



Curzen, N. et al. (2021) Fractional flow reserve derived from computed tomography coronary angiography in the assessment and management of stable chest pain: the FORECAST randomized trial. *European Heart Journal*, 42(37), pp. 3844-3852.

(doi: [10.1093/eurheartj/ehab444](https://doi.org/10.1093/eurheartj/ehab444))

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Deposited on: 29 July 2021

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Fractional Flow Reserve Derived from Computed Tomography Coronary Angiography in the Assessment & Management of Stable Chest Pain The FORECAST Randomised Trial

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Abstract

Background

Fractional flow reserve (FFR_{CT}) using computed tomography coronary angiography (CTCA) is a validated method for determining the presence of coronary artery disease and vessel-specific ischaemia. The clinical and economic impact of FFR_{CT} has never been assessed in a randomised trial.

Method

1400 patients with stable chest pain in 11 centres were randomised to CTCA with selective FFR_{CT} [Test arm] or routine assessment [Reference arm]. Primary endpoint was total cardiac costs at 9 months. Secondary endpoints included angina status, quality of life (QoL), major adverse cardiovascular & cerebrovascular events (MACCE), rate of invasive coronary angiography (ICA).

Results: Baseline demographics, angina & QOL status were similar between groups. In the reference arm, 439 (63%) had CTCA versus 674 (96.4%) in the test group, of whom 254 (37.7%) were referred for FFR_{CT}. 22% fewer patients in the test group underwent ICA (p=0.01), and ICA showing no obstructive disease was 52% lower in the test group. The rate of revascularisation was 13.9% (reference) vs 14.6% (test) (p=0.69). Mean total cardiac costs at 9 months were not significantly different (£1,605, test) versus (£1,491, reference) (log-linear difference = 0.11, 95% confidence interval (-0.02 to 0.25), p=0.10). MACCE (death, non-fatal MI, non-fatal stroke) occurred in 74(10.6%) in the reference arm versus 72(10.2%) in test arm (p=0.80). There was no significant difference in angina or QoL at 9 months.

Conclusion:

A strategy of CTCA with selective FFR_{CT} in patients with stable angina is cost neutral compared with routine evaluation, and has similar clinical outcomes, but with 22% fewer patients requiring ICA.

Keywords

Angina; FFR_{CT}; CT Coronary angiography; invasive coronary angiography

Introduction

The optimal approach to investigating patients who present with stable chest pain remains controversial. The majority of such patients in the UK are referred to Rapid Access Chest Pain Clinics (RACPC) that offer clinical assessment in a secondary care setting within 2 weeks of referral. Frontline clinical tests have traditionally assessed either the coronary arteries, for evidence of atheroma, or have employed stress techniques to reveal reversible myocardial ischaemia. The role of invasive assessment and treatment in patients with chronic coronary syndromes is especially controversial, particularly in the light of the recent ISCHEMIA trial¹, which indicated that, in most patients with stable angina, coronary revascularisation offers no prognostic benefit above and beyond optimal medical therapy, although it was effective at alleviating symptoms. It is, however, well established that use of the intracoronary pressure wire in patients with symptoms can help to identify, at both a patient- and vessel-specific level, appropriate targets for revascularisation. The addition of pressure wire data, such as fractional flow reserve (FFR), to angiographic assessment alone has been shown to result in profound differences in the management of patients with stable chest pain in both observational²⁻⁷ and randomised⁸⁻¹¹ studies. Specifically, the pressure wire identifies which lesions are physiologically significant, which is often discrepant with the angiographic assessment of lesion severity.¹² The ideal test to assess patients with new onset chest pain might therefore simultaneously provide information about the presence and extent of both coronary atheroma and myocardial ischaemia in a cost effective manner. Fractional flow reserve derived from computed tomography coronary angiography (FFR_{CT}) is a well validated test¹³⁻¹⁷ that provides information about both the coronary atheroma burden, via a standard computed tomography coronary angiogram (CTCA), and also FFR of all the major epicardial arteries by means of computerized algorithms using 3D

