**Comparison of Computed Tomogram Coronary Angiography (CTCA) alone versus CTCA with selective FFRCT in patients presenting with stable chest pain: a FORECAST trial substudy**

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**Conflict of Interest:**

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**Abstract**

**Aims:**

The original FORECAST trial was designed to compare a strategy of CTCA and selective FFRCT to standard care in patients attending Rapid Access Chest Pain clinics in UK centres. This is a prespecified analysis of the FORECAST trial to compare outcomes between the patients in the experimental arm (CTCA + selective FFRCT) and patients in the reference arm who underwent CTCA alone as their initial test of choice.

**Methods and results**

The FORECAST trial recruited 1400 patients randomised between 2 strategies: (i) initial test of choice at the discretion of the healthcare provider (standard care arm) or (ii) CTCA +/- FFRCT. Prior to randomization, clinicians stated their preference for choice of the first test if the patient were to be randomized to standard care. 459 patients (66%) in the standard care pathway were selected for CTCA as the first test of choice. Similarly, 453 (65%) of the patients who were subsequently randomised into the experimental arm were selected for CTCA as initial test prior to that randomisation.

This comparison is an intention-to-test (ITT) analysis comparing the post randomisation outcomes of the population of patients who were selected for CTCA as the test of first choice prior to randomisation (labeled as the CTCA stratum). The following comparisons were made: (i) primary trial outcomes at 9 months including (a) total cardiac costs, (b) use of other tests, (c) clinical events & (d) time to final management plan; (ii) a comparison between the CTCA stratum groups and the remainder of the standard care arm (i.e. patients randomised to standard care who were selected for an initial test other than CTCA).

Of the CTCA stratum patients, there was no significant difference between randomised groups in the median total cardiac costs at 9 months (£594 (IQR 570 – 1,127) in the experimental arm vs £594 (574 –­ 966) in the usual care arm (P=0.325)).

The number of additional non-invasive tests was significantly lower in the experimental group than in the standard care CTCA patients (43 patients (8.9%) vs 72 (16%), (P=0.005)). Time to final management plan was also significantly lower in the experimental arm (median 64 days (IQR 48-110) versus 75 days (55-126) (P<0.001)). There was no significant difference in the rate of adverse cardiac events.

Patients randomised to standard care who were not in the CTCA stratum had significantly higher median total cardiac costs when compared to either of the CTCA stratum groups, with median total cardiac costs of £908 (IQR 592 – 1,161) vs £594 (570-1,123) vs £594 (570-966), respectively (P<0.001).

**Conclusion:**

In this prespecified FORECAST substudy of patients whose clinicians preferred CTCA as the first test prior to randomisation, the CTCA +/- FFRCT strategy, when compared to CTCA alone, was cost neutral in the UK, and associated with significantly fewer additional noninvasive tests. Time to final management plan was also significantly lower in the experimental arm (median 64 days (IQR 48-110) versus 75 days (55-126) in the standard care CCTA arm (P<0.001)).

**Introduction**

The investigation of patients presenting with stable chest pain suspected to represent angina includes a menu of tests that assess coronary anatomy or physiology or both. The optimal approach remains contentious(1). In the UK, the NICE *CG95* guidelines(2) recommend computed tomography coronary angiography (CTCA) as the initial test in over 90% of such patientsand thereby minimises the early use of functional tests for myocardial ischaemia. Whilst PROMISE(3) suggested some advantage for CTCA over functional testing, CEMARC2(4) reported clinical equivalence between stress CMR versus the NICE-recommended pathway. Both trials reported a lower rate of invasive coronary angiography (ICA) in the functional testing group.

The advent of FFRCT has offered a test that provides data regarding both coronary atheroma and flow limitation. The evidence derived from PLATFORM(5), ADVANCE(6), FORECAST(7) and PRECISE(8) has consistently demonstrated that a strategy employing CTCA with FFRCT is associated with (i) a lower rate of ICA, (ii) lower proportion of ICA showing no significant coronary disease, (iii) no difference in clinical event rate, (iv) cost-saving or cost-neutralilty.

