

Stratified medicine using invasive coronary function testing in angina: A cost-effectiveness analysis of the British Heart Foundation CorMicA trial

R. Heggie^{a,*}, A. Briggs^b, B. Stanley^c, R. Good^d, P. Rocchiccioli^{d,e}, M. McEntegart^{d,e}, S. Watkins^d, H. Eteiba^d, A. Shaukat^d, M. Lindsay^d, K. Robertson^d, S. Hood^d, R. McGeoch^f, R. McDade^d, E. Yii^e, D. Collison^{d,e}, K. Oldroyd^{d,e}, T.J. Ford^{d,e,g}, C. Berry^{d,e,**}

^a Health Economics and Health Technology Assessment (HEHTA), Institute of Health & Wellbeing, 1 Lilybank Gardens, Glasgow, United Kingdom

^b London School of Hygiene & Tropical Medicine, 15-17 Tavistock Place, London, United Kingdom

^c Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow, Glasgow, United Kingdom

^d West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, United Kingdom

^e British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom

^f University Hospital Hairmyres, East Kilbride, United Kingdom

^g University of New South Wales, Sydney, New South Wales, Australia

ARTICLE INFO

Article history:

Received 7 April 2021

Received in revised form 27 April 2021

Accepted 10 May 2021

Available online 13 May 2021

Keywords:

INOCA
Stratified medicine
Cost-effectiveness

ABSTRACT

Aim: Coronary angiography is indicated in many patients with known or suspected angina for the investigation of coronary artery disease (CAD). However, up to half of patients with symptoms of ischaemia have no obstructive coronary arteries (INOCA). This large subgroup includes patients with suspected microvascular angina (MVA) and/or vasospastic angina (VSA). Clinical guidelines relating to the management of patients with INOCA are limited. Uncertainty regarding the diagnosis of patients with INOCA presents a health economic challenge, both in terms of healthcare resource utilisation and of quality-of-life impact on patients.

Methods: A cost-effectiveness analysis of the introduction of stratified medicine into the invasive management of INOCA, based on clinical and resource-use data obtained in the CorMicA trial, from a UK NHS perspective. The intervention included an invasive diagnostic procedure (IDP) of coronary vascular function during coronary angiography to define clinical endotypes to target with linked medical therapy. Outcomes of interest were mean total cost and QALY gain between treatment groups, and the incremental cost-effectiveness ratio. We undertook probabilistic sensitivity and scenario analyses.

Results: The incremental cost per QALY gained at 12 months was £4500 (£2937, £33264). Compared with a willingness-to-pay (WTP) threshold of £20,000 per QALY, the use of the IDP test is cost-effective. At this WTP threshold there is a 96% probability of the IDP being cost-effective, based on the uncertainty described by bootstrap analysis.

Conclusions: The burden of INOCA, particularly in women, is known to be significant. These findings provided new evidence to inform this unmet clinical need.

© 2021 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Coronary angiography is routinely performed in patients with suspected angina. Approximately four million elective coronary angiograms are performed each year in Europe and the United States

* Correspondence to: R. Heggie, Health Economics and Health Technology Assessment (HEHTA), Institute of Health & Wellbeing, 1 Lilybank Gardens, Glasgow G12 8RZ, United Kingdom.

** Correspondence to: C. Berry, British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom.

E-mail addresses: robert.heggie@glasgow.ac.uk (R. Heggie), colin.berry@glasgow.ac.uk (C. Berry).

[1,2]. However, up to half of patients with signs and/or symptoms of ischaemia have no obstructive coronary arteries (INOCA) presenting a diagnostic and therapeutic challenge for clinicians [2]. This large subgroup includes patients with suspected microvascular angina (MVA) and/or vasospastic angina (VSA) [3]. Coronary angiography is insensitive in visualising the micro-vessels [4]. Coronary angiography is also insensitive for coronary reactivity and a patient's susceptibility to vasospasm. The rationale for adjunctive coronary vascular function testing, in the form of an interventional diagnostic procedure (IDP) is as follows. Firstly, coronary angiography does not exclude a disorder of coronary vascular function, such as those relating to vasomotion or microcirculation [3]. Secondly, adjunctive coronary testing allows for the stratification of this

hitherto undifferentiated subpopulation [3]. This is important because discrimination between microvascular angina, vasospastic angina, both, or neither, allows for specific and distinct treatment regimes. Finally, adjunctive coronary function testing provides both patients and their physicians with prognostic information. Clinical guidelines relating to the management of patients with INOCA are limited by a lack of randomised controlled trials [5].

The uncertainty regarding the diagnosis of patients with INOCA presents a health economic challenge, both in terms of healthcare resource utilisation and of quality-of-life impact on patients. Patients with INOCA who remain undiagnosed are liable to re-present at primary or secondary care. This may result in additional GP consultations, outpatient cardiologist visits, diagnostic tests and repeat coronary angiography.