reconstruction and fluid dynamics modelling of the CTCA dataset. A similar discrepancy between the appearance and functional severity of lesions is seen using FFR_{CT} as is observed in invasive angiography and pressure wire, and this is the basis for the impact of FFR_{CT} upon decision-making and patient management over and above CTCA data alone.¹⁸ Thus, observational clinical studies such as PLATFORM¹⁹ and ADVANCE²⁰ have demonstrated that, in comparison to standard tests, use of FFR_{CT} is associated with a significantly lower requirement for invasive coronary angiography (ICA) and, in particular, a lower rate of ICA showing no obstructive coronary disease, without any increase in the rate of ischaemic clinical events. Furthermore, a prespecified analysis of PLATFORM indicated that use of CTCA with FFR_{CT} in a population of patients with new onset chest pain was cost saving in the subgroup who would have undergone ICA, and cost neutral in those who would have had a non-invasive test.²¹ Up to this point, there have been no randomised trials assessing the strategy of CTCA plus FFR_{CT}. In the United Kingdom (UK), the National Institute for Health & Care Excellence (NICE) issued a Medical Technologies Guidance in 2017,²² recommending that FFR_{CT} should be considered as a frontline test in patients with chest pain on the basis of both clinical efficacy and also with the expectation that it would be associated with substantial cost saving within the NHS system.

The FORECAST trial was designed to test the hypothesis that, in a population of patients presenting to RACPC, routine CTCA plus FFR_{CT} as a default strategy is superior, in terms of total cardiac resource utilisation at 9 months, when compared to routine clinical pathway algorithms recommended by NICE Guidance for Treatment of Chest Pain of Recent Onset.²³ Secondary aims were to assess the effect of an FFR_{CT} strategy on (a) quality of life, (b) angina

status, (c) subsequent clinical events including death, myocardial infarction (MI), revascularisation and stroke and (d) rate of invasive coronary angiography (ICA).

Methods

Trial Design & Oversight

FORECAST was an open label, multicentre, randomised, controlled clinical trial. The rationale and design have previously been described in full,²⁴ and the trial protocol is available in Supplementary Appendix A. The trial complies with the Declaration of Helsinki and was approved by the South Central Berkshire B Research Ethics Service Committee, UK (REC Reference 17/SC/ 0490, IRAS Project ID: 231037) and is registered at ClinicalTrials.gov (NCT03187639). The trial was investigator-initiated and funded by an unrestricted research grant from HeartFlow®, and the sponsor was University Hospital Southampton NHS Foundation Trust. The funder had no role in the design or conduct of the trial or in the data collection, analysis, or reporting. The trial steering committee oversaw the conduct of the trial, ensuring that: (a) it was conducted in a manner consistent with the protocol, (b) there was completeness of the data and (c) the analyses were performed according to the statistical analysis plan.

Patient Population

All screened patients were at least 18 years old and were attending RACPC for assessment of stable chest pain. A full list of exclusion criteria is available in the trial protocol in the supplementary material. [Supplementary Appendix A]. In brief, patients were excluded if they: had a history consistent with acute coronary syndrome, were deemed not to require a

test to investigate their symptoms, were unsuitable for CTCA, had a history of previous coronary revascularisation, had a life expectancy of less than 12 months.

Randomisation Groups

Patients were randomised, using an independent computerised system with block sizes of 2 and 4, to one of two assessment strategies: Usual Care (Reference Group) and CTCA with selective FFR_{CT} (Test Group). In the usual care group, patients were assessed according to routine clinical algorithms for that hospital, all of which were based upon the local interpretation and application of the NICE CG95 Guidance for Chest Pain of Recent Origin.²¹ Such pathways are dependent upon the pre-test likelihood of having important coronary disease. Patients in the Reference Group could therefore be referred for a variety of non-invasive tests (including stress echocardiography, stress cardiac magnetic resonance, nuclear medicine perfusion imaging, exercise tolerance test, and CTCA (without FFR_{CT})) or directly for ICA. In the Test Group, all patients were referred for CTCA as the initial test. By protocol, if this test demonstrated a stenosis of 40% or more in a coronary artery segment of diameter suitable for revascularisation by either stent or coronary artery bypass graft surgery then the CTCA would be sent for FFR_{CT} analysis. In this case, FFR_{CT} would provide FFR data for all major epicardial vessels. By convention, a completely occluded vessel is allocated an FFR of 0.5. The management decision taken by the supervising physician would then take into account both the CTCA and FFR_{CT} reports. By contrast, per protocol, patients in the Reference Group who underwent CTCA were not permitted to undergo FFR_{CT} analysis.