The FORECAST trial was designed to test a strategy of CTCA with selective FFRCT compared with standard care testing in patients attending Rapid Access Chest Pain clinics in UK centres. There was no difference in resource utilisation or quality of life, or in clinical events between the strategies, although there was a significantly lower rate of ICA in the selective FFRCT group. It is notable that CTCA was the investigation of choice in 65.5% in the standard care arm in FORECAST. This has led commentators to speculate as to the comparative performance of CTCA alone versus CTCA with selective FFRCT in these patients. A randomised comparison of this sort does not exist. In order to address this question in a hypothesis-generating fashion, we included in the FORECAST protocol a requirement that the frontline test to which the patient would have been allocated in standard care environment by the assessing physician, i.e. in the absence of the trial, was recorded just prior to randomisation. This generated a stratum of patients in both trial arms in whom the pre-randomisation allocation was CTCA (CTCA stratum). It is this stratum that we have used for comparison, as part of a prespecified substudy, in order to achieve a degree of matching between the groups. Our aim was to compare patients in this CTCA stratum randomised to standard care with those randomised to CTCA with selective FFRCT for the following parameters: (i) primary comparison at 9 months including (a) total cardiac costs, (b) use of other tests, (c) clinical events & (d) time to final management plan; (ii) a comparison between the 2 CTCA stratum groups and the remainder of the standard care arm (i.e. patients randomised to standard care who were referred for an initial test other than CTCA).

**Methods**

*Population & Comparison Groups*

This substudy was conducted on the FORECAST trial population (REC Reference 18/SC/0490, IRAS Project ID: 231037). The FORECAST trial (NCT03187639) has been described in detail previously(7,9). In brief, the trial prospectively enrolled 1400 patients with stable chest pain who were randomised into 2 groups: (a) standard care, in which case they were referred for an initial test of choice (CTCA, ICA, stress ECG, stress MRI, stress echo, nuclear perfusion scan) according to clinician discretion and local and/or national guidelines or (b) the experimental arm, consisting of CTCA followed by selective FFRCT for those patients with at least one lesion of >40% in any coronary artery of a size suitable for revascularisation.

The patients included in this substudy, which was prespecified in the trial statistical analysis plan, consist of those patients in whom CTCA was recommended as their initial test of choice *prior to randomisation* into either the standard care or CTCA with selective FFRCT experimental arm. This represents a CTCA stratum of patients who then went on to be randomised to standard care or experimental arms of the trial, with these 2 groups from the CTCA stratum being the focus for the primary comparison of this study.

The secondary analysis in this paper compares the above-mentioned groups from the CTCA stratum with the remaining of the standard care arm (i.e. those not chosen for CTCA prior to randomisation).

In this substudy data are derived from the main trial baseline demographics, initial tests, subsequent tests, time to final management plan, total cardiac costs at 9 months, Major Adverse Cardiovascular Events (MACE) at 9 months (defined as a composite of all-cause death, non-fatal myocardial infarction, stroke and cardiovascular hospitalization).

*Statistical analysis*

Statistical analysis was carried out using RStudio version 4.3.1, PBC (Boston, Massachusetts, USA). Continuous data are presented as mean (± standard deviation, SD) or median (+ interquartile range, IQR), as appropriate, depending on data distribution. Categorical data are presented as frequency and percentage. Characteristics were compared using the student t-test or Wilcoxon rank sum test as appropriate for continuous variables and Pearson chi-square test or the Fisher exact test for discrete variables. A two-sided *P-*value of 0.05 or less was considered to constitute statistical significance for all analyses.

**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, from which 1400 patients were randomized to either the standard care or the experimental (CTCA+/-FFRCT) arms of the trial [Figure 1A&1B]. In the experimental group, 674 (96%) patients underwent CTCA, of whom 254 (38%) had their scans referred for FFRCT analysis per protocol based upon the presence of at least one lesion of >40% in any epicardial coronary artery large enough to undergo stenting or bypass grafting. 39 (15%) of these scans could not be analysed for FFRCT due to technical/quality issues.

