Coronary artery disease

Clinical outcomes of fractional flow reserve by computed tomographic angiography-guided diagnostic strategies vs. usual care in patients with suspected coronary artery disease: the prospective longitudinal trial of \( FFR_{\text{CT}} \): outcome and resource impacts study

Pamela S. Douglas\(^1\)\*, Gianluca Pontone\(^2\), Mark A. Hlatky\(^3\), Manesh R. Patel\(^1\), Bjarne L. Norgaard\(^4\), Robert A. Byrne\(^5\), Nick Curzen\(^6\), Ian Purcell\(^7\), Matthias Gutberlet\(^8\), Gilles Rioufol\(^9\), Ulrich Hink\(^10\), Herwig Walter Schuchlenz\(^11\), Gudrun Feuchtner\(^12\), Martine Gilard\(^13\), Daniele Andreini\(^2\), Jesper M. Jensen\(^4\), Martin Hadamitzky\(^3\), Karen Chiswell\(^1\), Derek Cyr\(^1\), Alan Wilk\(^14\), Furong Wang\(^14\), Campbell Rogers\(^14\), and Bernard De Bruyne\(^15\), on Behalf of the PLATFORM Investigators†

\(^1\)Duke Clinical Research Institute, Duke University School of Medicine, 7022 North Pavilion DUMC, PO Box 17969, Durham, NC 27715, USA; \(^2\)Centro Cardiologico Monzino, IRCCS, University of Milan, Milan, Italy; \(^3\)Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA, USA; \(^4\)Department of Cardiology, Aarhus University Hospital, Aarhus Stedhospitalet, Denmark; \(^5\)Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; \(^6\)University Hospital Southampton NHS Trust, Southampton, UK; \(^7\)Freeman Hospital, Newcastle upon Tyne, UK; \(^8\)University of Leipzig Heart Centre, Leipzig, Germany; \(^9\)Hospices Civils de Lyon et CARMEN INSERM 1060, Lyon, France; \(^10\)Department of Cardiology, Johannes Gutenberg University Hospital, Mainz, Germany; \(^11\)LKH Graz West, Graz, Austria; \(^12\)Department of Radiology, Innsbruck Medical University, Innsbruck, Austria; \(^13\)Department of Cardiology, Cavale Blanche Hospital, Brest, France; \(^14\)HeartFlow, Redwood City, CA, USA; and \(^15\)Cardiovascular Centre Aalst, Aalst, Belgium

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Aims

In symptomatic patients with suspected coronary artery disease (CAD), computed tomographic angiography (CTA) improves patient selection for invasive coronary angiography (ICA) compared with functional testing. The impact of measuring fractional flow reserve by CTA (\( FFR_{\text{CT}} \)) is unknown.

Methods and results

At 11 sites, 584 patients with new onset chest pain were prospectively assigned to receive either usual testing (\( n = 287 \)) or CTA/\( FFR_{\text{CT}} \) (\( n = 297 \)). Test interpretation and care decisions were made by the clinical care team. The primary endpoint was the percentage of those with planned ICA in whom no significant obstructive CAD (no stenosis \( \geq 50\% \) by core laboratory quantitative analysis or invasive FFR < 0.80) was found at ICA within 90 days. Secondary endpoints including death, myocardial infarction, and unplanned revascularization were independently and blindly adjudicated. Subjects averaged 61 ± 11 years of age, 40% were female, and the mean pre-test probability of obstructive CAD was 49 ± 17%. Among those with intended ICA (\( FFR_{\text{CT}} \)-guided = 193; usual care = 187), no obstructive CAD was found at ICA in 24 (12%) in the CTA/\( FFR_{\text{CT}} \) arm and 137 (73%) in the usual care arm (risk difference 61%, 95%...
Introduction

