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Research paper

Randomized comparison of chest pain evaluation with FFR_{CT} or standard care: Factors determining US costs

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ABSTRACT

Background: FFR_{CT} assesses the functional significance of lesions seen on CTCA, and may be a more efficient approach to chest pain evaluation. The FORECAST randomized trial found no significant difference in costs within the UK National Health Service, but implications for US costs are unknown. The purpose of this study was to compare costs in the FORECAST trial based on US healthcare cost weights, and to evaluate factors affecting costs.
Methods: Patients with stable chest pain were randomized either to the experimental strategy (CTCA with selective FFR_{CT}), or to standard clinical pathways. Pre-randomization, the treating clinician declared the planned initial test. The primary outcome was nine-month cardiovascular care costs.
Results: Planned initial tests were CTCA in 912 patients (65%), stress testing in 393 (28%), and invasive angiography in 94 (7%). Mean US costs did not differ overall between the experimental strategy and standard care (cost difference +7% (+$324), CI −12% to +26%, p = 0.49). Costs were 4% lower with the experimental strategy in the planned invasive angiography stratum (p for interaction = 0.66). Baseline factors independently associated with costs were older age (+43%), male sex (+55%), diabetes (+37%), hypertension (+61%), hyperlipidemia (+94%), prior angina (+24%), and planned invasive angiography (+160%). Post-randomization cost drivers were coronary revascularization (+348%), invasive angiography (267%), and number of tests (+35%).

Abbreviations: CI, 95% confidence interval; CTCA, Computed tomography coronary angiography; FFR, Fractional flow reserve; FFR_{CT}, Fractional flow reserve derived from computed tomography coronary angiography; FORECAST, Fractional Flow Reserve Derived from Computed Tomography Coronary Angiography in the Assessment and Management of Stable Chest Pain; PLATFORM, Prospective Longitudinal Trial of FFR_{CT}: Outcomes and Resource Impacts; UK, United Kingdom; US, United States.

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Conclusions: Initial evaluation of chest pain using CTCA with FFR_{CT} had similar US costs as standard care pathways. Costs were increased by baseline coronary risk factors and planned invasive angiography, and post-randomization invasive procedures and the number of tests.
Registration at ClinicalTrials.gov (NCT03187639).

1. Introduction

There are many options for the evaluation of patients with stable chest pain suspected to be due to myocardial ischemia.[1] Stress testing has been the mainstay of diagnostic evaluation, with detection of reversible myocardial ischemia by either electrocardiography, echocardiography, nuclear perfusion imaging, or cardiac magnetic resonance imaging. Non-invasive computed tomography coronary angiography (CTCA) is now an alternative to these functional tests, and provides an anatomic evaluation of the coronary arteries. An evaluation strategy based on CTCA had similar clinical outcomes as an evaluation strategy based on functional testing in the PROMISE randomized trial,[2] and the most recent clinical guidelines for the evaluation and diagnosis of chest pain gave Class I recommendations to both CTCA and stress imaging.[3] CTCA is a very sensitive technique to detect coronary stenoses, but the visual appearance of a coronary lesion is not necessarily a good indication of its functional significance.[4,5] The recent development of fractional flow reserve measurement based on the CTCA dataset (FFR_{CT}) offers the possibility of obtaining both anatomic and functional data from a single examination,[5] which might be the most cost-effective strategy to evaluate chest pain.[6]

Observational studies suggest that an evaluation strategy for stable chest pain based on CTCA with selective FFR_{CT} might be both clinically effective and cost-saving, particularly among patients who otherwise would otherwise undergo invasive coronary angiography.[5–11] The FORECAST randomized trial was designed to test whether an initial evaluation strategy based on CTCA with selective FFR_{CT} would be superior, in terms of resource utilization and quality of life, than standard evaluation strategies in patients with stable chest pain.[12] The trial was conducted in the National Health Service of the United Kingdom (UK), and recently reported equivalent clinical and economic outcomes.[13] Given that the economic structure of health care in the United States (US) is different from that of the UK, the costs of evaluation and treatment may be different as well. The purpose of this prespecified sub-study was therefore to evaluate the economic outcomes of the FORECAST trial in a US context. We also sought to examine the costs in more depth, including results in different segments of the population, and to determine the impact of clinical characteristics on costs.

2. Methods

The design and main results of the FORECAST trial have been previously reported.[12,13] In brief, patients with low risk, stable chest pain, who were at least 18 years of age and referred to one of eleven UK Rapid Access Chest Pain Clinics were screened for eligibility. Patients were excluded if they had a history consistent with acute coronary syndrome, did not require further testing to evaluate their symptoms, were unable to undergo a CTCA, had a history of previous coronary revascularization, or had a life expectancy of less than 12 months. Eligible patients who consented to participate were randomized to either: 1) the standard care strategy, following local clinical pathways based on UK chest pain guidelines[14]; or 2) the experimental strategy, consisting of an initial CTCA with selective FFR_{CT} analysis in patients found to have at least one coronary stenosis of 40% or more in a coronary segment of sufficient caliber for revascularization.

Patients in the standard care strategy could be referred to either a stress test (i.e., exercise electrocardiography, stress echocardiography, stress nuclear medicine perfusion imaging, or stress cardiac magnetic resonance), a CTCA without FFR_{CT}, or directly to invasive coronary angiography. Prior to randomization, the treating clinician recorded the initial diagnostic test that would be performed in the event the patient were randomized to the standard care strategy. The test chosen *a priori* was used to classify patients into one of three strata of planned initial evaluation: stress testing, CTCA, and invasive coronary angiography.