The British Heart Foundation (BHF) Coronary Microvascular Angina (CorMicA) trial was a randomised, controlled, developmental clinical trial of stratified medicine in patients with known or suspected angina undergoing clinically-indicated coronary angiography in the National Health Service.

The CorMicA study design and main trial results have been described in detail elsewhere [3,6,7]. In summary, 391 patients with angina undergoing invasive coronary angiography (standard care) were recruited between November 2016 and December 2017. 151 patients without angiographically obstructive CAD were randomised to either the intervention group (standard care, plus IDP-guided stratified medical therapy and cardiac rehabilitation) ($n = 76$) or control group (standard care, plus medical therapy and cardiac rehabilitation) ($n = 75$). The IDP consisted of guidewire-based assessment of coronary flow reserve, index of microcirculatory resistance, fractional flow reserve, followed by vasoreactivity testing with acetylcholine. Following the IDP, clinicians were able to update their diagnosis, if indicated, based on this additional information, and to tailor patient medical therapy and cardiac rehabilitation accordingly. The intervention resulted in a mean improvement of 13.6 units in the Seattle Angina Questionnaire summary score (primary outcome) at 12 months (95% CI: 7.3–19.9; $p < 0.001$).

The aim of this study was to undertake a cost-effectiveness analysis of the BHF CorMicA trial, using resource use and quality of life data from the trial, to estimate the potential cost-effectiveness of the use of the IDP among INOCA patients undergoing routine coronary angiography.

2. Methods

2.1. Overview

An economic evaluation was undertaken using clinical and resource use data obtained from the CorMicA feasibility trial and from the wider literature. We employed the standard methodology for an economic evaluation alongside a clinical trial [8]. A conceptual model was designed and presented to illustrate the patient pathway and to facilitate interpretation of the trial data.

2.2. Study perspective

The economic evaluation was undertaken from the perspective of the National Health Service (NHS) of the United Kingdom (U.K.) for cost year 2018/19, adhering to contemporary practice guidelines and the NICE reference case [9].

2.3. Time horizon

The economic evaluation estimated the cost and quality-of-life (QALY) gained, by trial arm, over the 1-year time horizon of the BHF CorMicA trial.

2.4. Discount rate

The discounting of NHS costs and health outcomes was not necessary for the economic evaluation as the CorMicA trial was limited to a 1-year time horizon.

2.5. Conceptual model of the CorMicA trial

We developed a conceptual model to illustrate the clinical pathway for each clinical strategy (Fig. 1).

The conceptual model begins with a patient with signs and/or symptoms of angina who has received coronary angiography and are subsequently diagnosed with no obstructive coronary artery disease (NOCAD). At this point, the standard care procedure would end.

In line with the CorMicA trial, patients may then receive either a “sham test” (control group) or the IDP (intervention group). In the control group branch of the model, patients receive the IDP but the results are not disclosed to the attending clinicians who are therefore blind to the IDP results. Patients then receive the standard of care for patients with signs and/or symptoms of angina but no CAD.

In the intervention group branch of the conceptual model, patients receive the IDP. Physicians were informed of the IDP results and were able to revise their initial diagnosis, which was based on the angiogram and all of the other available clinical information (e.g. prior non-invasive test results, medical history). Based on this new information, patients could either receive a diagnosis of positive or negative (for the purposes of the conceptual model, a positive diagnosis for any of the MVA or VSA endotypes is categorised as “positive”). Patients were then subsequently offered alternative medication and/or lifestyle modification advice depending on their revised diagnosis. If patients were subsequently diagnosed as “negative”, anti-anginal therapies were discontinued.

2.6. Resource use and cost analysis

Resource use estimates were obtained from the CorMicA trial, published literature and expert opinion (the CorMicA clinical trial team) (Table 1). Medication, participation in a cardiac rehabilitation programme, and IDP costs were included in the base case analysis.

Anginal medications were measured at baseline, 6 months and 12 months in the trial. Based on these data, we measured the proportion of the year a patient spent on each medication. We then estimated the proportion of the year spent on each medication by the mean patient in each trial arm. Relevant unit costs were adjusted to annual costs for each medication and attached to the time spent on medication to obtain the mean cost of medication by trial arm. The cost of the IDP was included for all patients in the intervention group only. The unit cost of a cardiac rehabilitation cost was attached to the number of patients reporting attendance at a cardiac rehabilitation programme at 12 months. Medication cost, IDP test cost and cardiac rehabilitation programme cost were combined to obtain a mean total patient cost by trial arm.

All unit costs were collected or converted into UK pounds sterling (£) for the price year 2018/19. Unit costs were collected from routine sources such as the British National Formulary [10], Personal Social Services Resource Unit (PSSRU) [11] and NHS Reference Costs [12]. Some unit costs were obtained from NHS Reference Costs or from local sources (NHS Golden Jubilee National Hospital) (Table 1).