Stable chest pain is a common clinical presentation that often requires further investigation using non-invasive or invasive testing. The goals of testing include clarifying the diagnosis, documenting the presence or absence of coronary artery disease (CAD), and directing subsequent care, whether revascularization, intensified medical treatment, or both, while maximizing efficiency and patient safety. The recently completed PROMISE 3 and SCOT-HEART 4 trials suggest that an evaluation strategy based on coronary computed tomographic angiography (CTA) increases diagnostic certainty, improves efficiency of triage to invasive catheterization, and may reduce radiation exposure when compared with functional stress testing, with similar rates of cardiac events. Moreover, in PROMISE, CTA increased the rate of invasive catheterization by almost 50% compared with functional testing, and over a quarter of these patients did not have obstructive CAD identified by invasive angiography. Since CTA provided only anatomic information and invasive fractional flow reserve (FFR) was rarely used, revascularizations guided by a CTA strategy were generally performed without evidence of the functional significance of coronary stenoses, at variance with practice guidelines. This is an important consideration since CTA in PROMISE doubled the rate of coronary revascularization compared with functional testing.

A diagnostic strategy that provides both anatomic and functional data could address this limitation and potentially afford enhanced efficiency and safety. Recently, a non-invasive method to determine data could address this limitation and potentially afford enhanced efficiency and safety. Recently, a non-invasive method to determine anatomic information and invasive fractional flow reserve (FFR) was rarely used, revascularizations guided by a CTA strategy were generally performed without evidence of the functional significance of coronary stenoses, at variance with practice guidelines. This is an important consideration since CTA in PROMISE doubled the rate of coronary revascularization compared with functional testing.

Study participants

PLATFORM subjects were symptomatic outpatients ≥18 years old without known CAD, but with an intermediate likelihood of obstructive CAD, whose physician had planned non-emergent, non-invasive, or invasive cardiovascular testing to evaluate suspected CAD. Exclusion criteria were (i) acute coronary syndrome or clinical instability, (ii) previously documented CAD, (iii) contraindications to CTA, and (iv) needed emergent or urgent procedure. Additional exclusion criteria included recent cardiovascular testing (<90 days) (see Supplementary material online, Table S1 for full inclusion and exclusion criteria).

Methods

Study design

PLATFORM is a prospective, consecutive cohort study utilizing a comparative effectiveness observational design (ClinicalTrials.gov number NCT01943903). The study was conducted with fidelity to the protocol (see Supplementary material online). Local or central institutional review boards approved the study at the 11 enrolling European sites and at Duke Clinical Research Institute (DCRI); all subjects provided written informed consent.

Study procedures

Subjects were enrolled in two consecutive cohorts assigned to receive the planned usual care testing or CTA/FFRCT testing. All sites enrolled patients into both cohorts, and each site had to complete enrolment of the planned number of usual care subjects before enrolling any CTA/FFRCT subjects. Each cohort was subdivided into two groups based on the evaluation plan decided upon before enrolment in the study: non-invasive testing (any form of stress testing or CTA without FFRCT) or invasive coronary angiography (ICA) (Figure 1). For balance, no centre could enrol >30 subjects in either planned non-invasive group or >145 subjects in the trial.

In the CTA/FFRCT cohort, all subjects underwent CTA instead of the planned non-invasive or invasive evaluation. Fractional flow reserve by computed tomographic angiography analyses were performed centrally when requested by the site (recommended if the CTA revealed ≥30% stenosis or if the patient was referred to ICA). Optimal medical therapy was encouraged in all groups, and local physicians made all subsequent clinical decisions following standard practice, including cancelling or ordering additional testing or procedures. Follow-up visits were performed at 90 days, 6 months, and 12 months from study entry. Enrolment began on 10 September 2013 and was completed on 26 November 2014. There were no major protocol amendments. This article reports 90-day clinical results.