The primary endpoint for the trial was total cardiac costs over nine months. The use of cardiac resources was recorded prospectively, and included invasive and non-invasive tests, revascularisation procedures, hospital admissions due to a cardiovascular cause (including myocardial infarction, arrhythmia, heart failure, coronary revascularisation, and other cardiac-related admissions), outpatient clinic and emergency department visits, and cardiac medications. Data were collected through direct patient contact by research staff at each center, as well as from local healthcare records.

The total cost for each patient in the trial was calculated by counting the number of units of each resource used during the nine months following randomization (e.g. the number of exercise ECGs), assigning a cost to each resource based on a standardized price list (e.g. $170 for each exercise ECG, Appendix A), then totaling the cost of all the resources used by each patient during the trial. The present analysis is based on cost weights using the national average costs from the United States Medicare system for tests, procedures, hospitalizations, and visits, and internet pharmacy costs for 90-day supplies of cardiac medications (Appendix A). The previous report from FORECAST[13] used cost weights based on tariffs in the UK National Health Service.

The statistical analysis used an intention-to-treat approach and compared nine-month costs for the individual patients randomly assigned to each strategy. Nine-month total cardiac costs were compared using the non-parametric Wilcoxon rank-sum test because of the skew in cost data. Costs were also compared in the three prespecified strata of planned initial test (stress test, CTCA, or invasive angiography) declared *a priori*.

Total costs were tested for their association with baseline factors in a multivariable model that used the natural logarithm of nine-month cost as the dependent variable and baseline factors (Table 1) as independent variables. We used tests of statistical interaction to assess effect modification by stratum of planned initial evaluation. We performed exploratory

Table 1
Baseline Characteristics by random assignment.

Baseline characteristics	Standard Care Group	Experimental Group
	n = 700	n = 699
Age (years)*	59.6 (10.8)	60.0 (10.9)
Sex		
Male	364 (52%)	359 (51%)
Female	336 (48%)	340 (49%)
Race		
White	641 (92%)	635 (91%)
Other	59 (8%)	64 (9%)
Smoking		
Never	319 (46%)	348 (50%)
Former	276 (39%)	259 (37%)
Current	104 (15%)	92 (13%)
Diabetes	86 (12%)	91 (13%)
Hypertension	234 (33%)	266 (38%)
Hyperlipidemia	198 (28%)	231 (33%)
Chronic Kidney Disease	10 (1%)	12 (2%)
Family History of CAD	426 (61%)	416 (60%)
Previous Myocardial Infarction	3 (0.4%)	5 (0.7%)
Previous Angina	219 (31%)	188 (27%)
Planned Initial Test		
CTCA	459 (66%)	453 (65%)
Stress Testing	193 (28%)	200 (29%)
Invasive Angiography	48 (7%)	46 (7%)

* – Mean (standard deviation).

analyses that included post-randomization factors as independent variables to examine which factors were primary drivers of the observed costs.

The trial complies with the Declaration of Helsinki, was approved by the South Central Berkshire B Research Ethics Service Committee (REC Reference 18/SC/0490, IRAS Project ID: 231,037) and is registered at ClinicalTrials.gov (NCT03187639). The trial funder (HeartFlow) had no role in the design, conduct, analysis, or reporting of the results. The trial sponsor was University Hospital Southampton Research and Development Department, Southampton, UK.

3. Results

As reported previously,[13] 1399 patients were randomized between December 2017 and July 2019 at one of eleven participating Rapid Access Chest Pain Clinics in the UK. The baseline characteristics of the 700 patients randomized to standard care strategy were similar to those of the 699 patients randomized to the experimental strategy (Table 1). In the standard care group, 430 patients (61%) had CTCA as their initial test, 187 (27%) had a stress test, 47 (7%) had an invasive coronary angiogram, and 36 (5%) had no initial test (Table 2). In the experimental strategy group, 674 patients (96%) had a CTCA, 220 (31%) of whom had an FFR_{CT} performed according to the protocol, and 25 (4%) had no initial test.

The total number of tests done was similar among patients assigned to the experimental strategy and patients assigned to standard care pathways (mean 1.32 vs 1.36, p = 0.31). Two or more tests were done in 23% of patients in the experimental strategy, versus 29% in the standard care strategy (Table 2). Invasive angiography was performed in significantly fewer patients in the experimental strategy (19%) than in the standard care strategy (25%, p = 0.01), while use of coronary revascularization was similar in both groups (Table 3).

3.1. US cost weight analyses

Using US cost weights, the mean total cardiac costs during the nine-month follow-up period did not differ significantly between the experimental strategy and standard care: costs were $324 higher (+7%) in the experimental strategy ($5215 vs $4891, p = 0.76); the bootstrap confidence interval for the difference in costs ranged from $591 lower (−12%) to $1258 higher (+26%). The distribution of costs was skewed upward by the minority of patients with higher costs, such that the median costs were much lower than the mean costs in both groups (Fig. 1).

