).¹² Subjects will complete the baseline Seattle Angina Questionnaire Short

Form and QOL questionnaire (EQ-5D-5 L) before proceeding to diagnostic testing. Subjects who do not complete the first test within 30 days of providing informed consent will be considered screening failures. All subjects will be considered as “enrolled” upon initiation of the first test according to their group as previously described.

Coronary computed tomography angiography scan protocol

Coronary computed tomography angiography will be performed with single- or dual-source CT scanners. Each site will follow local coronary cCTA scanning protocols that meet the quality standards defined by the Society of Cardiac Computed Tomography.¹⁴

Coronary computed tomography angiography data set analysis

The analysis will be performed according to accepted guidelines for reporting.¹⁴ In each coronary artery, coronary atherosclerosis will be defined as any tissue structures larger than 1 mm² that exist either within the

Figure 2

Case example 1. A 59-year-old symptomatic female patient for atypical angina with family history for CAD, hypertension, smoking, and intermediate pretest likelihood of CAD with positive exercise electrocardiogram. The cCTA multiplanar reconstruction of left anterior descending artery showed a 45% (**A**, circle) and 55% stenosis involving origin of first diagonal branch (**B**, circle) with FFR_{CT} of 0.83 (**C**).

coronary artery lumen or adjacent to it that can be discriminated from the surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. Site investigators, unblinded to patient characteristics and symptoms, will evaluate luminal diameter stenosis in each segment of the coronary tree using the 18-segment model.¹⁴ Coronary lesions will be quantified for stenosis by visual estimation, and stenosis severity will be classified as none (0% luminal stenosis), very mild (1%-29% luminal stenosis), mild (30%-50% luminal stenosis), moderate (51%-70% luminal stenosis), obstructive (71%-90% luminal stenosis), sub-occluded (91%-99% luminal stenosis), occluded (100% luminal stenosis), or nonevaluable. A stenosis >50% is considered significant from anatomic point of view.

Fractional flow reserve measured by cCTA analysis

The analysis will be performed at HeartFlow core laboratory (HeartFlow, Inc) as previously described.^{8,11} Briefly, 3-dimensional blood flow simulations in the coronary vasculature will be performed with the use of updated proprietary software with quantitative image-quality analysis, improved image segmentation, refined physiologic models, and increased automation. The subject anatomy during a mid-diastolic time point will be modeled because this time point usually corresponds to the best imaging resolution. The simulations will use a 3-dimensional model of the aortic root and epicardial coronary arteries extracted from cCTA data and separate physiologic models, representing the heart, distal coronary vasculature, and downstream aortic conditions. The parameters of the models will be assigned by customizing coronary physiologic data to each individual patient-specific model. Coronary blood flow will be simulated under conditions that model intravenous infusion of adenosine to enable a comparison with pressure and flow data obtained during ICA. The simulation results will consist

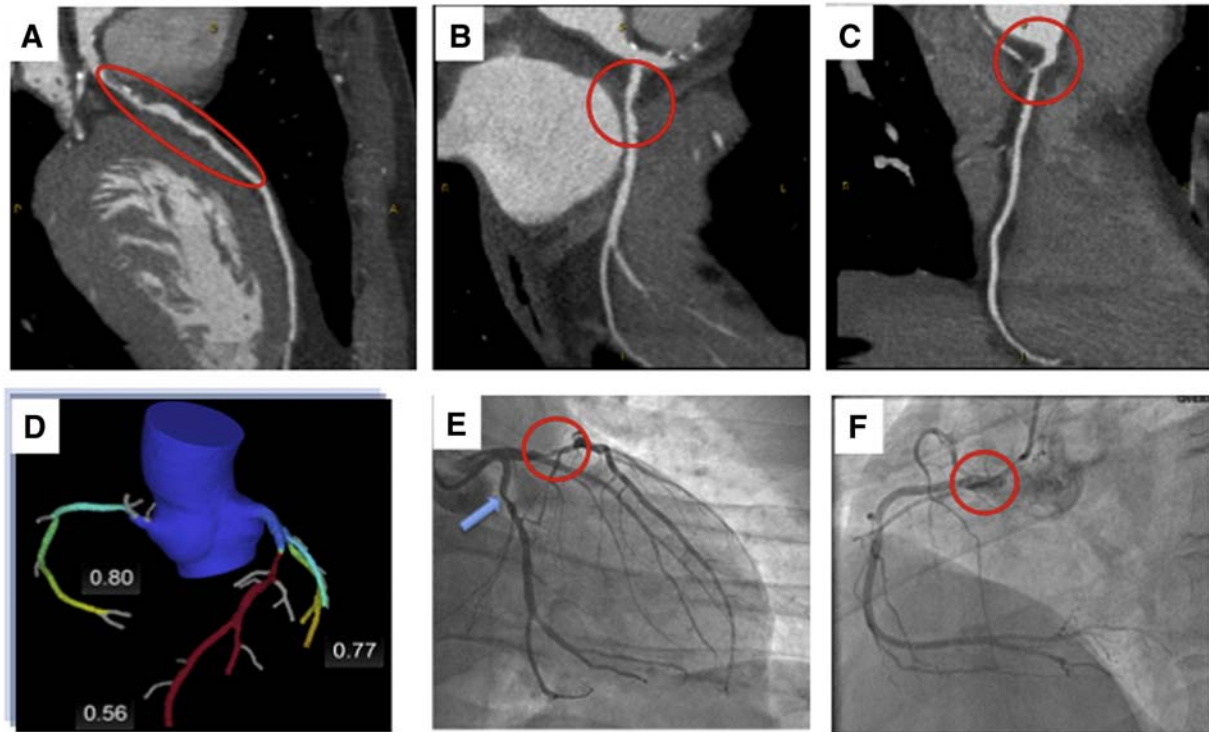
of pressure and flow in the proximal aorta and epicardial coronary arteries. An $FFR_{CT} \leq 0.80$ is considered pathologic.