Diagnostic non-invasive and invasive testing

All usual care testing, including CTA, was performed and interpreted locally according to standard practices at the enrolling site. All CTAs utilized a ≥64-slice multi-detector, single- or dual-source CT scanner and followed scanning protocols satisfying Society of Cardiac Computed Tomography quality standards. An independent angiographic core laboratory (DCRI) performed all quantitative coronary angiography (QCA) measurements using QAngio software (Medis, the Netherlands) according to standard procedures.
Fractional flow reserve by computed tomographic angiography analysis was performed centrally (HeartFlow) as previously described. Briefly, three-dimensional blood flow simulations in the coronary vasculature were performed using proprietary software, with quantitative image quality analysis, image segmentation, and physiological modeling using computational fluid dynamics. Coronary blood flow was simulated under conditions that modeled intravenous adenosine to mirror pressure and flow data and the FFR numeric values that would have been obtained during an invasive evaluation. Data provided to the clinical site included the lowest FFRCT numeric value in each coronary distribution, and color-scale representations of the coronary tree showing FFRCT values in all vessels 1.8 mm in diameter (see Supplementary material online for a sample FFRCT report).

Effectiveness and safety endpoints

The primary endpoint was the rate of ICA within 90 days that showed no obstructive CAD in patients who had invasive testing planned before enrollment, comparing those receiving usual care to those allocated to CTA/FFRCT. Obstructive disease was defined as either (i) an invasively measured FFR ≤ 0.80 in any segment, regardless of degree of stenosis, or (ii) QCA stenosis ≥ 50% in a vessel ≥ 2.0 mm diameter without an invasively measured FFR > 0.80 in the same distribution (see Supplementary material online, Table S2 for endpoint definitions). A secondary endpoint was the comparison of the rate of ICA with no obstructive CAD in those with planned non-invasive testing. The major safety endpoint was a composite of major adverse cardiovascular events (MACE) at 90 days: all-cause mortality, myocardial infarction (MI), and unplanned hospitalization for chest pain leading to urgent revascularization. An independent clinical events committee (DCRI) adjudicated all MACE in a blinded fashion based on standard, prospectively determined definitions.

Cumulative radiation exposure within 90 days of study entry included all cardiovascular tests and invasive procedures, including CTA, myocardial perfusion imaging, and ICA. Radiation exposure for study CTAs was calculated from dose length product measured in mGy cm using the formula mSv = (dose length product) × 0.014, or was imputed using the median measured value; other exposures were imputed using standard published doses of 7 mSv for ICA, 15 mSv for percutaneous coronary intervention, and 14 mSv for myocardial perfusion imaging.

Statistical analysis

The primary endpoint (rate of ICA showing no obstructive CAD in patients with invasive testing planned prior to enrollment) was compared between the usual care invasive testing vs. CTA/FFRCT-guided care arms. The risk difference and 95% confidence interval (CI) were determined, and a one-sided Wald test (α error = 0.025) for a risk difference < 0 was used to evaluate whether CTA/FFRCT was superior to usual testing. Enrolment of 380 subjects in the planned invasive care arm (190 usual care and 190 CTA/FFRCT-guided) was estimated to provide the study with 90% power to detect a 50% reduction in the frequency of ICA documenting non-obstructive CAD at a one-sided 0.025 level of significance, assuming an event rate of 30% in the usual care arm and 15% in the CTA/FFRCT-guided arm, and a dropout rate of 10%.
All statistical assessments were independently confirmed by DCRI. All analyses were performed comparing patients as allocated, either in aggregate or within the planned non-invasive or invasive test groups. Exceptions to this include four additional analyses of the primary endpoint: (i) reanalysis in propensity score matched subpopulations of subjects using age, sex, diabetes, smoking status, and type of angina (see below); (ii) assessment in pre-specified subgroups: age, sex, race/ethnicity, diabetes status, pre-test probability of obstructive CAD (updated Diamond and Forrester score), and country of enrolment; (iii) acceptable image quality population excluding subjects in the CTA/FFRCT arm with unavailable or uninterpretable CTA images; and (iv) best practices per care and CTA/FFRCT CT-guided care cohorts. Continuous variables are presented as mean ± SD and were compared using the Pearson test, or with Fisher’s exact test if cell frequencies were not sufficient. Categorical variables are presented as counts (percentages) and were compared using the Pearson χ² test, or with Fisher’s exact test if cell frequencies were not sufficient.

The level of statistical significance was set to 0.0025 using the Bonferroni correction to adjust for multiple comparisons.