3.2. Stratified analyses

Prior to randomization, the enrolling clinician recorded the initial test that would be performed in the event the patient was randomized to the standard care strategy. Overall, 912 patients (65%) had CTCA planned as the initial test, 393 patients (28%) had a stress test planned as the initial test, and 94 patients (7%) had invasive angiography planned as the initial test. Patients with invasive angiography planned as the initial test were older, more likely to be male, and have hypertension, hyperlipidemia, and a history of prior angina (Table 4). Among patients who were randomized to standard care, the type of the test actually performed was the same as the planned test in 661 of the 664 patients (99.5%) who had an initial test performed.

Table 2
Initial Test and number of follow-up tests, by randomly assigned strategy.

Initial test performed		Number of follow-up tests performed		
Standard care group	(N = 700)	None	One	Two or more
Non-invasive tests				
CTCA	430 (61%)	308 (72%)	77 (18%)	45 (11%)
Stress echo	103 (15%)	80 (78%)	14 (14%)	9 (9%)
Perfusion scan	13 (1.8%)	11 (85%)	2 (15%)	0 (0%)
Stress MRI	1 (0.1%)	0 (0%)	1 (100%)	0 (0%)
Exercise ECG	70 (10%)	33 (47%)	31 (44%)	6 (9%)
Invasive tests				
Coronary angiogram	47 (6.7%)	33 (70%)	12 (26%)	2 (4%)
No initial test done	36 (5.1%)	27 (75%)	6 (17%)	3 (8%)
TOTAL	700 (100%)	492 (70%)	143 (20%)	63 (9%)
Experimental group	(N = 699)	None	One	Two or more
CTCA + FFRct	220 (31%)	107 (49%)	79 (36%)	34 (15%)
CTCA alone	454 (65%)	409 (90%)	28 (6%)	17 (4%)
No initial test done	25 (3.6%)	17 (68%)	3 (12%)	5 (20%)
TOTAL*	699 (100%)	533 (76%)	110 (16%)	56 (8%)

The stratum of planned initial test was associated with total costs, and affected the relative costs of the randomized groups (Fig. 1). The mean total costs were significantly higher among all patients in the invasive angiography planned stratum ($13,115) than in either the CTCA planned stratum ($4531), or the stress test planned stratum ($4311). The relative costs of the experimental strategy and standard care differed among the strata, with $547 lower costs (−4%) in the invasive stratum (interaction p-value = 0.23), $65 lower costs (−1%) in the stress test stratum (interaction p-value 0.40), and $627 higher costs (+15%) in the CTCA stratum (the reference stratum for interaction testing).

Within the stratum of patients who had CTCA planned as the initial test, the number of patients who had two or more tests was lower among patients assigned to the experimental strategy than in patients assigned to the standard care strategy (Table 3). Fewer patients assigned to experimental strategy had an invasive coronary angiogram (17% vs 19%) in the planned CTCA stratum (Table 3). The total medical costs during the trial were slightly, but not significantly, higher in the patients assigned to the experimental strategy in the CTCA-planned stratum: $4845 vs $4218, p = 0.92 (Fig. 1).

Within the stratum of patients with stress testing planned as the initial test, the number of patients who had two or more tests was lower in patients assigned to experimental strategy than to the standard care strategy (Table 3). Significantly fewer patients assigned to the experimental strategy went on to invasive coronary angiography (15% vs 22%, p < 0.001), while similar numbers of patients underwent coronary revascularization (Table 3). The total medical care costs were slightly, but not significantly, lower with the experimental strategy in the planned stress testing stratum: $4289 vs $4354, p = 0.76 (Fig. 1).

Within the stratum of patients who had invasive coronary angiography planned as the initial test, the number of tests done were significantly higher in the experimental strategy than for standard care (Table 3). Significantly fewer patients assigned to the experimental strategy (63%) than in the standard care group (96%) eventually had an invasive coronary angiogram (Table 3). The total cost of care during the trial was slightly, but not significantly, lower in the patients assigned to the experimental strategy ($12,836 vs $13,383, p = 0.86) in the planned invasive angiography stratum (Fig. 1).