Trial Endpoints

The primary endpoint was total cardiac resource utilisation at 9 months. The resource utilisation model incorporated all cardiac-related hospital interaction, including invasive and non-invasive tests, revascularisation procedures, hospital admissions and outpatient

attendances due to a cardiac cause (including MI, arrhythmia, heart failure, revascularisation) and cardiac medications. Data were collected using direct patient contact by research staff at each centre, as well as from local healthcare records. The total medical costs over nine months of follow up were determined for each patient as the sum, over all specified resources, of the numbers of each resource used multiplied by a UK standardized cost weight (tariff).

The 2 principal secondary endpoints were: (a) quality of life (as assessed using the EQ-5D-5L questionnaire²⁵) and (b) angina status (as assessed using the Seattle Angina Status questionnaire²⁶). All patients were asked to complete these questionnaires at baseline and 9 months follow up.

Other prespecified secondary endpoints at 9 months follow up included: major adverse cardiac and cerebrovascular events ((MACCE), a composite of all cause death, non-fatal MI, stroke); unplanned revascularisation; rate of ICA and rate of ICA showing unobstructed coronaries (no stenosis of $\geq 50\%$).

Statistical Analysis

The sample size calculation and statistical analysis plan have been described in detail previously.²⁴ In brief, the power calculation for the primary endpoint was based upon data from the economic analysis of the PLATFORM study²¹, specifically using the UK-based outcomes and applying cost weights from the University Hospital Southampton NHS Trust RACPC for the calendar year 2015. Cost differences of 20% between the reference and test groups were taken as being plausible and of importance, given that the PLATFORM economic substudy observed relatively large differences in per-patient costs within the invasive stratum (32% change), and smaller differences in the per-patient cost within the non-invasive stratum (25% change). The standard deviation (SD) of the natural logarithm of

cost found in PLATFORM was 1.3, which suggested that a sample size of 700 patients per group would provide 90% power to detect a 20% difference in costs between groups, assuming no loss to follow up. A loss to follow up of as much as 12% of enrolled patients would still provide 85% power to detect a 20% cost difference in the setting of moderate cost variability (SD 1.3), and provide 80% power in the setting of higher cost variability (SD 1.4).

Statistical analysis of the trial data was determined in advance and is available in the Supplementary Material. [Supplementary Appendix B]. The Statistical Analysis Plan of the trial conforms to the International Conference on Harmonisation E9 guidelines and reported using the 'Consolidation Standards of Reporting Trials' (CONSORT) guidelines.

Categorical data are presented as counts and percentages. Continuous variables are presented as means and standard deviations and analysed with parametric tests if normally distributed, or, if skewed, they are presented as medians and interquartile ranges, and analysed with non-parametric tests (i.e. Mann Whitney U). The analysis of the binary clinical outcomes is based on frequency of the events, and conducted using chi-square tests, within an intention-to-treat framework. A two-sided p-value of 0.05 or less is considered to constitute statistical significance for all analyses.

The analysis of the primary outcome employs an intention-to-treat approach to compare nine-month costs per patient between individuals randomly assigned to FFR_{CT} and individuals randomly assigned to standard care. Nine months total cardiac costs are compared using non-parametric tests (e.g., the Wilcoxon rank-sum test), or a two sample t-test based on means of the natural logarithm of cost in each group, because of the skew in cost data.