In the primary analysis of this substudy, patients who had CTCA specified as the test of first choice prior to randomisation make up the CTCA stratum. This included 912 patients of the entire study population (65.5%) with 459 patients (65.5%) randomised to the standard care arm, and 453 patients (65%) to the experimental arm (CTCA+/-FFRCT). Table [1] shows the demographics of patients in CTCA stratum included in this study and indicates that the groups are well matched. (Supplementary appendix table 1 shows demographics of CTCA stratum patients included here, versus invasive stratum and non-CTCA non-invasive stratum).

241 (34%) patients in the standard care arm were referred to an initial investigation other than CTCA following their assessment, of whom 193 (80%) patients had an initial non-invasive stress test (stress ECG, stress echocardiography, nuclear perfusion scan or stress cardiac MRI) and 48 (20%) patients were referred directly for invasive coronary angiography (ICA). These patients, along with the primary analysis patients comprised the population for the secondary analysis in this substudy.

Primary analysis: comparison in pre-randomisation CTCA stratum population between standard care randomised arm and CTCA+/-FFRCT randomised arm

*Cardiac-related resource utilisation*

There was no significant difference in the median total cardiac costs between the standard care or experimental groups of the CTCA stratum (£594 (IQR 570 – 996) vs £594 (570 – 1,127), (P= 0.325)). [Table 2].

*Further investigations*

In the CTCA stratum, there was a significantly lower rate of further non-invasive tests in in the experimental randomised arm compared to the standard care randomised arm, with 43 patients (8.9%) in the experimental arm requiring further non-invasive investigations (stress echo, stress ECG, stress MRI and nuclear perfusion scan) versus 72 (15.7%) in the standard care arm (P=0.005).

There was no difference in the rate of invasive coronary angiography (ICA) between the groups (17% vs 19%, P=0.551). A breakdown of the comparative number of alternative tests is shown in Table [3].

*Time to final management plan*

Time to a final management plan (i.e. time from initial assessment at the chest pain clinic to reaching a final management plan) was significantly lower in the experimental arm compared to the standard care group from the CTCA stratum (median of 64 days (IQR 48-110) versus 75 days (55-126) (P<0.001)) [Table 4].

*Clinical Events*

There is no statistically significant difference between the 2 CTCA stratum groups in terms of myocardial infarction (MI), cerebrovascular accident (CVA), all-cause mortality and/or cardiac hospitalization [Table 5].

Secondary Analysis: Comparison between the 2 CTCA stratum groups & the standard care patients whose pre-randomisation test choice was not CTCA.

*First choice test:*

Out of the 193 patients of the standard arm whose initial test of choice was anon-invasive test other than CTCA (non-CTCA), 106 (55%) patients were referred for stress echocardiogram, 73 (38%) stress ECG, 13 (6.8%) nuclear perfusion scan, 1 patient (0.5%) stress cardiac MRI. Altogether, 48 patients in this group were referred for ICA.

*Cardiac-related resource utilisation*

The non-CTCA stratum subgroup of the standard care arm had significantly higher median total cardiac costs when compared to either of the CTCA stratum groups (i.e. the randomised experimental arm or the standard care arms), with median total cardiac costs of £908 (IQR 592 – 1,161) vs £594 (570-1,123) vs £594 (570-966), respectively (P<0.001). [Table 6].

*Clinical events*

There was no statistically significant difference in the rate of major adverse cardiac outcomes between the 3 subgroups including MI, CVA, cardiac hospitalisations and/ or cardiac death. [Table 7].

**Discussion**

This prespecified substudy of the FORECAST trial was focused on the important group of patients who were chosen, prior to randomization, to undergo CTCA as the initial test to evaluate their chest pain. We were able to compare the outcomes within this stratum of patients according to their subsequent randomized allocation to have their CTCA followed either by standard care testing or by selective FFRCT. The main findings are as follows: (a) the CTCA + selective FFRCT strategy is cost neutral compared to CTCA alone; (b) compared to CTCA alone, the rate of non-invasive testing was significantly lower in the CTCA + selective FFRCT group and (c) the time to final management plan was significantly lower in the experimental arm than the CTCA group of the standard care arm. Finally, patients not allocated to CTCA as the test of first choice incurred significantly greater costs than those with CTCA as their first test.