2.7. Quality-of-life analysis

Quality-of-life (QoL) outcomes were based on the EuroQoL-5D (EQ-5D-5L) questionnaire and collected at baseline, 6 and 12 months in the CorMicA trial participants and expressed as health utility indices.

Quality adjusted-life years were calculated using the area-under-the-curve method (AUC) [13]. The AUC was estimated for each

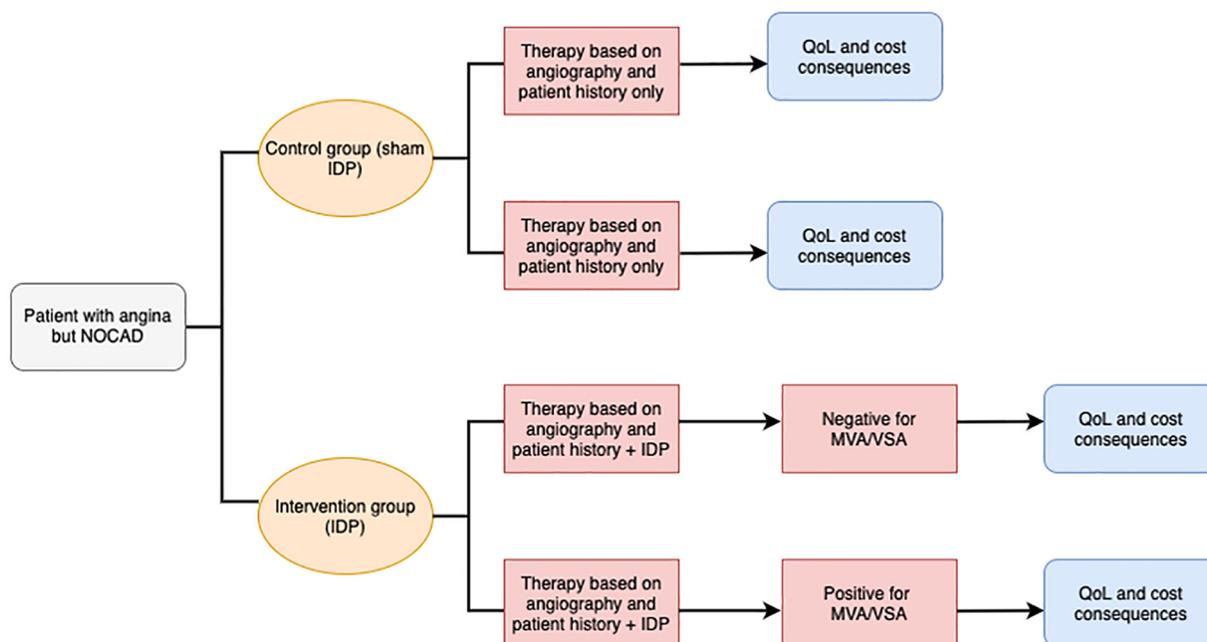


Fig. 1. Conceptual model of the clinical pathway associated the intervention and control group.

individual in the trial by weighting the time between EQ-5D health utility measurement in the trial by their health utility value over that time period.

2.8. Cost-effectiveness analysis

Mean cost and QALY gain per patient, by trial arm, was estimated by using a generalized linear model (GLM) and adjusting for potential confounding factors (age, sex, BMI and trial arm). The appropriate family

for the GLM was selected based on the results of the modified Park’s test. Our final cost model was based on the log link and gamma family and our final QALY model was based on the identity link and Gaussian family. There were few missing resource-use or EQ-5D data in the CorMicA trial (<5%). Where missing data existed, multiple imputation by chained equations (MICE) was used to impute missing data [14]. All analyses were conducted using Stata 14 (StataCorp).

The outcomes of interest are mean costs, mean quality adjusted life year (QALY) gained, and the incremental cost-effectiveness ratio

Table 1 Resource use item and unit cost.