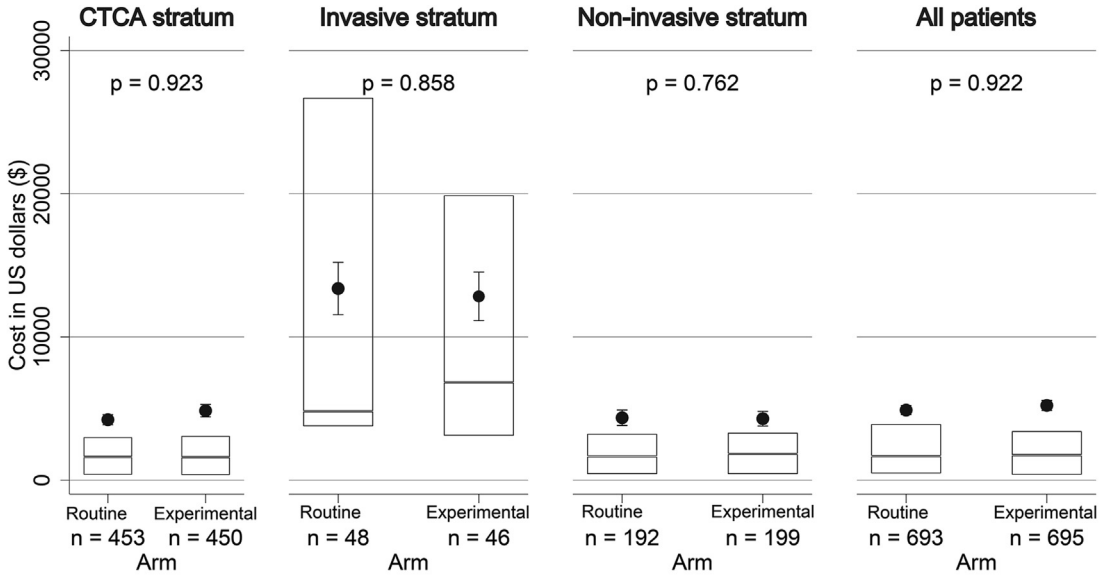
3.3. Correlates of cost

Several baseline, pre-randomization factors were significantly correlated with nine-month costs (Table 5). Older age, male sex, diabetes, hypertension, and hyperlipidemia were strong predictors of higher costs in unadjusted models (all p < 0.001), and remained significant, independent predictors of cost in a model that contained all baseline clinical factors (Table 5). A pre-randomization plan to perform invasive angiography as the initial test was associated with a 260% increase in total costs during the study (p < 0.001), even after adjustment for other baseline factors (Table 5). Random assignment to the experimental strategy was not a significant predictor of costs, either with or without adjustment for other baseline factors (Fig. 2 and Table 5).

In an exploratory analysis that included post-randomization factors, the strongest predictor of total cost was performance of coronary revascularization, followed by use of invasive angiography, and total number of tests performed (Table 5). After adjustment for these post-randomization factors, the only baseline factors that remained

Table 3
Initial stratum of planned test and follow-up tests and procedures, by randomized strategy.

			Number of patients with tests					
Stratum	Randomized strategy	N	None	One	≥Two	Non-invasive only	Invasive angiogram	CABG or PCI
CTCA	Standard	459	23 (5%)	311 (68%)	125 (27%)	349 (76%)	87 (19%)	56 (12%)
CTCA	Experimental	453	11 (2%)	344 (76%)	98 (22%)	364 (80%)	78 (17%)	59 (13%)
Stress Test	Standard	193	2 (1%)	127 (66%)	64 (33%)	148 (77%)	43 (22%)	22 (11%)
Stress Test	Experimental	200	5 (3%)	160 (80%)	35 (18%)	166 (83%)	29 (15%)	24 (12%)
Invasive	Standard	48	2 (4%)	33 (69%)	13 (27%)	0 (0%)	46 (96%)	19 (40%)
Invasive	Experimental	46	1 (2%)	15 (33%)	30 (65%)	16 (35%)	29 (63%)	19 (41%)
TOTAL	Standard	700	27 (4%)	470 (67%)	203 (29%)	497 (71%)	176 (25%)	97 (14%)
TOTAL	Experimental	699	17 (2%)	412 (59%)	270 (39%)	546 (78%)	136 (19%)	102 (15%)



	CTCA stratum		Invasive stratum		Non-invasive stratum		All patients	
	Routine (453)	Experimental (450)	Routine (48)	Experimental (46)	Routine (192)	Experimental (199)	Routine (693)	Experimental (695)
Median (-/+IQR)	1621 (361 to 3018)	1603 (334 to 3092)	4812 (3745 to 26722)	6826 (3079 to 19903)	1653 (404 to 3241)	1838 (404 to 3323)	1673 (456 to 3923)	1740 (361 to 3433)
Mean (-/+ 1 SE)	4218 (3862 to 4575)	4845 (4411 to 5280)	13383 (11553 to 15212)	12836 (11141 to 14530)	4354 (3812 to 4896)	4289 (3778 to 4801)	4218 (4574 to 5207)	5215 (4970 to 5589)

Fig. 1. Cost by random assignment and the planned initial test. The vertical axis indicates the 9-month costs in US dollars. The boxes show the median cost (center line), the 75th percentile (top line) and the 25th percentile (bottom line). The circle shows the mean cost, and the error bars show ± one standard error of the mean. The p-values are for the comparison between the experimental group and the standard care group, overall and in the three strata of intended initial test.

significantly associated with total costs were age, being an ex-smoker, hypertension and hyperlipidemia (Table 5).

3.4. Sensitivity analyses

The overall results were not sensitive to the cost of FFR_{CT} testing. When the cost of FFR_{CT} was increased from $631 to $1000 in the analysis, the relative cost of the experimental strategy increased from +7% (confidence interval −12% to +26%) to +9% (confidence interval −10% to +28%). When the cost of FFR_{CT} was reduced to zero, the relative cost of the experimental strategy decreased from +7% to +3% (confidence interval −16% to +21%).

As previously reported,[10] all results were materially unchanged when the analyses were repeated using UK cost weights instead of US cost weights. Total costs were 7% higher (confidence interval −12% to +26%) in the experimental strategy using US cost weights, and 12% higher (confidence interval −2% to +28%) using UK cost weights.

Results were consistent in subgroups defined by age, sex, diabetes, and prior history of angina (Fig. 3).