The NICE *CG95* guidelines recommend CTCA as the default first test in over 90% of patients presenting with stable new onset chest pain. This theoretically largely eliminates the need for functional tests for ischaemia in such patients. Given the body of evidence that detecting coronary atheroma in this population is associated with prognostic benefit, probably via more optimal application of disease-modifying medical therapy, as seen in SCOT-HEART(10), the logic behind this recommendation is clear. Furthermore, trials such as COURAGE(11) and ISCHEMIA(12) have consistently indicated that, in stable patients with angina without significant left main disease, there is no additional prognostic benefit for revascularisation over and above optimum medical therapy (OMT). However, in front line clinical practice, such considerations are not so clear cut.

Firstly, it is often the case that we require a definitive diagnosis regarding the patient’s symptoms, and specifically whether they represent angina (i.e. myocardial ischaemia) or not. The presence of even significant CAD in isolation does not correlate closely in many cases with whether the chest pain symptoms are due to myocardial ischaemia or not. Hence, a functional test may also be required, even if the patient is committed to disease-modifying therapy. Secondly, in those patients whose symptoms do demand revascularisation, the availability of data about flow limitation and downstream myocardial ischaemia can play an important role in the targeting of appropriate vessels and lesions, especially for those patients committed to PCI(13). Thirdly, an assessment of the presence and extent of myocardial ischaemia is associated with better clinical outcome, although the relative predictive association of ischaemic burden compared with atheroma burden with adverse events is contentious(14,15). Finally, the correlation between anatomical lesion severity and flow limitation causing downstream ischaemia is poor except in the case of very mild and very severe lesions. Given these factors, the availability of both atheroma extent and severity and vessel-specific flow limitation, as offered by FFRCT, has several theoretical advantages.

Clinical studies, including PLATFORM(5), ADVANCE(6), FORECAST(7) and PRECISE(8) have consistently demonstrated that a selective FFRCT strategy has the following benefits: (a) reduced rate of ICA; (b) reduced rate of ICA yielding no stenosis of ≥50%; (c) no increase in clinical event rate, despite fewer ICA; (d) similar rate of revascularisation; (e) cost neutrality or saving. In the main FORECAST trial, the overall strategy of selective FFRCT in the study overall showed cost neutrality and significantly fewer ICA.

In the current substudy, which was prespecified and included in the statistical analysis plan of FORECAST, we have performed a comparison between patients who are matched by being in the pre-randomisation stratum of allocation to CTCA alone, and who then went on to be randomised to either the standard care arm or the experimental arm of CTCA and selective FFRCT. The need for this analysis was further stimulated by the commentary in response to the main FORECAST results that questioned (i) whether the high proportion of patients in the usual care arm who had CTCA might have diluted any benefit of the CTCA+/-FFRCT strategy in the test arm and (ii) whether FFRCT would have any additional advantage over CTCA alone in this population, given that there has never been a randomised comparison of this nature.

Our current findings suggest that there may indeed be some clinical advantage to the selective FFRCT strategy in terms of (i) reduced non-invasive testing burden and (ii) reaching a final management plan faster, this being achieved in a cost neutral manner. These benefits are seen without any difference in clinical events. These data indicate that there would be merit in a head-to-head randomised comparison of these two strategies. It is certainly likely that confirmation of these findings would yield a strategy considered preferable to patients given that it would offer fewer tests and a quicker final plan.