Medication	Dose	Cost per pill	Cost per year	Source
Statin	40 mg daily	£0.03	£11	BNF
Beta-blocker	2.5 mg daily	£0.03	£11	BNF
Calcium channel blocker	120 mg daily	£0.03	£29	BNF
Isosorbide mononitrate	20 mg daily	£0.05	£36	BNF
Nicorandil	40 mg daily	£0.06	£45	BNF
ACE inhibitor	10 mg daily	£0.07	£27	BNF
Ranolazine	1000 mg daily	£0.82	£595	BNF
Ivabradine	14 mg daily	£0.12	£90	BNF
Nitroglycerin (spray)	1 bottle per 3 months	£12	£12	BNF
IDP (test)	Resource use	Unit cost	Source	
Catheter lab time	Per hour	£400	NHS Golden Jubilee costing records	
Acetylcholine test	Per vial	£7	BNF	
Adenosine	Per vial	£3	BNF	
Diagnostic coronary guidewire ^{a,b}	Per guidewire	£350	NHS Golden Jubilee costing records	
Other costs	Resource use	Unit cost	Source	
Cardiac rehabilitation programme	Per programme	£279	NHS Reference costs	
Re-presentation package of care (scenario analysis only)	Resource use	Unit cost	Source	
Coronary angiogram	Per test	£1379	NHS Reference costs	
GP appointment	Per appointment	£37	PSSRU 2018	
Cardiology outpatient appointment	Per appointment	£134	PSSRU 2018	
Blood test, U&E renal test, lipids test, Hba1c test	Per test (one of each test)	£7	NHS Reference costs	

^a The diagnostic coronary guidewire used in this study was PressureWire X (Abbott Vascular, Santa Clara, CA).

^b One third of patients in the CorMicA trial had a guidewire in place prior to IDP. For this reason, the cost of a guidewire is applied to two thirds of patients in the intervention group (rather than every patient).

(ICER), expressed as the cost per QALY. The estimated ICER is compared with a willingness-to-pay (WTP) threshold of £20,000 per QALY gained, which is a commonly accepted cost-effectiveness threshold used by the National Institute for Health and Care Excellence (NICE) in the United Kingdom.

2.9. Sensitivity analysis

The distribution of incremental mean costs and QALYs produced by a bootstrap analysis were presented on the cost-effectiveness plane. Cost-effectiveness acceptability curves (CEACs) were used to present the uncertainty in the decision regarding the most cost-effective option, over a variety of monetary willingness-to-pay threshold.

2.10. Scenario analyses

Data on the number of previous coronary angiograms among patients enrolled in the CorMicA trial indicated that approximately one third (51 out of 151) of patients had “at least one previous coronary angiogram” [15]. This aligns with the experience of clinical experts involved in both the trial, and in the routine care of this patient population, which suggests that patients with signs and symptoms of angina, but no obstructive coronary artery disease are liable to re-present in primary or secondary care.

Given the large potential cost associated with these re-presentations, we modelled the impact of IDP testing on reducing the proportion of patients re-presenting to primary and secondary care with signs/symptoms of angina following coronary angiography. To implement this scenario in the model, we assumed that patients diagnosed as negative for microvascular or vasospastic angina following IDP testing did not re-present with suspected angina, and that a proportion of patients in the control group do re-present. For patients who re-present, we proposed a typical “package of care” associated with a re-presentation, including: one coronary angiogram, three GP appointments, two cardiology outpatient appointments and standard care diagnostic tests (U&E, lipids, Hba1c). In the CorMicA trial, data on repeat visits to primary care or hospital outpatient clinics were not prospectively captured, as such there is some uncertainty as to the true impact of adjunctive functional test in a real-world setting.

The unit costs associated with these resources are given in Table 1. Based on the utilisation of each resource required, we estimated a cost associated with an angiogram package of care of £1786. We estimated the impact on the mean cost per patient in the control group if one third, one fifth, and one tenth of patients re-present in primary care.

2.11. Ethical approval

The West of Scotland Research Ethics Committee approved the study (REC 1 reference 16/WS/0192).

2.12. Patient and public involvement

CorMicA researchers engaged with the patient population (service users) and the British Cardiovascular Care Partnership in the design of the CorMicA trial.

3. Results

The baseline characteristics of the patient population are given in Table 2. The median age in the study was 61 years old, with the majority of the study participants being female (73.5%). There was a high prevalence of cardiovascular risk factors. Participants had impaired quality of life at baseline, as reflected by EQ-5D-5L health status (mean: 0.60, s.d.: 0.29) and SAQ Summary Score (mean 50.8, s.d.: 18.1).

3.1. Resource use results

The mean time spent on medication was greater in seven out of the nine medications included in the intervention group, compared with the control group (Table 3). Thirty patients (40%) reported attending a cardiac rehabilitation programme in the intervention group, compared with 12 patients (16%) in the control group. All patients in the intervention group received the IDP test, compared with none in the control group.

3.2. Cost results

The total mean cost per patient in the control arm of the trial was £103 and was comprised solely of medication and cardiac rehabilitation programme costs (Table 4). The total mean cost per patient in the intervention group was £568 and was comprised of the costs of the IDP, medication and cardiac rehabilitation programme. This equates to an incremental cost of £465 at 12 months associated with the intervention group.

3.3. Quality-of-life results

We estimated the mean QALY gain using the AUC approach. Patients in the control group had a mean QALY of 0.548 at 12 months, compared with 0.652 in the intervention group (Table 4). This equates to a mean QALY gain of 0.104 at 12 months in patients in the intervention group.