Although extensive analysis of baseline characteristics indicated no significant differences between the cohorts, since group assignment was not randomized, a sensitivity analysis of the primary endpoint was performed using propensity score matching (see Supplemental material online for propensity scoring methods used). The propensity score was estimated based on age, sex, diabetes, smoking status, and type of angina using multivariable logistic regression, and subjects were matched using a greedy algorithm.

All analyses were performed using SAS version 9.3 (Cary, NC, USA), and a P-value of <0.05 was considered statistically significant, unless otherwise specified. No interim analyses were performed.

### Results

#### Study population

The study population (Figure 1) consisted of 584 enrolled and consented patients followed for 90 days. Complete 12-month follow-up is planned; 90-day data were obtained in 563 subjects (96.4%).

### Table I Baseline characteristics of the study participants, according to study group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Planned non-invasive test (N = 204)</th>
<th>Planned invasive test (N = 380)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Usual care strategy (n = 100)</td>
<td>FFRCT-guided strategy (n = 104)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
<td>57.9 ± 10.7</td>
<td>59.5 ± 9.3</td>
</tr>
<tr>
<td>Female sex, no. (%)</td>
<td>34 (34.0)</td>
<td>44 (42.3)</td>
</tr>
<tr>
<td>Racial/ethnic minority (self-reported), no. (%)</td>
<td>5 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Cardiac risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, mean ± SD (kg/m²)</td>
<td>26.0 ± 3.0</td>
<td>27.3 ± 3.9</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>38 (38.0)</td>
<td>57 (54.8)</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>8 (8.0)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Dyslipidaemia, no. (%)</td>
<td>22 (22.0)</td>
<td>28 (26.9)</td>
</tr>
<tr>
<td>Current or past tobacco use, no. (%)</td>
<td>52 (52.0)</td>
<td>59 (56.7)</td>
</tr>
<tr>
<td>Mean number of risk factors ± SDa</td>
<td>1.2 ± 0.93</td>
<td>1.4 ± 0.92</td>
</tr>
<tr>
<td>Pre-test probability of obstructive CAD ± SDb (%)</td>
<td>44.5 ± 15.3</td>
<td>45.3 ± 16.8</td>
</tr>
<tr>
<td>Relevant medications, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>29 (29.0)</td>
<td>45 (43.3)</td>
</tr>
<tr>
<td>Statin</td>
<td>24 (24.0)</td>
<td>29 (27.9)</td>
</tr>
<tr>
<td>Anginal type, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical angina</td>
<td>8 (8.0)</td>
<td>18 (17.3)</td>
</tr>
<tr>
<td>Atypical angina</td>
<td>91 (91.0)</td>
<td>80 (76.9)</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>1 (1.0)</td>
<td>6 (5.8)</td>
</tr>
</tbody>
</table>

BMI, body mass index (weight in kilograms divided by the square of the height in metres); CAD, coronary artery disease; CT, computed tomographic angiography; SD, standard deviation.

aIncludes hypertension, diabetes, dyslipidaemia, and tobacco use.
bMean pre-test probability of obstructive CAD ± SD calculated by updated Diamond and Forrester score.¹⁶
Baseline characteristics

Patient age averaged 60.9 years and 231 (39.6%) were women (Table 1). Diabetes was present in 13.7%, hypertension in 54.3%, history of smoking in 53.9%, and dyslipidaemia in 34.8% (Table 1). Typical chest pain was the presenting symptom in 123 (21.1%) and atypical pain in 435 (74.5%). The mean pre-test probability of obstructive CAD was 49 ± 17%. All baseline characteristics were similar between the usual care and FFRCT-guided care cohorts and within the planned non-invasive and invasive test groups.

Allocation and testing

Among the 204 participants who had a non-invasive test planned for cardiac evaluation, 100 were allocated to usual care (Figure 1). The non-invasive tests performed are listed in Supplementary material online, Table S3. One hundred and four patients were allocated to CTA/FFRCT, and 39 patients (37.5%) had at least one site interpreted as ≥50%. Fractional flow reserve by computed tomographic angiography was requested in 67 patients (64.4%), but was not completed in 7 (10.4%), due to poor image quality or inadequate acquisition.