Results

Between December 2017 and July 2019 , 2494 patients with stable chest pain attending one of the 11 participating Rapid Access Chest Pain Clinics were screened for study entry, and 1400 patients were randomized [Figure 1]. Baseline characteristics were well balanced between the reference and test groups [Table 1]. Seven patients in the reference group and 4 in the test arm were excluded from the analysis because they discontinued trial participation before any costs were incurred (i.e. no tests, medication or procedures were ever initiated).

Initial Tests

Among the 700 patients randomised to usual care, 439 (62.6%) had CTCA as the initial test, 187 (26.7%) had a stress test, and 47 (6.7%) had an invasive coronary angiogram (Table 2). Nine CTCA in the usual care group (2.1%) were erroneously referred for FFR_{CT} analysis, but the test results were not used in clinical management.

In the test group, 674 (96.4%) patients underwent CTCA, of whom 254 (37.7%) were referred for FFR_{CT} analysis, per protocol, because a lesion of 40% or more was seen in an epicardial coronary artery. In a further 5 cases, despite the CTCA not meeting the study criterion, the scans were sent for, and underwent, FFR_{CT} analysis. Of the 254 patients meeting this criterion, 215 did get FFR_{CT} results and 39(15.4%) of them could not be analysed, usually due to technical issues with the scan. Of those 215 patients undergoing FFR_{CT}, there was at least one epicardial vessel with FFR_{CT}≤0.8 in 125(58.1%), and in 100(46.5%) of the cases ICA was subsequently performed, whereas a non-invasive stress test was requested in 13(6.0%).

Tests and revascularisation procedure at 9 months

Over 9 months of follow up, 127 additional non-invasive tests were performed in the usual care group and 76 additional non-invasive tests were performed in the test group (Table 3).

The use of ICA was higher in the reference arm than in the test arm: 182 procedures in 175 patients in the reference arm versus 156 procedures in 136 patients in the test arm, a reduction of 14% in the number of invasive angiograms ($p=0.02$) and a reduction of 22% in the number of patients undergoing invasive angiography ($p=0.01$). The number of invasive angiograms showing no obstructive epicardial lesion was 52% lower in the test group: 62 (34%) in the reference arm and 30 (19%) in the test arm.

The overall rate of coronary revascularisation did not differ significantly between the groups: 13.9% in reference group vs 14.6% in the test group ($p=0.69$). Specifically, 75 percutaneous coronary intervention (PCI) procedures were undertaken in 69 (9.8%) patients in the reference group, compared with 88 PCI in 74 (10.6%) patients in the test group (Table 3), and 28 patients in each arm underwent CABG surgery.

In total, 28(4.0%) patients in the reference group had invasive pressure wire assessment compared to 18 (2.6%) in the test arm, $p=0.18$.

Primary Endpoint: Total Cardiac Costs at 9 months

Mean total cardiac costs at 9 months were not significantly different in the test (£1,605, 95% confidence interval (CI) £1,439 to £1,772) and routine (£1,491, 95% CI £1,339 to £1,644) arms (log-linear difference = 0.11, 95% CI (-0.02 to 0.25), $p=0.10$). Median costs were 9.5% lower in the test group (£600, 95% CI £592 to £609 vs. £660, 95% CI £580 to £760). Resource consumption patterns differed between the randomised groups, with significantly lower use of invasive coronary angiography in the test group, similar numbers of hospitalizations, visits to outpatient clinics and emergency departments, and similar

patterns of medication use (Table 5). The pattern of non-invasive test use varied significantly by design between the two randomised groups (Table 5).

Nine month total costs varied according to the test chosen *a priori* to be ordered in the event the patient were randomised to the reference group. In the 94 patients who had an invasive angiogram designated as the initial test to be used if they were randomised to the reference group, mean costs were 6.5% lower in the test group (£3702 vs £3958, log-linear difference = -0.17, 95% CI (-0.65 to 0.30), p=0.46). In the 903 patients who had CTCA designated as the initial test of choice, mean costs were 20.0% higher in the test group (£1527 vs £1272, log-linear difference = 0.22, 95% CI (0.05 to 0.39), p=0.01). In the 391 patients who had stress testing designated *a priori* as the initial test of choice, mean costs were 6.8% lower in the test group than in the reference group (£1297 vs £1392, log-linear difference = -0.05, 95% CI (-0.28 to 0.17), p=0.64).