Invasive coronary angiography protocol

Invasive coronary angiography will be performed by certified interventional cardiologists following usual clinical indications and imaging standards set forth by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Society for Cardiac Angiography and Interventions.¹⁵ Coronary segments will be classified by using the American Heart Association Classification system.¹⁵ Angiograms will be analyzed at the clinical site by clinicians unblinded to the clinical history of patients and to noninvasive test findings. If a stenosis > 40% is identified, the angiogram will be sent to an independent quantitative coronary angiography (QCA) core laboratory. At the QCA core laboratory, the severity of coronary stenosis will be quantified in 2 orthogonal planes by identifying the minimum diameter and reference diameter for all stenosis, and the percentage of stenosis is derived accordingly. If a total occlusion is observed, all segments distal to that occlusion will not be assessed. Additional invasive evaluation by intravascular ultrasound, optical coherence tomography, or FFR will be performed if clinically indicated according to the local institutional protocol. Results interpreted as showing any stenosis $\geq 50\%$ will be interpreted by an independent core laboratory using quantitative angiography, whose interpretation will be the basis of the primary analysis. A secondary analysis using stenosis severity classified at the clinical site will also be performed.

Primary decision treatment

The clinical team will review the diagnostic data available and make treatment recommendations, which will be categorized as (1) no changes to treatment, (2) medical

Figure 3

Case example 2. A 72-year-old symptomatic male patient with atypical angina and intermediate pretest likelihood of CAD and positive exercise electrocardiogram. The cCTA showed multiple 70 to 90% stenoses of left anterior descending artery (LAD) (**A**, circle) and 2 focal significant stenoses on proximal segments of left circumflex artery (LCX) (**B**, circle) and right coronary artery (**C**, circle). The FFR_{CT} showed values below 0.8 on the LAD and LCX suggesting a 2-vessel disease (D). The ICA confirmed lesions on LAD and LCX (**E**, circles), while showing no significant stenosis on right coronary artery (**F**, circle).

therapy, (3) additional noninvasive or invasive evaluation, and/or (4) PCI or CABG. Treatment recommendations, date of final recommendation, and identification of professional consultations contributing to the recommendations will be documented in the electronic "case report form" (CRF).

Follow-up

Patient follow-up will be performed by office visit or phone visit at 90 (+30/-15) days and 365 (+30/-15) days after the enrolment. The Seattle Angina Questionnaire Short Form and EQ-5D-5L QOL questionnaires will be administered at each visit; and the use of specific medications such as statins, aspirin, and antiplatelet agents will be recorded. The following clinical events will also be recorded: (a) noninvasive or invasive coronary diagnostic tests; (b) planned clinic or hospital visits for evaluation or treatment of CAD; (c) unplanned hospitalization due to persisting or increasing complaints of chest pain with or without ST-T changes leading to urgent revascularization performed within the same hospitalization; (d) vascular events related to invasive diagnostic or therapeutic coronary procedures occurring

within 14 days of invasive procedure; (e) nonfatal myocardial infarction as previously described¹⁶; and (f) cardiovascular death defined as any death due to immediate cardiac or vascular cause or noncardiovascular death, defined as any death not covered by the above definition. Unwitnessed death and death of unknown cause will be classified as cardiovascular death.