There are several important limitations to this study. Firstly, the groups are matched only according to their pre-randomisation stratum. Discussion regarding techniques such as propensity matching were considered to be inappropriate in this population, and unnecessary given trial design. As shown in Table 1, the groups are, in fact, well matched. Secondly, we cannot know why clinicians preferred CTCA over other initial tests. Another potential consideration of the trial is that the costs in this study were based on UK National Health Service cost tariffs, and may not be generalizable to other countries with different cost structures in their health delivery systems, though the trial investigators have conducted a comparative analysis comparing costs in the FORECAST trial based on US healthcare cost weights with results showing that initial evaluation using CTCA ± FFRCT had similar US costs as standard care pathways(16). Third, in the experimental group, 15% of patients could not have the intended FFRCT analysis as a consequence of variety of technical issues relating to quality of the CTCA scan. This rate of failure has gradually declined in front line practice since this trial recruited in association with improvements in scanner quality as well as an awareness of the importance of acquisition standards including routine nitrates and attaining lower target heart rates.

In conclusion, this prespecified substudy indicates that the strategy of CTCA with selective FFRCT is associated with the need for fewer non-invasive tests and a faster time to a final management plan than a strategy of CTCA alone, despite equivalent total cardiac costs and clinical outcomes. These findings indicate that a formal randomised comparison between CTCA alone and selective FFRCT is now warranted in these patients.

**Tables and Figures**

**Table 1**: Demographics of patients in the CTCA stratum who were randomised to either experimental arm (CTCA +/- FFRCT) or standard care

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Standard Care CTCA arm**,  N = 459 | **Experimental arm (CTCA +/-FFRCT)**,  N = 453 | ***P*-value** |
| **Age** | 58 (50-67)1 | 59 (51-67)1 | 0.5422 |
| **Gender** |  |  | 0.6953 |
| Male | 230 (50.1%) | 221 (48.9%) |  |
| Female | 229 (49.9%) | 232 (51.1%) |  |
| **BMI** | 28.6 (25.3 - 32.9)3 | 28.7 (25.3 - 33.6)3 | 0.6952 |
| **Ethnicity** |  |  | 0.1193 |
| White | 413 (90.0%) | 400 (88.0%) |  |
| Asian or Asian British | 26 (5.7%) | 39 (8.6%) |  |
| Black of Black British | 8 (1.7%) | 8 (1.8%) |  |
| Chinese or other | 9 (2.0%) | 3 (0.7%) |  |
| Mixed | 3 (0.7%) | 1 (0.2%) |  |
| Prefer not to answer | 0 (0.0%) | 2 (0.4%) |  |
| **Family history of CAD** | 281 (61.2%) | 279 (61.6%) | 0.1503 |
| **History of angina** | 157 (34.2%) | 135 (29.8%) | 0.1543 |
| **History of MI** | 0 (0.0%) | 4 (0.9%) | 0.0604 |
| **Diabetes Mellitus** | 53 (11.5%) | 60 (13.2%) | 0.4363 |
| **Hypertension** | 149 (32.5%) | 160 (35.3%) | 0.3623 |
| **Hyperlipidaemia** | 120 (26.1%) | 140 (30.9%) | 0.1113 |
| **Renal impairment** | 7 (1.5%) | 10 (2.2%) | 0.4744 |
| *1* Median(IQR)  *2* Wilcoxon rank sum test  3 Pearson's Chi-squared test  4 Fisher’s exact test | | | |

**Table 2**: Total costs in CTCA stratum, comparing the randomised arms in sterling pounds (£) presented as mean, standard deviation (SD), median and interquartile range (IQR):

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Standard Care CTCA arm**, N = 459 | **Experimental arm (CTCA +/-FFRCT)**, N = 453 | ***P*-value** |
| **Mean** | 1,272 | 1,527 | 0.057*1* |
| **SD** | 1,777 | 2,220 |  |
| **Median** | 594 | 594 | 0.325*2* |
| **IQR** | 570 – 966 | 570 – 1,127 |  |
| *1* Welch Two Sample t-test  2 Wilcoxon rank sum test | | | |