3.5. Employment

At baseline, 579 patients (41%) were working full-time, 169 (12%) were working part-time, and 648 (46%) were not currently employed. The number of days taken off from work for tests or treatment of chest pain did not differ significantly (p = 0.18) between the 368 employed patients assigned to the experimental strategy (mean 3.4 days, SD 12.8; median 0 days), and the 380 employed patients assigned to the standard care strategy (mean 2.4 days, SD 9.1, median 0 days). A similar number of patients lost one or more days of work: 112 (30%) in the experimental group and 109 (29%) in the standard care group.

3.6. Evaluation time

The time to reach a definitive management plan was significantly shorter (p < 0.001) among patients assigned to the experimental strategy compared with standard care pathways (mean 2.7 vs. 3.0 months, median 1.9 vs. 2.2 months). Similarly, the time to completion of initial management was significantly shorter (p < 0.001) in the experimental

Table 4
Baseline clinical characteristics by stratum of planned initial test.

Baseline characteristics	CTCA Stratum	Invasive Stratum	Stress test stratum
	n = 912	n = 94	n = 393
Age (years)	58.6	68.7	60.5
Sex			
Male	451 (49%)	59 (63%)	213 (54%)
Female	461 (51%)	35 (37%)	180 (46%)
Race			
White	813 (89%)	84 (89%)	376 (96%)
Other	99 (11%)	10 (11%)	17 (4%)
Smoking			
Never	443 (49%)	46 (49%)	178 (45%)
Former	336 (37%)	43 (46%)	156 (40%)
Current	132 (14%)	5 (5%)	59 (15%)
Diabetes	113 (12%)	13 (14%)	51 (13%)
Hypertension	309 (34%)	44 (47%)	147 (37%)
Hyperlipidemia	260 (29%)	48 (51%)	121 (31%)
Chronic Kidney Disease	17 (2%)	2 (2%)	3 (1%)
Family History of CAD	560 (61%)	54 (57%)	228 (58%)
Previous Myocardial Infarction	4 (0.4%)	0 (0%)	4 (1%)
Previous Angina	292 (32%)	65 (69%)	50 (13%)

Table 5
Relative effects of clinical factors to increase total cost (ratios).

	Model Adjustment for:		
Baseline Factors	None	Baseline Only	Baseline & Follow-up
Assigned to Experimental	1.09	1.05	1.11
Invasive Stratum	5.33**	2.60**	1.16
Stress Test Stratum	1.04	0.95	0.99
Age (per 10 years)	1.68**	1.43**	1.19**
Male Sex	1.67**	1.55**	0.98
Diabetes	2.34**	1.37*	1.09
Current Smoking	0.98	1.17	1.06
Former Smoker	1.37**	1.15	1.15*
Hypertension	2.60**	1.61**	1.71**
Hyperlipidemia	3.32**	1.94**	1.91**
Chronic Kidney Disease	2.06*	1.27	1.00
Prior Angina	1.86**	1.24*	0.87
Follow-up Factors	None	Baseline Only	Baseline & Follow-up
Invasive angiography	13.85**		2.67**
Coronary revascularization	20.86**		3.43**
Number of tests	2.77**		1.35**

* – $p < 0.05$, ** – $p < 0.001$.

strategy than with standard care pathways (mean 2.8 vs 3.1 months, median 2.0 vs. 2.3 months).

4. Discussion

There are many options for the initial evaluation of patients with chest pain, based either on detection of myocardial ischemia with a functional study (e.g., stress testing) or the detection of coronary disease with angiography. It has been uncertain whether one evaluation strategy leads to better clinical outcomes, or is more efficient by virtue of using fewer medical resources, thus having lower costs. The FORECAST randomized trial tested, for the first time, whether a strategy of initial CT coronary angiography with selective FFR_{CT} testing would improve clinical and economic outcomes compared with the standard clinical care pathways. The present analysis found that an evaluation strategy based on FFR_{CT} had no significant effect overall on costs using US-specific cost weights, even though it significantly reduced the use of invasive coronary angiography. Only 7% of the trial population had planned initial invasive coronary angiography, however, and in this small, yet important, subgroup the experimental strategy reduced invasive angiography by a third and lowered costs by 4%.

The first report from FORECAST used the UK National Health Service tariffs to calculate the costs of care,[13] whereas the present prespecified secondary analysis examined the costs based on US national average reimbursements in the Medicare system. The overall results were quite consistent, despite the substantial differences in resource costs between the UK and the US. This finding is important for the interpretation of the FORECAST results in the US healthcare system, but not unexpected, since the resource use patterns are the primary determinants of overall cost. In this study the strongest determinants of total costs were the use of coronary revascularization and use of invasive coronary angiography, which are far more costly than any of the non-invasive tests, including FFR_{CT}, both in the US and in the UK.

The present analysis confirms and extends the observations in the non-randomized, observational PLATFORM study.[10] In PLATFORM, costs were significantly lower in patients managed with CTCA and FFR_{CT}, but 65% of the patients in PLATFORM had planned invasive angiography, compared with just 7% of the patients in FORECAST. In PLATFORM, costs were significantly lower with FFR_{CT} in the invasive stratum, and there was no significant difference in costs in the non-invasive stratum (interaction p-value < 0.01). This same pattern is evident in FORECAST (Fig. 1), with a trend towards lower costs in the invasive angiography planned stratum, and similar costs in the remaining patients, but the power to test for an interaction in FORECAST was low because of the small number of patients with planned invasive angiography. PLATFORM also did not include a CCTA alone option, which also may have lowered costs in the invasive angiography stratum. Randomized trials of CTCA in patients for whom invasive angiography was planned have reported that CTCA alone can reduce invasive angiography and costs.[15–17]