3.4. Cost-effectiveness results

The incremental cost per QALY gained at 12 months was £4500 (£2937, £33264) (Table 4). Compared with a willingness-to-pay (WTP) threshold of £20,000 per QALY, this suggest that the use of stratified medicine with the IDP and linked medical therapy is a cost-effective use of resources.

3.5. Sensitivity analysis

A visual illustration of the uncertainty surrounding the mean incremental cost and QALY gain in the intervention group over 1000 iterations of bootstrap analysis plotted on the cost-effectiveness plane is presented in Fig. 2. The x-axis represents the incremental QALY gain, and the y-axis represents the incremental cost, associated with the intervention group compared with the control group. The majority of the cost and QALY estimates are placed in the north-east quadrant of the cost-effectiveness plane, suggesting that the use of the intervention is associated with an incremental cost and incremental QALY gain.

The probability of the intervention being cost-effective, compared with the control group, is given for alternative willingness-to-pay for QALY gain thresholds in Fig. 3. At a WTP threshold of £20,000 per QALY gained, there is a 96% probability of the intervention being cost-effective, based on the uncertainty described by our bootstrap analysis.

3.6. Scenario analysis

We explored the impact on our cost-effectiveness results of making an assumption regarding the number of re-presentations that might be avoided as result of the introduction of stratified medicine involving IDP testing with linked therapy. Including the cost of re-presentations has the impact of increasing the cost-effectiveness of the intervention, compared with the base-case scenario (Table 5). A reduction in the proportion of patients who re-present for angiograms has the impact of reducing the cost-effectiveness associated with the intervention. However, for all re-presentation scenarios considered, the intervention was still either highly cost-effective or cost-saving.

Table 2
Baseline demographic and clinical characteristics of the CorMicA patient population.

	All (n = 151)	Control (n = 76)	Intervention (n = 75)
Age	61 (53, 68)	60 (53, 68)	62 (54, 69)
Female	111 (73.5%)	58 (76.3%)	53 (70.7%)
BMI (kg/m ²)	29.7 (25.6, 34.7)	29.7 (25.6, 34.0)	29.6 (25.7, 34.8)
Smoker	27 (17.9%)	14 (18.4%)	13 (17.3%)
Previous myocardial infarction	24 (15.9%)	13 (17.1%)	11 (14.7%)
Previous stroke or TIA	20 (13.2%)	13 (17.1%)	7 (9.3%)
Diabetes mellitus	29 (19.2%)	15 (19.7%)	14 (18.7%)
Dyslipidaemia	120 (79.5%)	61 (80.3%)	59 (78.7%)
Family history of CVD	105 (69.5%)	51 (67.1%)	54 (72.0%)
Predicted 10-year CHD risk ^a	18.6 (10.6, 31.4)	18.1 (9.7, 27.9)	19.0 (11.9, 38.9)
Aspirin	131 (86.8%)	67 (88.2%)	64 (85.3%)
Beta-blocker	101 (66.9%)	51 (67.1%)	50 (66.7%)
Calcium channel blocker	52 (34.4%)	28 (36.8%)	24 (32.0%)
Nitrates	71 (47.0%)	38 (50.0%)	33 (44.0%)
Statin	126 (83.4%)	66 (86.8%)	60 (80.0%)
Nicorandil	26 (17.2%)	15 (19.7%)	11 (14.7%)
ACE inhibitor or angiotensin receptor blocker	68 (45.0%)	35 (46.1%)	33 (44.0%)
Total cholesterol (mmol/L)	3.55 (0.98)	3.57 (1.06)	3.52 (0.90)
HDL cholesterol (mmol/L)	1.2 (0.4)	1.2 (0.3)	1.2 (0.4)
Baseline angina questionnaire: non-angina			
Definite (typical) angina	97 (64.2%)	42 (55.3%)	55 (73.3%)
Probable (atypical) angina	54 (35.8%)	34 (44.7%)	20 (26.7%)
Seattle angina questionnaire			
Seattle Angina (summary) score	50.8 (18.1)	49.0 (17.2)	52.6 (18.9)
Angina limitation	52.1 (24.4)	52.4 (24.3)	51.9 (24.7)
Angina stability	44.7 (24.4)	41.4 (25.3)	48.0 (23.2)
Angina frequency	59.3 (23.5)	54.9 (21.3)	63.7 (25.0)
Angina treatment satisfaction	81.9 (19.5)	81.9 (20.0)	81.8 (19.1)
Angina quality of life	40.9 (21.7)	39.7 (21.7)	42.1 (21.9)
Quality of life (EQ5D-5L)			
Index value	0.60 (0.29)	0.58 (0.30)	0.62 (0.28)
VAS score	66.3 (20.5)	67.9 (21.1)	64.6 (19.8)
Stress electrocardiogram (performed)			
Negative (normal)	13 (13.7%)	6 (13.0%)	7 (14.3%)
Inconclusive	37 (39.0%)	18 (39.1%)	19 (38.8%)
Abnormal	45 (47.4%)	22 (47.8%)	23 (46.9%)
Radionuclide myocardial perfusion (performed)			
Negative or inconclusive	58 (38.4%)	30 (39.5%)	28 (37.3%)
Abnormal	28 (48.3%)	17 (56.7%)	11 (39.3%)
Abnormal	30 (51.7%)	13 (43.3%)	17 (60.7%)

Values are median (interquartile range), n (%), or mean +/- SD.