**Table 3**: Further investigations required for CTCA stratum by randomised group

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Standard Care CTCA arm**,  N = 459 | **Experimental arm (CTCA +/-FFRCT)**,  N = 453 | ***P*-value** |
| Total number of patients who required additional non-invasive testing | 72 (15.7%) | 43 (8.9%) | **0.005***1* |
| Stress Echo | 19 (4.1%) | 9 (2.0%) | 0.083*2* |
| Perfusion scan | 19 (4.1%) | 4 (0.9%) | **0.002***2* |
| Stress MRI | 11 (2.4%) | 9 (2.0%) | 0.826*2* |
| Stress ECG | 28 (6.1%) | 26 (5.3%) | 0.818*1* |
| Invasive coronary angiography (ICA) | 86 (18.7%) | 78 (17.2%) | 0.551*1* |
| *1* Pearson's Chi-squared test  *2* Fisher’s Exact test | | | |

**Table 4**: Time period required between randomisation and reaching a final management plan in days represented as median (IQR) and mean (SD) in CTCA stratum by randomised group

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Standard Care CTCA arm**,  N = 459 | **Experimental arm (CTCA +/-FFRCT)**,  N = 453 | ***P*-value** |
| **Median** | 751 | 641 | **<0.001***1* |
| **IQR** | 55-126 | 48-110 |  |
| **Mean** | 993 | 883 | 0.016*2* |
| **SD** | 67 | 66 |  |
| **No management plan finalised** | 18 | 20 |  |
| *1* Wilcoxon rank sum test  *2* Two Sample t-test | | | |

**Table 5**: Incidence of adverse cardiac events in CTCA stratum by randomised group

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Standard Care CTCA arm**, N = 459 | **Experimental arm (CTCA +/-FFRCT)**, N = 453 | ***P*-value***2* |
| Any Cardiac event \* | 44 (9.6%) | 44 (9.7%) | 0.948*1* |
| Any MI | 1 (0.2%) | 6 (1.3 %) | 0.068*2* |
| Death | 0 (0.0%) | 2 (0.4%) | 0.246*2* |
| CVA | 0 (0.0%) | 0 (0%) | N/A |
| Hospital admission for cardiac cause | 44 (9.6%) | 42 (9.3%) | 0.871*1* |
| Any revascularisation | 56 (12.2%) | 59 (13.0%) | 0.708*1* |
| PCI\*\* | 44 (9.3%) | 43 (9.2%) | 0.962*1* |
| CABG \* | 11 (2.6%) | 15 (4.0%) | 0.422*1* |
| *1* Pearson’s Chi-squared test  *2* Fisher's exact test  \*(MI, myocardial infarction; CVA, cerebrovascular accident; CABG, coronary artery bypass grafting) | | | |

**Table 6**: Comparison in total cardiac costs between the 2 CTCA stratum groups and patients randomised to standard care, whose pre-randomisation test of choice was not CTCA (non-invasive and ICA), in sterling pounds (£) represented in mean (SD) and median (IQR)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **ICA-first**  **Standard care,**  N = 48 | **Non-CTCA first non-invasive standard care**,  N = 193 | **Standard Care CTCA arm**,  N = 459 | **Experimental arm (CTCA +/-FFRCT)**,  N = 453 | ***P*-value** |
| Mean | 3,958 | 1,392 | 1,272 | 1,527 | **<0.0011** |
| SD | 3,313 | 1,812 | 1,777 | 2,220 |  |
| Median | 1,988 | 908 | 594 | 594 | **<0.0011** |
| IQR | 1,697 – 4,708 | 592 – 1,161 | 570 - 966 | 570 - 1,127 |  |
| *1* Kruskal-Wallis rank sum test | | | | | |