Major adverse cardiac and cerebrovascular events at 9 months

The overall rate of major adverse cardiac and cerebrovascular events (MACCE) (including death, non-fatal MI, non-fatal stroke) was 74(10.6%) in the reference arm versus 72(10.2%) in the test arm (p=0.80). Individual components of MACCE are shown in Table 4. There were 2 deaths in the trial, both in the test arm, and both were non cardiac in origin (metastatic cancer and progressive lung fibrosis). There were 3 MIs (including 1 non-ST elevation and 2 ST elevation) in the reference arm compared with 9 (9 non-ST elevation) in the test arm.

Quality of Life and Angina Status

Seattle Angina Questionnaire scores showed impairment at baseline (median score of 65 on a scale from 0 to 100 in both randomised groups) that improved significantly over nine

months of follow-up (to a median score of 95.8 in both randomised groups). Scores improved to a similar degree in the test group (mean change 23.1, median change 23.3) and the reference group (mean change 25.0, median change 22.8), with no significant difference in the change in scores from baseline to nine months ($p=0.23$, Figure 3). The same pattern was evident in the EQ-5D scores over follow-up: both groups showed reduced quality of life at baseline (median score 0.7 on a scale from 0 to 1 in both groups) that improved over follow-up (to a median score of 0.8 at nine months in both groups), with no significant difference in the change in scores (0.1 in both groups, $p=0.61$).

Discussion

FORECAST is the first randomised trial to assess CTCA with selective FFR_{CT} as a default strategy for the evaluation of patients presenting with stable chest pain. The main findings of the trial are as follows. First, that, contrary to the estimates of extensive cost saving by NICE in the Medical Technologies Guidance, there is no significant difference at 9 months in a low risk population attending RACPC between the cost of cardiac care between the test strategy of CTCA followed by selective FFR_{CT} and the strategy of usual care. Second, that there were no significant differences in symptom improvement, quality of life, MACCE or coronary revascularisation between the groups. Third, that the strategy of CTCA and selective FFR_{CT} led to 22% fewer patients undergoing ICA, with 52% fewer patients having no significant obstructive coronary artery disease on invasive angiography.

FORECAST was designed with a primary endpoint of total cardiac cost because we anticipated that clinical outcomes would be similar in a well-managed population of stable patients with chest pain, irrespective of the initial testing strategy, but that a strategy based

on CTCA and selective FFR_{CT} would be more efficient, with lower resource use and cost than usual care pathways.

With regard to a total cardiac cost endpoint, the adoption of this technology in routine clinical practice will inevitably depend upon it being deemed affordable within a discrete health economy. In the UK, the 2017 Medical Technologies Guidance on FFR_{CT}²² predicted substantial cost savings for the NHS with the adoption of FFR_{CT}, using modelling partially based upon previous economic analysis from observational studies such as PLATFORM. Specifically, the prespecified economic outcomes analysis in PLATFORM demonstrated dominance for a strategy of CTCA with FFR_{CT} in the stratum of patients in whom an invasive approach was planned, but that FFR_{CT} was cost neutral in the stratum in whom a non-invasive investigation was the initial evaluation. In FORECAST, we formally tested the hypothesis that there would be a meaningful cost saving for a strategy of CTCA plus selective FFR_{CT} by using the cost range obtained in this PLATFORM model. In fact, we observed no difference in overall costs between the CTCA with selective FFR_{CT} strategy and usual care. There are 2 potential ways of interpreting this headline result. The fact that the test strategy failed to yield a reduction of overall cardiac care costs of at least 20% could be seen as a negative outcome, especially for a trial conducted exclusively within the NHS system in which NICE had predicted substantial cost savings, and accordingly invested in the test by including FFR_{CT} in its Innovation and Technology Payment programme. An alternative interpretation of the FORECAST result is a positive one, in that the CTCA/FFR_{CT} approach has not cost the health system any extra resource, despite reducing ICA rates, and with no increase in ischaemic event rates.