Accordingly, the following definitions will be used:

1. Major cardiac event (MACE) defined as composite variable including all-cause death, nonfatal myocardial infarction, and unplanned hospitalization for CAD leading to urgent revascularization. All potential MACE will be adjudicated by an independent clinical events committee.
2. Major cardiac event rate plus vascular complication defined as MACE plus vascular events related to invasive diagnostic or therapeutic coronary procedures, occurring within 14 days of invasive procedure.
3. Resource utilization composite variable comprising noninvasive cardiac testing, cardiac medication use, invasive diagnostic and therapeutic coronary

procedures, CAD-related hospitalizations, treatment of MACE, and treatment of vascular events related to invasive diagnostic or therapeutic coronary procedures.

Radiation exposure of medical diagnostic tests

For cCTA, the dose length product, defined as total radiation energy absorbed by patient's body, will be measured in milliGray (mGy) \times centimeters, and the effective radiation dose will be calculated as the product of dose length product times a conversion coefficient for the chest ($\kappa = 0.014$ mSv/mGy \times cm).¹⁷ For ICA, the effective radiation dose will be calculated by multiplying the dose area product by a conversion factor ($\kappa = 0.21$ mSv/mGy \times cm²) for lateral and posteroanterior radiation exposure in the chest area.¹⁷ For other diagnostic tests using ionizing radiation, the overall effective radiation dose will be estimated according to the data available in the literature.

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Effectiveness analysis

The primary end point will compare, in all patients with planned ICA, the difference at 90 days between standard clinical management and cCTA/FFR_{CT}-guided strategy in the rate of coronary angiography showing no obstructive CAD, defined as no stenosis $\geq 50\%$ by QCA in a vessel > 2.0 mm by quantitative coronary angiography or no invasively measured FFR ≤ 0.80 . The secondary end points will include the rate of ICA showing no obstructive disease in patients with planned noninvasive testing, and, in all groups, will compare (a) 90-day MACE rates, (b) MACE rate plus vascular complications, (c) resource utilization at 90 and 365 days, (d) per protocol analysis of primary end point in which group 2B patients who will undergo ICA without FFR_{CT} supporting the need for invasive evaluation will be excluded from the analysis, (e) change in QOL at 90 and 365 days, and (f) cumulative medical radiation exposure at 365 days.

Although the PLATFORM study is not a randomized trial, a number of design features enhance the methodological rigor of the study including the requirement of performing FFR_{CT} in cohort 2, analysis by group allocation rather than by actual care received, and inclusion of cohort 1 as contemporaneous usual care "control" patients. Two additional prespecified analyses of the primary end point are also included: the rate of finding no obstructive CAD among only the ICA patients and re-analysis by an independent central adjudicated determination of whether the FFR_{CT} results suggest a need for invasive catheterization.

Statistical analysis

General considerations

Statistical analyses will be performed using SAS or StatXact software or an equivalent. Data obtained from clinical records and entered into electronic case report/forms will be provided in separate data listings showing individual subject values. Baseline clinical characteristics will be summarized by counts and percentages for categorical data and by medians and interquartile ranges for continuous data.

End point analysis

Superiority (lower rate) in group 2B compared with group 1B of frequency of ICA documenting nonobstructive CAD at 90 days will be assessed and tested at the 1-sided 0.025 type I error rate. For the primary end point analysis, ICA findings interpreted by the independent QCA core laboratory will be used. A powered secondary end point analysis defined as noninferiority of cohort 2 with respect to the cohort 1 MACE rates at 90 days will be assessed and tested at the 0.05 type I error rate using 3% noninferiority margin. Events adjudicated by a clinical events committee will be the basis of this analysis. Secondary end point analysis comprising cost and clinical outcomes, QOL changes from baseline at 90 and 365 days, and cumulative radiation exposure at 365 days as previously described will be assessed and tested at the 1-sided 0.025 type I error rate between cohort 1 versus cohort 2, group 1A versus 2A, and group 1B versus 2B.

Propensity score matching analysis

Propensity score matching will be used to correct for any selection bias between cohorts with respect to the following covariates: age, sex, diabetes, smoking status, and angina status. Propensity score matching will be used on the primary end point only if selection bias is found between group 1B and 2B. Propensity score matching will be used on the secondary end points only if selection bias is found between cohorts 1 and 2 or group 1A and 2A. If ≥ 2 of the compared baseline characteristics are found to differ across cohorts, a logistic regression will be used with cohort as the dependent variable and all compared baseline characteristics as the independent variables. If the baseline characteristics with suspected selection bias are found to be significant predictors of cohort, then propensity scores will be obtained from the regression coefficients of the biased baseline characteristics. If the biased baseline characteristics are not found to be significant, then selection bias will be considered insignificant, and propensity score matching will be stopped. If the biased baseline characteristics are found to be significant, a new data set will be created by matching propensity scores between the cohorts. Matching will be done using nearest matching paradigm where cohorts will be matched based on propensity score, and

propensity score differences >0.5 will be considered unmatched.