**Table 7**: Incidence of adverse cardiac events between the 2 CTCA stratum groups and patients randomised to standard care, whose pre-randomisation test of choice was not CTCA (non-invasive and ICA)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **ICA -first**  **Standard care,**  N = 48 | **Non-CTCA first non-invasive standard care**,  N = 193 | **Standard Care CTCA arm**,  N = 429 | **Experimental arm (CTCA +/-FFRCT)**, N = 436 | ***P*-value** |
| **Any Cardiac event (Death, cardiac hospitalization, MI or CVA)** | 15 (31%) | 15(7.8%) | 44 (9.6%) | 44 (9.7%) | **<0.001** |
| **Any MI** | 1 (2.6%) | 1(0.5%) | 1 (0.2%) | 6 (0.7%) | 0.2 |
| **Death** | 0 (0%) | 0 (0%) | 0 (0%) | 2 (0.2%) | 0.4 |
| **CVA** | 0 (0%) | 1(0.5%) | 0 (0%) | 0 (0%) | 0.2 |
| **Hospital admission for cardiac cause** | 15 (31%) | 15 (7.8%) | 44 (9.6%) | 42 (9.3%) | **<0.001** |
| **Any revascularization** | 19 (40%) | 22 (11%) | 56 (12%) | 59(13%) | **<0.001** |
| **CABG** | 10 (21%) | 6 (3.1%) | 12 (2.6%) | 16 (3.5%) | **<0.001** |
| **Time to final management plan** | 49  (33 - 96) | 40  (20 - 77) | 75  (55 - 126) | 64  (48 - 110) | **<0.001** |
| *1* Kruskal-Wallis rank sum test, Fisher's exact test | | | | | |

F

Enrolment

Assessed for eligibility (n= 2494)

Excluded (n= 1094)

* Not meeting inclusion criteria (N=407)
* Declined to participate (N= 206)
* Other reason (N= 481)

First choice test (n=1400)

Non-invasive non-CTCA stratum

(n=393)

* Stress Echocardiogram (n=235)
* Stress ECG (n=126)
* Perfusion scan (n=27)
* Stress cardiac MRI (n=5)

Invasive stratum (ICA)

(n=94)

CTCA stratum

(n=912)

**Figure 1A**: Diagram demonestarting first chice test for patients included in FORECAST trial which is deviced into invasive stratum, CTCA stratum and non-invasive non-CTCA stratum (ICA: invasive coronary angiogram; CTCA: computed tomography coronary angiography)

Randomisation

FORECAST trail population

(n=1400)

Standard Care arm

(n=700)

* CTCA initial test of choice (n=459)
* ICA initial test of choice (n=48)
* Other non-invasive test initial test of choice (n=193)

Experimental arm

(n=700)

* CTCA initial test of choice (n=453)
* ICA initial test of choice (n= 46)
* Other non-invasive test initial test of choice (n=200)
* Withdrew consent from study for all data (n=1)

**Figure 1B**: Diagram representing the first initial test selection for the entire FORECAST population, randomised to either Standard Care arm or Experimental arm (CTCA+/- FFRCT)

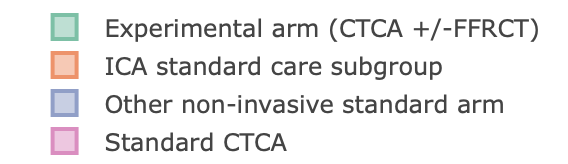
A diagram of a diagram

Description automatically generated with medium confidence

*P*=0.3

**Figure 2:** Total cardiac costs at 9 months in CTCA stratum by randomisation group represented as median (IQR). Distribution at 9-months costs in pound sterling (£) by randomised assignment. The top line of each box is the 75th percentile, the bottom line is the 25th percentile, and the line inside the box is the median (50th percentile).

A graph of different colored squares

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***P*<0.001**

**Figure 3:** Total cardiovascular costs at 9 months in the 4 patients subgroups from left to right; CTCA stratum experimental arm (CTCA+/- FFRCT); non CTCA stratum standard care invasive subgroup; non CTCA stratum standard care non invasive subgroup, CTCA stratum standard care group. Represented as median (IQR). Distribution of 9-months costs in UK pounds by randomised assignment. The top line of each box is the 75th percentile, the bottom line is the 25th percentile, and the line inside the box is the median (50th percentile).

**Data Availability Statement**

The data underlying this article were analysed using data originally collected for the FORECAST trial (NCT03187639) by permission from Southampton Clinical Trials Unit MP 131, Southampton General Hospital, UK. Data will be shared on request to the corresponding author with permission of Southampton Clinical Trials Unit.

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