The second reason for the choice of the resource utilisation primary endpoint in FORECAST was that previous studies have consistently indicated that the benefit of FFR_{CT} has been to

reduce the requirement for ICA, and to substantially reduce the proportion of ICA yielding unobstructed coronary arteries, but without any difference in the rate of subsequent clinical ischaemic events such as MI, revascularisation or death. For example, in PLATFORM, the rate of ICA was reduced by 61% in the FFR_{CT} cohort, and, furthermore, in those patients in whom ICA was intended, the rate of unobstructed coronaries at ICA was 73% in the usual care arm and 12% in the FFR_{CT} arm.²⁸ The clinical event rates were low in both groups at 1 year. Further, in the ADVANCE Registry of patients having CTCA/FFR_{CT} in routine clinical practice, the rate of unobstructed coronaries at ICA was 14.4% in patients with FFR_{CT} ≤0.8 compared with 43.8% in those with FFR_{CT} >0.8.²⁰ In addition, no death/myocardial infarction (MI) occurred within 90 days in patients with FFR_{CT} >0.80 (n = 1529), whereas 19 (0.6%) MACE (comprising death, MI or unplanned admission for ACS leading to revascularisation) (p = 0.0008) and 14 (0.3%) death/MI (p= 0.039) were observed in subjects with an FFR_{CT} ≤0.80. Based upon the consistency of these and other results, we therefore expected that the CTCA/FFR_{CT} strategy in FORECAST would yield less ICA but no difference in clinical event rates compared with usual care. On this basis, the rate of clinical events would clearly not have proved a satisfactory primary endpoint for our trial. Indeed, our results demonstrating equivalent rates of clinical events, as well as the 22% fewer patients having ICA, and the substantial reduction in the rate of unobstructed coronary arteries in the FFR_{CT} group, are remarkably consistent with the previous observational studies.

In FORECAST, quality of life and angina status improved to a similar degree in both the reference and test groups by nine months of follow up. This result is consistent with the one year data from PLATFORM, in which the five-item EuroQOL score did not differ significantly between the groups overall.²⁷ The improvements seen in both groups are likely due to clinicians actively treating all subjects to relieve anginal symptoms, resulting in similar use of

anti-anginal medications and similar rates of coronary revascularization (Table 5). From a patient perspective, achieving similar quality of life and angina outcomes with less use of invasive procedures represents a potential advantage for the strategy of CTCA with selective FFR_{CT}.

There are some limitations of FORECAST. First, and most important, is that we were unable to predict during the planning stage of the trial at exactly what rate CTCA would be used in the reference group, because the national CG95 Guidance by NICE regarding Chest Pain of Recent Onset was revised during this time in 2016 and recommended that CTCA became the default test for the majority of such patients attending RACP clinics. However, the infrastructure in many areas of the NHS at the time of this revised guidance was not equipped with the appropriate resource to comply, and so there has been a consequent major expansion in these facilities, and hence a lag in access to CTCA, in the last few years. The FORECAST trial, however, was based upon a pragmatic design: the CTCA with FFR_{CT} strategy versus routine care, whatever tests that should include, and was never intended to provide a comparison with CTCA alone. However, with the majority of patients in the usual care group undergoing CTCA, the contrast between the test and reference groups in FORECAST was potentially diminished. Indeed, the increasing dominance of CTCA as the default test for patients presenting with stable chest pain may also explain the lack of cost saving in our trial. A recent cost-effectiveness analysis using an individual-based Markov microsimulation model for low risk stable chest pain based upon the PROMISE population indicated that an anatomical approach using CTCA is superior compared to functional testing.²⁸

A second limitation of the trial is that we chose cardiac costs, rather than total medical costs, as the primary endpoint outcome. Total cardiac costs have the advantage of being

most likely to be affected by the alternative strategies, and being simpler for the local research teams to document. It seems unlikely that non-cardiac costs would be affected by the management strategies, but we cannot exclude the possibility that total medical costs differed, even though the cardiac costs did not. Third, costs in this study were based on United Kingdom National Health Service cost tariffs, and may not be transferable to other countries with different cost structures in their health delivery systems. In an attempt to address this, one pre-specified sensitivity analysis for this trial is to apply the results of FORECAST to US-specific cost tariffs, and this is the subject of ongoing analysis.