Among the 380 participants who had an invasive catheterization (ICA) planned, 187 were allocated to and received ICA (usual care) and 193 patients were allocated to and received a CTA/FFRCT; 118 patients (61%) had a stenosis ≥50%. Fractional flow reserve by computed tomographic angiography was requested in 134 (69.4%) but was not completed in 17 (12.7%). Overall, there was one reported adverse event from CTA testing, a mild contrast reaction.

Outcome measures

Rates of ICA and findings of no obstructive disease by QCA and/or FFR in the planned non-invasive testing group are shown in Table 2. There was no difference in the secondary endpoint of the cohort rate of ICA which did not show obstructive CAD according to QCA: 6.0% usual care vs. 12.5% CTA/FFRCT; P = 0.95 (Table 2).

Among patients in the planned invasive testing groups, 187 patients (100%) underwent an ICA within 90 days in the usual care cohort, and 137 (73.3%) catheterizations did not show obstructive disease by QCA and/or FFR (Figure 2, Table 2). In the CTA/FFRCT cohort, 76 (39.4%) underwent ICA, with 24 (31.6%) catheterizations showing no obstructive CAD. The primary endpoint of the rate of ICA which did not show obstructive CAD in the planned invasive testing group was found in substantially more subjects in the usual care arm at 137 (73.3%) of 187 compared with 24 (12.4%) of 193 in the CTA/FFRCT arm (risk difference 60.8%, 95% CI 53.0–68.7%, P < 0.0001). Propensity score matching resulted in inclusion of 148 patients in each group and yielded similar results (72% usual care vs. 12% CTA/FFRCT, P < 0.0001; see Supplementary material online, Table S4), as did analysis of acceptable CTA image quality (CAD was not found in 11.4% of the CTA/FFRCT arm), and a best practices/per protocol analysis (obstructive CAD was not found in 7.2%). Results were also similar in all subgroups examined (see Supplementary material online, Table S5).

Only two MACE events occurred in the planned ICA group assigned to CTA/FFRCT-guided care. One was a peri-procedural MI in a subject whose CTA was of insufficient quality for FFRCT analysis, and the other was hospitalization for urgent revascularization.

<table>
<thead>
<tr>
<th>Table 2 Ninety-day outcomes according to study group</th>
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<tbody>
<tr>
<td>Planned non-invasive test (n = 204)</td>
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<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Invasive catheterization without obstructive CAD by core lab quantitative coronary angiography</td>
</tr>
<tr>
<td>No. (%)</td>
</tr>
<tr>
<td>Risk difference, % (95% CI)</td>
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<tr>
<td>Invasive catheterization without obstructive CAD by site interpretation</td>
</tr>
<tr>
<td>No. (%)</td>
</tr>
<tr>
<td>Risk difference (95% CI)</td>
</tr>
<tr>
<td>Secondary endpoint composite, MACE, no. (%)</td>
</tr>
<tr>
<td>All-cause death</td>
</tr>
<tr>
<td>Non-fatal MI</td>
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<tr>
<td>Hospitalization with urgent revascularization</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>MACE or vascular complications, no. (%)</td>
</tr>
<tr>
<td>Cumulative radiation exposure (enrolment to 90 days)</td>
</tr>
<tr>
<td>Mean ± SD (mSv)</td>
</tr>
<tr>
<td>Median (IQR) (mSv)</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; CTA, computed tomographic angiography; MI, myocardial infarction; MACE, major adverse cardiovascular events; CI, confidence interval; IQR, inter-quartile range; SD, standard deviation.
following a CTA/FFRCT showing severe CAD. There were no events in the 61% of CTA/FFRCT patients in whom ICA was cancelled. Vas- cular complications were similarly rare (Table 2). Rates of MACE and vascular complications were too low to assess non-inferiority.