We found that many baseline clinical factors were significantly associated with higher cost (Table 4). The baseline factors of older age, male sex, diabetes, hyperlipidemia, and a history of prior angina were each significant and independent predictors of cost, with much stronger effects on cost than that of random assignment to the experimental strategy (Fig. 2). Interestingly, the effects of many of these baseline clinical factors appeared to be mediated through their impact on the subsequent use of invasive angiography and coronary revascularization, since their strengths of association with cost were greatly attenuated after adjustment for these post-randomization factors (Table 4). One interpretation of these results is that because these baseline factors predict the presence of obstructive coronary disease, they are associated with having abnormal non-invasive tests, which in turn leads to follow-up invasive tests and procedures to confirm, and treat, the underlying coronary lesions.

CTCA was the planned initial test in 65% of patients in FORECAST, and it appears that the high use of CTCA in the standard care arm diminished the contrast between the two randomized groups. In the CTCA stratum, both randomized groups had the same initial test, so the trial essentially compared the consequences of evaluating an abnormal CTCA either with FFR_{CT} or with other tests. Interestingly, in the CTCA planned stratum, 27% of patients randomized to standard care had two or more tests performed (Table 3), compared with 26% who had an FFR_{CT} performed as part of the experimental strategy, and the mean number of tests in the two groups was very similar (1.35 vs 1.34). Additional tests were ordered based on physician choice in the standard care arm, whereas FFR_{CT} testing was performed by protocol in the experimental strategy whenever an obstruction $\geq$ 40% was found in a segment suitable for revascularization. It is likely that selective use of FFR_{CT} after an abnormal CTCA, based on the need to document ischemia prior to planned coronary revascularization, rather than simply based on the angiographic appearance, might be a more efficient use of FFR_{CT}, and still lead to equivalent clinical outcomes. A formal comparison between randomized patients within the planned CTCA stratum in FORECAST is currently ongoing.

In assessing economic outcomes, the relative costs of the resources are very important. In this study, the cost assigned to FFR_{CT} ($631) was higher than that of the most commonly used alternative tests, particularly exercise electrocardiography ($170) and stress echocardiography ($404), but was lower than the cost of stress nuclear perfusion imaging ($955) and invasive

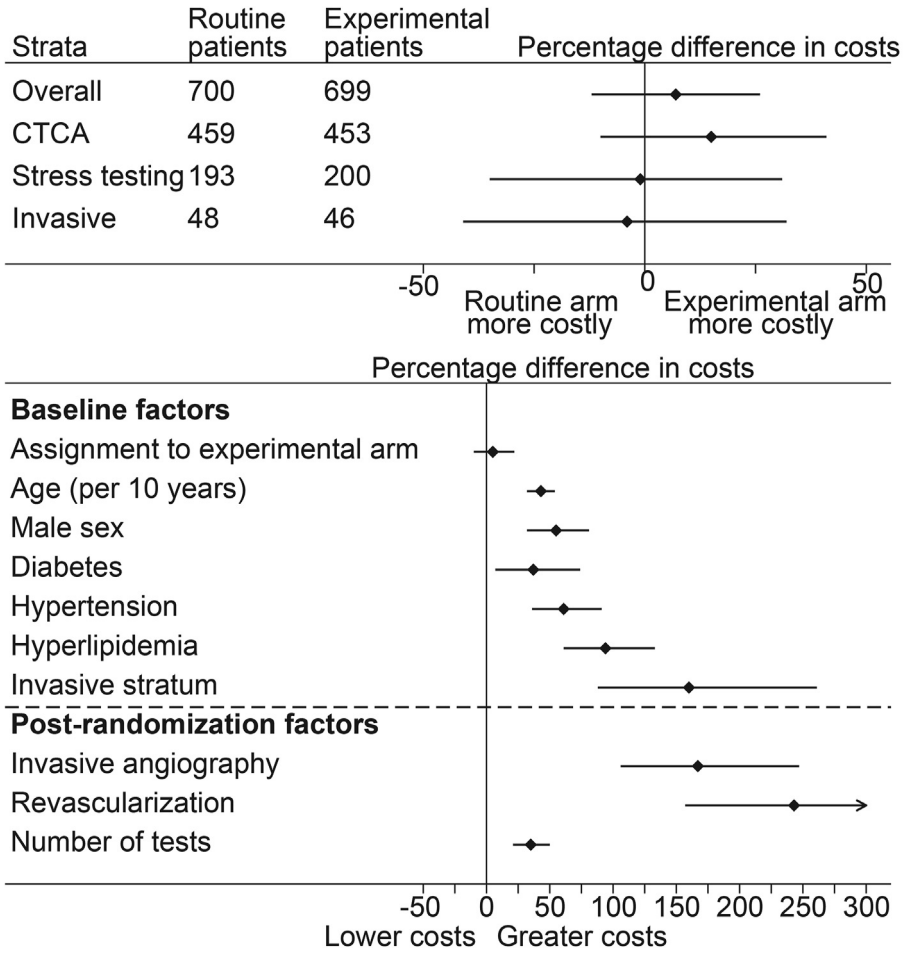


Fig. 2. Factors affecting 9 month costs. The percentage increase in 9 month costs (points) and associated 95% confidence intervals according to: random assignment to the experimental strategy or routine care, overall and in strata of intended initial test (top panel); baseline, pre-randomization factors affecting cost (middle panel); and post-randomization factors affecting cost (bottom panel).