^a ASSIGN risk score.

Table 3

Mean resource use (proportion and 95% confidence intervals) and mean cost (£), by trial arm.

	Standard care with control	Standard care with stratified medicine	Standard care with control	Standard care with stratified medicine
	Resource use (proportion and 95% CIs)		Mean cost per patient (£)	
Medication				
Statin	0.59 (0.50, 0.69)	0.79 (0.70, 0.89)	6.81 (5.77, 7.85)	9.157 (8.10, 10.21)
Beta-blockers	0.52 (0.44, 0.60)	0.58 (0.49, 0.66)	5.99 (5.04, 6.94)	6.67 (5.711, 7.63)
Nitroglycerin	0.34 (0.26, 0.41)	0.79 (0.71, 0.86)	4.11 (3.19, 5.02)	9.48 (8.55, 10.40)
Nicorandil	0.11 (0.04, 0.17)	0.15 (0.08, 0.21)	5.13 (2.18, 8.07)	6.80 (3.82, 9.79)
ACE	0.36 (0.26, 0.46)	0.51 (0.40, 0.61)	9.89 (7.22, 12.56)	13.69 (10.98, 16.40)
Ranolazine	0.02 (0.00, 0.04)	0.01 (0.00, 0.03)	12.50 (0.00, 28.41)	7.28 (0.00, 23.40)
Ivabradine	0.02 (0.00, 0.04)	0.01 (0.00, 0.03)	1.79 (0.00, 3.70)	0.90 (0.00, 2.83)
CCB	0.20 (0.11, 0.29)	0.42 (0.33, 0.52)	6.04 (3.32, 8.76)	12.60 (9.84, 15.35)
Isonitrate	0.26 (0.17, 0.35)	0.34 (0.25, 0.43)	9.59 (6.33, 12.84)	12.56 (9.27, 15.86)
Cardiac rehabilitation programme	12 (16%)*	30 (40%)*	43.53 (16.20, 70.66)	112.44 (86.15, 141.33)
IDP test				
Catheter lab time	0	20 min	0	133
Acetylcholine test	0	1 vial	0	7
Adenosine	0	1 vial	0	3
Diagnostic coronary guidewire	0	Two thirds of patients	0	233

* p-value (difference in proportion) = 0.001.

Table 4
Mean costs, mean QALYs, and cost-effectiveness ratio (and 95% confidence intervals) for the intervention group and control group.

Cost analysis	Mean medication cost (£)	Cardiac rehab programme (£)	IDP cost	Total cost
Control group	£61 (40, 81)	£44 (21, 67)	N/A	£103 (77, 128)
Intervention group	£80 (62, 98)	£112 (80, 143)	£376 (€410)	£568 (419, 714)
Difference	£19 (−8, 46)	£68 (29, 107)	£376 (€410)	£465 (397, 530)
QALY analysis	Mean QALY		95% confidence interval	
Control group	0.548		0.488, 0.609	
Intervention group	0.652		0.589, 0.714	
Difference	0.104		0.018, 0.190	
Cost-effectiveness results	Incremental Costs (£)	Incremental QALYs	Incremental cost-effectiveness ratio (ICER) (£)	
Control group				
Intervention group	£465 (397, 530)	0.104 (0.018, 0.190)	£4500 (2937, 33264)	

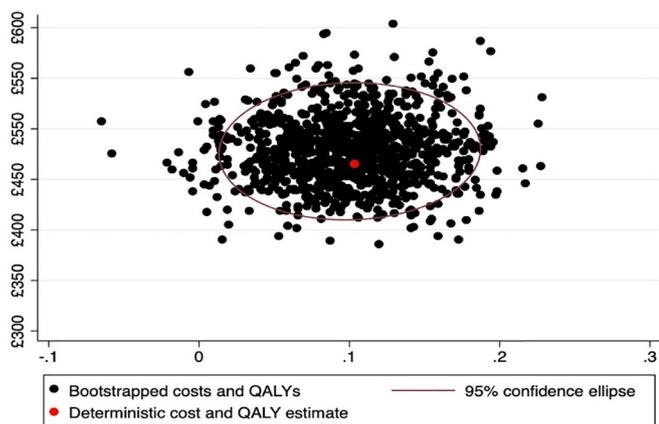


Fig. 2. Cost-effectiveness plane: incremental mean total costs and QALYs associated with the intervention group.