Cumulative radiation exposure in patients with an intended non-invasive evaluation is shown in Table 2. In patients with an intended invasive evaluation, cumulative radiation exposure to 90 days was similar in the usual care cohort (9.4 mSv) and the CTA/FFRCT co-hort (9.9 mSv, \(P = 0.2\)). Across both CTA/FFRCT cohorts, CTA radiation averaged 5.2 ± 5.4 mSv (9.0 ± 6.7 mSv for retrospectively scanned, 3.0 ± 1.6 mSv for prospectively gated scans).

There were no differences in rates of revascularization in subjects allocated to CTA/FFRCT vs. usual care in either the planned non-invasive or planned invasive testing arms; \(P = 0.29\) and 0.58.

**Information available for invasive catheterization and revascularization**

In subjects in the planned non-invasive group proceeding to ICA or revascularization, there were no differences between the two arms in the proportion with functional data available (see Supplementary material online, Table S6).

In subjects in the planned invasive group proceeding to ICA, functional information was available in 83 of the 187 (44.4%) usual care subjects compared with 74 of 76 (97.4%) in the CTA/FFRCT group; \(P < 0.0001\). Among those proceeding to revascularization, functional information was available in 30 of 59 (50.8%) in the usual care cohort vs. 53 of 55 (96.3%) patients in the CTA/FFRCT; \(P < 0.0001\).

**Discussion**

Current guidelines recommend that stable chest pain patients be evaluated with non-invasive stress testing, yet the rates of invasive angiograms showing no obstructive CAD remain high.\(^{18,19}\) The PLATFORM study showed that, in patients with planned ICA, a diagnostic strategy based on CTA/FFRCT yield a significantly lower rate of ICA showing no obstructive CAD. In patients with planned non-invasive testing, there was no difference between use of CTA/FFRCT and usual care. Clinical events through 90 days were rare with either strategy.

The goals of the diagnostic evaluation of patients with stable chest pain include identifying those individuals needing catheterization as well as those who cannot benefit, and providing optimal guidance for subsequent care. Two recent trials provide evidence that non-invasive visualization of the coronary arteries using CTA enhances diagnostic certainty and appropriately alters diagnostic and therapeutic plans, with comparable clinical outcomes.\(^3,4\) However, CTA increased the rate of referral to ICA and revascularization by up to 50%.\(^3\) Because the use of adjunctive invasive measures such as FFR to assess haemodynamic significance was rare, keeping with current practice,\(^20\) a CTA-only strategy resulted in revascularization with little understanding of the ischaemia-producing potential of coronary lesions, as recommended for appropriate revascularization and optimal outcomes.\(^5,21,22\) Our data demonstrate that it is possible to obtain both anatomic and functional information non-invasively, and that doing so reduces the rate of finding no obstructive CAD at catheterization among those with planned ICA.

The low adverse clinical event rate in PLATFORM is similar to recent trials\(^3,4\) and indicates that studies of non-invasive testing in a contemporary chest pain population should, in addition to clinical events, consider use of endpoints such as changes in care plans, efficiency of diagnosis, and quality of information guiding care. To this end, the remarkable reduction in the primary endpoint of not finding obstructive CAD at ICA, and the lower overall rate of ICA, coupled with the higher rate of revascularizations informed by haemodynamic significance or ischaemia, suggest that use of CTA/FFRCT more effectively triages patients for invasive procedures than usual care strategies.
The rate of finding no obstructive CAD in our usual care ICA patients was high, but was determined by core laboratory QCA. The corresponding rate using site visual readings was lower (57%), identical to population studies, reporting that 54–62% of elective catheterizations do not have obstructive disease. The higher rate by QCA is consistent with known differences between the two assessment techniques.

Although FFR_{CT} is a relatively new technique, PLATFORM demonstrates that it is feasible and safe in busy clinical settings. Overall, 90% of CTAs had acceptable image quality for analysis, and radiation averaged 5.2 ± 5.4 mSv, less than the average level of 14 mSv noted in the literature for nuclear stress testing. Use of FFR_{CT} improved the availability of functional data available in those referred to ICA (96% CTA/FFR_{CT} vs. 45% usual care), and those referred to revascularization (95% CTA/FFR_{CT} vs. 55% usual care), allowing compliance with current recommendations supporting use of both anatomic and functional data in decision-making. While still high, the rate of revascularization performed without functional data in usual care patients is improved from previous reports of 55%.