The significant reduction in death and non-fatal MI seen at 5 years in the SCOT HEART trial²⁹ in the cohort undergoing CTCA in addition to routine care compared to routine care alone indicates that there is considerable prognostic benefit from identifying coronary atheroma and initiating disease-modifying medical therapy in this population using CTCA alone. Indeed, the findings of FORECAST raise an important question that the trial cannot answer: namely, what place does FFR_{CT} have in routine clinical practice above and beyond a default approach using CTCA? Given the findings from SCOT HEART and then ISCHEMIA, one could speculate that, rather than using FFR_{CT} in every patient with stable chest pain who has a certain degree of atheroma on their CTCA, rather we should treat them all with optimal medical therapy, and only then request FFR_{CT} analysis retrospectively if their chest pain does not settle on medical therapy. In these patients with ongoing symptoms, the ability to perform FFR_{CT} retrospectively using the initial CTCA dataset would then potentially be an attractive option to predict a revascularisation strategy, whilst limiting the number of FFR_{CT} analyses requested initially. Such an approach would also be consistent with the sub-analysis of the PROMISE trial³⁰ which demonstrated the excellent discriminatory role of

describing degrees of coronary atheroma by CTCA in patients presenting with suspected angina, even in the absence of any functional testing for ischaemia, for predicting the primary endpoint of death, myocardial infarction and hospitalisation for unstable angina. We speculate, therefore, based upon the current and previous results, that the optimal application of FFR_{CT} in the setting of chronic coronary syndrome may be in patients who have had an initial assessment by CTCA that led to a management plan of optimal medical therapy, and in whom such treatment had failed to render them free of angina. FFR_{CT} analysis using the CTCA dataset could then be used to dictate the need for revascularisation and, further, to determine the most appropriate strategy as part of the shared decision-making process with the patient.

In conclusion, a strategy of CTCA with selective FFR_{CT} in patients presenting with stable angina is cost neutral compared with routine clinical evaluation pathways, and leads to similar clinical outcomes, including major adverse cardiovascular events, anginal symptoms, and quality of life. The CTCA/FFR_{CT} strategy did, however, result in a significantly lower proportion of patients undergoing invasive coronary angiography, without reducing the use of coronary revascularisation.

Acknowledgements

FORECAST is an investigator-initiated trial & was supported by an unrestricted research grant from HeartFlow.

The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

GPM is supported by an NIHR Research Professorship (2017-08-ST2-007) & by the NIHR Leicester Biomedical Research Centre & the NIHR Leicester Clinical Research Facility.

The authors would like to acknowledge the support received from the Research & Development Department of University Hospital Southampton NHS Foundation Trust

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FIGURE LEGENDS

Figure 1 **Consort Diagram**

Figure 2 **Primary Endpoint: Total Cardiac Costs at 9 months**

Costs include non-invasive tests (CTCA, FFR_{CT}, Stress Echo, Perfusion Scan, Stress CMR, Exercise ECG), invasive tests (ICA, Invasive FFR, PCI, CABG), hospitalisations (for MI, Stroke, Transient Ischemic Attack or other cardiac cause), emergency department visits, cardiac outpatient visits and medications (Statin, Aspirin, Beta Blockers, Calcium Blockers, Clopidogrel, Ticagrelor, Prasugrel, Oral Nitrate, ACE Inhibitor, ARB and Alpha Blockers).

Mann-Whitney U test for the distribution of costs by arm. $p=0.96$

Figure 3 **Principal Secondary Endpoints**

(a) Quality of Life and (b) Angina Status at Baseline and 9 months

There was no significant difference between the quality of life or angina scores comparing the reference versus the test groups at 9 months using a T test.