Sample size determination

The frequency of ICA documenting nonobstructive CAD is expected to be 30% in group 1B and 15% in group 2B. Thus, 346 subjects will yield 90% power to declare superiority of group 2B with respect to group 1B at 1-sided 0.025 level of significance, based on the Fisher option of Proc Power in SAS 9.3, assuming asymptotic normal distribution and using normal approximation method. Assuming a dropout rate of approximately 10%, a total of 380 group 1B and 2B subjects should be enrolled (190 group 1B subjects and 190 group 2B subjects). The true MACE rate for both groups is expected to be 2%. Should the MACE rate for cohort 1 and 2 be 2%, then 540 subjects will yield 80% power to declare noninferiority of cohort 2 with respect to cohort 1 at 1-sided 0.05 level of significance with 3% noninferiority margin. Sample size was calculated using χ^2 option of Proc Power SAS 9.3 assuming asymptotic normal distribution and using normal approximation method. Group 1B and group 2B subjects and additional 200 group 1A and group 2A subjects (100 subjects each) are enrolled, then total sample size of 580 subjects will yield 82% power to reject both first (i) and second (ii) null hypotheses.

Discussion

The appropriateness of indications for referral to ICA and coronary revascularization and their related costs have recently caused great interest in the health care community.¹⁸⁻²⁰ European Society of Cardiology clinical guidelines recommend an observational strategy in patients with a low likelihood of CAD, direct referral for invasive evaluation for patients at high risk for CAD, and noninvasive stress testing for patients with intermediate pretest likelihood of CAD.²¹ Intermediate-risk patients are the most common population referred for clinical evaluation, but the diagnostic yield of elective ICA in this setting has been low despite the extensive use of noninvasive stress testing. In a US national registry, the prevalence of obstructive CAD was only one-third among consecutive patients with suspected CAD referred to ICA, despite most study population had a prior noninvasive test.¹ These data suggest that current strategies to make decisions regarding the indication for ICA need to be improved substantially.

Coronary computed tomography angiography has been proven to be a robust technique for diagnosis² and prognostic stratification of patients with suspected CAD^{4,5} with low radiation exposure.³ However, its accuracy is challenged by the limited spatial resolution and coronary calcification.⁶ Indeed, cCTA is less effective in calcified lesion quantification with a risk of

misdiagnosis usually due to an overestimation of CAD even in cases where a high-definition scanner is used.⁶ This limitation is partially responsible for the high false-positive rate and for the frequent need for additional and expensive second level functional tests after equivocal cCTA. Moreover, the need for functional evaluation of CAD has been underscored by the results of the FAME trials showing improved outcomes when invasive FFR is used to guide coronary revascularization.^{19,20} Fractional flow reserve measured by cCTA using computational fluid dynamics at rest and under simulated maximal coronary hyperemic conditions has been recently developed⁸ with the aim of improving the specificity and positive predictive value of cCTA alone and providing combined noninvasive anatomic and functional assessment of CAD in a 1-step scan without the need of additional functional tests in case of obstructive CAD at anatomic evaluation. Prospective multicenter studies have validated the accuracy of FFR_{CT} compared with invasive FFR.⁹⁻¹¹ In early studies, FFR_{CT} increased the C statistic from 0.75 up to 0.91 when compared with cCTA alone in a segment based model and from 0.68 to 0.81⁹ at the patient level.¹⁰ More recently, the NXT trial,¹¹ using the improved FFR_{CT} algorithms, has demonstrated per-patient sensitivity of 86% and specificity of 79%, with C statistic of 0.9 as compared with invasive FFR. More importantly, in patients with intermediate stenoses and in patients with calcium score >400 , the diagnostic performance of FFR_{CT} remained unchanged, and FFR_{CT} reduced by 68% the number of false-positive cases due to calcified lesions. The validation of FFR_{CT} suggests its use may be cost effective in intermediate-risk patients. A simulation of the impact of FFR_{CT} as gatekeeper to guide the selection of patients for ICA and PCI predicted 30% lower costs and 12% fewer events at 1 year compared with the standard of care.²² Whether these results can be achieved in real clinical world clinical practice is the crucial question that will be addressed by the PLATFORM study.

Trial status

The first subject was enrolled in October 2013, and the enrolment will be completed by the end of November 2014.

Conclusions

The PLATFORM study will provide information to patients, health care providers, and other stakeholders about the most effective and efficient technologies for the diagnosis and management in symptomatic patients with an intermediate risk of CAD.

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Disclosures

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