4. Discussion

Our cost-effectiveness analysis of the CorMicA trial found that the introduction of stratified medicine, including an adjunctive interventional diagnostic procedure for the management of patients with signs and symptoms of angina when obstructive coronary artery disease is excluded by the angiogram, is likely to be associated with an increase in patient quality-of-life and an increase in health-related resource use

over the trial period. With a mean incremental cost of £465 and incremental QALY gain of 0.104 per patient, we estimate an incremental cost-effectiveness ratio of £4500. Hence, our results find that stratified medicine in this patient population and setting is likely to be cost-effective in a UK setting.

The CorMicA trial participants had substantial impairment in quality-of-life at baseline, as reflected by EQ-5D-5L health status [16] and SAQ Summary Score [17,18]. Our results have provided insights into the mechanisms of treatment effect. We have found that that the benefit is determined to an appreciable extent by changes in medication aligned to the endotype. Other factors, such as participation in cardiac rehabilitation and control of vascular risk factors, are also relevant. The potential reduction in repeat coronary angiogram procedures (and related cost saving) in patients with persisting symptoms of angina, as a result of introducing IDP testing, has the potential to increase the cost-effectiveness of IDP testing.

The burden of INOCA, particularly in women, is known to be significant [19]. Three quarters of the trial participants were female. Cardiology trials generally enrol more males than females, not least since coronary artery disease predominately affects men. Accordingly, CorMicA provides new data that is particularly relevant to heart disease in women.

To date, there are no comparable studies. CorMicA was the first, randomised controlled trial of stratified medicine in angina. INOCA includes a large sub-population, representing almost half of all-comers, presents an unmet clinical need, that are usually discounted from clinical trials. It is noteworthy that the health-related quality of life, as measured by EQ5D-5 L and SAQ scores, were lower in CorMicA (patients with NOCAD), compared with recent clinical trials of patients with obstructive coronary artery disease (ORBITA [17], ISCHEMIA [18]).

This is the first study to investigate the health-related resource use implications of the introduction of adjunctive coronary function testing in patients with INOCA. There is no long-term evidence on the representation rate of patients with signs and symptoms of angina with a negative diagnosis of macrovascular angina following coronary angiography. In the CorMicA trial population, one in three patients had a history of prior coronary angiography indicating a persisting health burden and related demand on primary and secondary care. This can be explained by the limitations of the standard, angiography-guided care to reduce the health need of affected patients. The International Coronary Microvascular Angina (iCorMicA) trial which will randomise 1500 patients in Europe, is designed to address this evidence gap in multiple centres in different healthcare settings (ClinicalTrials.gov Identifier: NCT04674449). However, scenario analysis of our results suggests that, even when varying the proportion of patients expected to represent for angiograms, stratified medicine involving the IDP test is still highly likely to represent a cost-effective use of resources. Indeed, even if no patients re-present (base case results), this clinical strategy is still likely to be cost-effective. In addition, our analysis included only

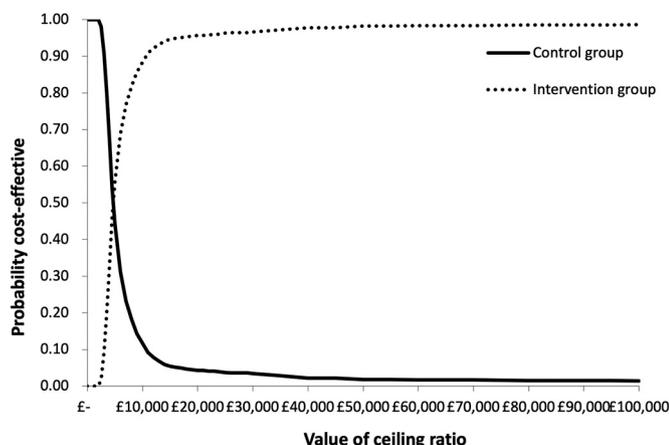


Fig. 3. Cost-effectiveness acceptability curve (CEAC): probability of cost-effectiveness at alternative WTP thresholds.

Table 5
Sensitivity analysis results: cost-effectiveness results including potential re-presentations avoided.

		Mean costs (£)	Mean QALYs	Incremental costs (£)	Incremental QALYs	Incremental cost-effectiveness ratio (ICER) (£)
One third of patients re-present	Control group	£698	0.548			
	Intervention group	£568	0.652	£-130	0.104	Dominated
One fifth of patients re-present	Control group	£460	0.548			
	Intervention group	£568	0.652	£108	0.104	£1038
One tenth of patients re-present	Control group	£282	0.548			
	Intervention group	£568	0.652	£286	0.104	£2750

costs attributable to the UK NHS healthcare system – we did not attempt to capture non-healthcare system costs, such as productivity costs (both absenteeism and presenteeism). This cost to the individual and to society from such losses has been shown to be significant [20].