PLATFORM adds substantially to both the PROMISE and SCOT-HEART trials. Compared with PROMISE, the addition of FFR_{CT} functional information in PLATFORM to the anatomic CTA information prevented the reported ~50% increase in catheterizations and revascularizations. PLATFORM builds on SCOT-HEART’s finding of increased diagnostic certainty with CTA by noting cancelation of ICA in 61% of the CTA/FFR_{CT} arm and a dramatically lower rate of finding no obstructive CAD. Like these studies, PLATFORM provides prospective data essential to evaluating and optimizing the role of non-invasive testing as a gatekeeper to catheterization.

While PLATFORM has many strengths, it is important to note that the sample size and follow-up duration are insufficient to detect an impact on clinical outcomes. Although not randomized, PLATFORM differs substantially from most observational studies by requiring a carefully controlled ‘experimental’ intervention in the CTA/FFR_{CT} groups, and core lab angiographic reading. The study’s rigour is further enhanced by basing all analyses on the prospective allocation of patients into cohorts regardless of actual care. Use of an initial roll-in group of usual care ‘control’ patients provided a detailed, real-time snapshot of contemporaneous practice at enrolling centres, rather than using historical controls. Even in a randomized trial it would have been impossible to blind investigators to the results of testing since they are needed for clinicians to determine downstream care. Further, the current approach reflects clinical research trends favouring pragmatic design and effectiveness (vs. efficacy) evaluations. The multiple sensitivity analyses of the primary endpoint, yielding similar results, document that our findings are robust and free of significant verification bias.

In conclusion, when used as an alternative diagnostic strategy to guide care in those with planned invasive catheterization, CTA/FFR_{CT} was associated with a significantly lower rate of angiography showing no obstructive CAD.

**Authors’ contributions**


**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Acknowledgements**

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**Conflict of interest:** P.S.D. has received grants from HeartFlow during the conduct of the study and other support from GE Medical Systems outside the submitted work; M.A.H. has received grants from HeartFlow during the conduct of the study; M.R.P. has received grants from HeartFlow during the conduct of the study, and grants from Jansen, Johnson & Johnson, Astra Zeneca, NHLBI, and AHRQ, and personal fees from Astra Zeneca, Bayer, and Otsuka outside the submitted work; R.A.B. has received grants from HeartFlow during the conduct of the study and personal fees from B. Braun, Biotronik, and Boston Scientific outside the submitted work; N.C. has received grants from Boston Scientific outside the submitted work; C.R. has received grants from HeartFlow during the conduct of the study, and personal fees from Siemens Medical Solutions, Boston Scientific, and Medtronic; and personal fees from GE Healthcare, outside the submitted work; M.H. has received grants from Siemens Healthcare outside the submitted work; D.A. has received grants and personal fees from GE Healthcare, outside the submitted work; G.R. has received grants from HeartFlow outside the conduct of the study, and personal fees from Siemens and Philips; and personal fees from GE Healthcare, outside the submitted work; F.W. and C.R. have received personal fees and other support from HeartFlow outside the conduct of the study and outside the submitted work; B.D.B. has received grants from Abbott, St. Jude Medical, and Medtronic, and other support from St. Jude Medical, Boston Scientific, Opsens, Omega Pharma, Siemens, Edwards, GE, Sanofi, HeartFlow, and Bayer outside the submitted work.

**Appendix**

**PLATFORM trial organization**

Sites, principal/site investigators, and staff

Milan, Italy: Principal Investigator: Gianluca Pontone; Site Investigators: Antonio Bartorelli, Daniele Andreini, Mauro Pepi, Francesco Alamanni; Staff: Erika Bertella, Saima Mushtaq, Virginia Beltrama,
Clinical operations

Duke Clinical Research Institute, Durham, NC, USA
Beth Martinez

HeartFlow, Redwood City, CA, USA
Auben Debus, Judi Jaeger, Furong Wang, Alan Wilk

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