coronary angiography ($2019). The cost of any of these initial tests was, however, only a fraction of the total cost of evaluation and treatment (mean of $5425), so simply comparing the costs of the initial tests can be misleading. In particular, while the price tag for the initial test is easily known, the effect of that test on subsequent management is unknown, and a randomized trial provides an unbiased comparison of the consequences of choosing the initial test. FORECAST was designed to compare the consequences of alternative initial testing strategies, including their economic consequences, in a rigorous fashion. These comparisons were facilitated by the *a priori* declaration of the initial test that was planned to be used in the event the patient was randomized to standard care, since there were great differences in the clinical characteristics of patients who had planned invasive and non-invasive evaluation (Table 4). Indeed, the stratum of planned initial testing was the strongest baseline factor predictive of total costs in the trial (Table 5).

The experimental strategy in FORECAST led more quickly to a definitive management plan and completion of initial evaluation and treatment by an average of 9 days. The use of FFR_{CT} testing was thus more efficient in this trial, and this is likely to make the strategy more attractive to patients, especially when also considering the 22% lower rate of invasive coronary angiography. Use of the cardiac catheterization laboratory was also more efficient in the experimental strategy because the number of invasive angiograms that did not lead to a PCI was reduced. Additionally, the experimental strategy did not require patients to return for a follow-up stress test, since the FFR_{CT} analysis could be performed within 24 h using the previously obtained CTCA dataset. It is unlikely that a follow-up stress test could be performed within a day or two, so that evaluation can be completed sooner in the experimental strategy.

There are several important limitations to this study. The major limitation is that after design of the trial, care guidelines and subsequently routine practice in the UK shifted towards CTCA as a first-line test to evaluate patients with stable chest pain, so almost two-thirds of the participants were designated *a priori* to have a CTCA rather than a non-invasive stress test. With most participants in both arms receiving an initial CTCA, the power of the trial to show differences in clinical and economic outcomes was potentially blunted. The results in the stress testing stratum were, however, similar to the results in the overall trial (Table 3, Fig. 1), which suggests that these findings are relevant to practice settings that rely more on stress testing, such as the US. A related limitation is that in this low-risk population, only 7% of participants were recommended for initial invasive coronary angiography, again reducing the contrast between the randomized groups. The primary endpoint was cardiovascular care costs over nine months, which may have been too short to show any long-term savings from the experimental strategy, although prior studies of similar duration have shown reductions in the costs of initial evaluation and management.[10] This trial was conducted in clinically stable outpatients, not among patients with acute chest pain or patients being evaluated in an emergency department, so the findings should not be extrapolated to those clinical settings. Finally, the trial was conducted in the UK National Health System, and the effect of the experimental strategy on the time to definitive management would likely have been shorter in the US. Nevertheless, avoiding the need to return for follow-up testing would also occur in the US context, and so it is likely that evaluation time would be shorter in other healthcare systems.

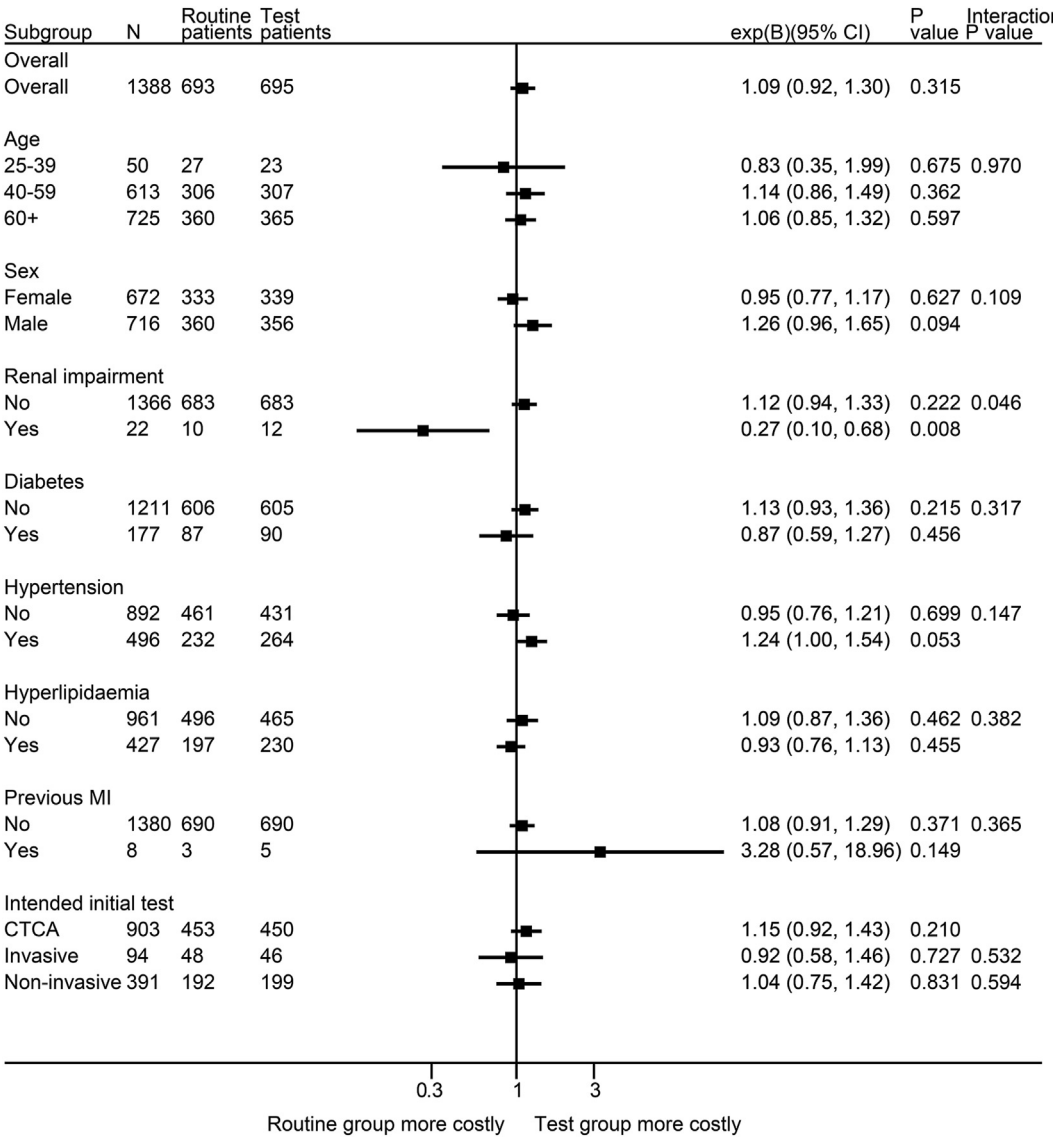


Fig. 3. Cost by baseline factors and random assignment. The relative effect of assignment to the experimental group compared with the standard care group is displayed overall, and within subgroups defined by baseline clinical characteristics. The relative effect on cost is expressed as the ratio: the 1.09 indicates 9% higher costs in the experimental group, based on a log-linear model of costs. The 95% confidence limits on the point estimate are indicated by the length of the error bars around square showing the overall effect on random assignment on cost in each clinical group. The p-values are for comparison between experimental and standard care in each group; the interaction p-value assesses the heterogeneity of treatment effect by the clinical factor.

In conclusion, an initial evaluation based on CT coronary angiography with selective FFR_{CT} did not reduce costs significantly among low-risk patients with stable chest pain, based on US costs, even though it did significantly reduce the use of invasive coronary angiography and the time needed to complete the work-up. The overall cost of initial management was increased in patients with more cardiovascular risk factors, and the use of coronary revascularization and invasive coronary angiography were the strongest determinants of overall cost.

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Appendix A

US Cost Weights used in this analysis.

Resource	Cost Weight Source (National averages)	Cost Weights (US Dollars)
DIAGNOSTIC TEST		
Exercise ECG	CPT 93017	170
Stress Echo	CPT 93351	404
Perfusion Imaging (SPECT)	CPT 78452 plus 93015	955
Perfusion Imaging (PET)	CPT 78492	1532
Stress cMRI	CPT 75559 plus 93105	576
cCTA	CPT 75574	334
CAC score	CPT 75571	108
FFRct	Outpatient fee	631
Invasive Angiography	CPT 93454	2019
FFR (cath)	CPT 93571	77
Out-patient visit	CPT 99214	110
ED visit	CPT 99284	122
HOSPITAL ADMISSIONS		
PCI	DRGs 246-251	14,243
CABG	DRGs 233-236	32,585
MI Admission	DRGs 280-285	7,314
Stroke Admission	DRGs 061-068	8,123
Transient Ischemic Attack	DRG 069	4,774
Heart Failure	DRGs 291-293	7,353
Angina or Chest Pain	DRG 311, 313	4,351
Arrhythmia	DRGs 308-310	5,162
Other CV conditions	DRGs 314-316	9,938
Heart valve replacement	DRGs 216-221	41,159
MEDICATIONS	Goodrx.com price for 90 day supply	
Aspirin	Aspirin 81 mg	3
Statin	Pravastatin 40 mg	141
Clopidogrel	Clopidogrel 75 mg	325
Prasugrel	Prasugrel 10 mg	1013
Ticagrelor	Ticagrelor 90 mg	706
Beta Blocker	Atenolol 50 mg	35
Calcium Channel Blocker	Diltiazem 60 mg	31
ACE Inhibitor	Enalapril 20 mg	52
ARB	Losartan 50 mg	148
Alpha Blocker	Prazosin 2 mg	67
Diuretic	Furosemide 20 mg	26
Oral Nitrate	Isosorbide dinitrate 20 mg	86

Cost weights for diagnostic tests are an average of 1) the 2020 national reimbursement rates for the physician fee schedule and 2) the 2020 Hospital Outpatient Prospective Payment System schedule (technical fee plus professional fee). The national physician fee schedule rate for FFR_{CT} was imputed as one-third the fee for invasive coronary angiography, consistent the relative fees for these tests in the National Hospital Outpatient PPS schedule.

Hospital reimbursements were set using Diagnosis Related Group (DRG) weights and a national conversion factor of $5796.63 and physician fees based on length of stay and procedure. The final cost for each diagnosis was a weighted average of the cost of individual DRGs, weighted by the frequency of admissions nationally in the individual DRG.

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