The diagnostic management of stable chest pain is also evolving. CT coronary angiography (CTCA) has very high sensitivity for coronary artery disease and moderately high specificity for discriminating obstructive lesions. CTCA is recommended as the first line test in patients presenting with stable chest pain in the National Health Service [21] and is increasingly adopted in Europe [22], including the United States [23]. The functional significance of coronary artery lesions may be assessed using adjunctive FFR-CT, however, since CTCA does not provide information on ischaemia (the metabolic consequence of angina), the implications of this strategy for patients with INOCA are uncertain. The CorCTCA trial is prospectively assessing this evidence gap and a health economic analysis will also be undertaken [24].

The quality-of-life improvement in the intervention group is believed to be a result of both pharmacological and non-pharmacological factors, including participation in cardiac rehabilitation. The IDP identifies INOCA in patients who otherwise would have received a false negative diagnosis and ineffective treatment. Our results suggest that the benefit is determined to an appreciable extent by changes in medication aligned to the endotype. Other factors, such as participation in cardiac rehabilitation and control of vascular risk factors, are also relevant. Further research aimed at understanding the mechanism by which this quality-of-life increase is generated seems warranted.

5. Conclusion

We undertook an economic evaluation of the CorMicA trial to estimate the cost-effectiveness of introducing stratified medicine using an adjunctive interventional diagnostic procedure with mechanistically-targeted medical therapy for the management of patients with signs and symptoms of angina. Our results suggest that the introduction of this clinical strategy is likely to be cost-effective. The economic benefits of IDP testing increase further if we incorporate plausible assumptions regarding repeat angiograms in patients with persistent sign/symptoms of angina.

Source of funding

This work was funded by a British Heart Foundation grant (PG/17/25/32884, RE/13/5/30177, and RE/18/6/34217).

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Contributorship statement

All authors were involved in drafting the article or revising it critically for important intellectual content, and also for final approval of the version to be published. RH, A.B, T.F and C·B also made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data. C.B is responsible for the overall content of the CorMicA trial and associated outputs.

Declaration of competing interest

A.B., B.S., R.G., H.E., A.S., M.M.L., S.H., E.Y., R.McD. have no relevant disclosures. C·B. is employed by the University of Glasgow which holds consultancy and research agreements with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Corvoentis, GSK, HeartFlow, Menarini, Neovasc, and Siemens Healthcare. K.G.O. has received consultant and speaker fees from Abbott Vascular and Boston Scientific. He is employed by Biosensors. S.W. has received consultant and speaker fees from Boston Scientific. P.R. has received consultant and speaker fees from Astra Zeneca. K.R. has received educational support from Abbott Vascular and speaker fees from Astra Zeneca. RMT has acted as an advisor for Novartis. MME has a proctoring agreement with Boston Scientific and Vascular Perspectives. T.F. and DC have received speakers fees from Abbott Vascular.

Acknowledgments

The authors acknowledge the patients, the staff members, and the British Heart Foundation, who supported this study. We thank the trial clinical events committee including Dr. Andrew Hannah and Dr. Andrew Stewart, Aberdeen Royal Infirmary.

References

- [1] S. Cook, A. Walker, O. Hugli, M. Togni, B. Meier, Percutaneous coronary interventions in Europe: prevalence, numerical estimates, and projections based on data up to 2004, *Clin. Res. Cardiol.* 96 (2007) 375–382.
- [2] M.R. Patel, E.D. Peterson, D. Dai, M. Brennan, R. Redberg, V. Anderson, et al., Low diagnostic yield of elective coronary angiography, *N. Engl. J. Med.* 362 (2010) 886–895.
- [3] T. Ford, B. Stanley, R. Good, P. Rocchiccioli, M. McEntegart, S. Watkins, et al., Stratified medical therapy using invasive coronary function testing in angina, *J. Am. Coll. Cardiol.* 72 (23 Part A) (2018 Dec) 2841–2855.
- [4] T.J. Ford, D. Corcoran, C. Berry, Stable coronary syndromes: pathophysiology, diagnostic advances and therapeutic need, *Heart* 104 (2018) 284–292.
- [5] G. Montalescot, U. Sechtem, S. Achenbach, F. Andreotti, C. Arden, A. Budaj, et al., 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology, *Eur. Heart J.* 34 (2013) 2949–3003.
- [6] T.J. Ford, D. Corcoran, K.G. Oldroyd, M. McEntegart, P. Rocchiccioli, S. Watkins, et al., Rationale and design of the British Heart Foundation (BHF) Coronary Microvascular Angina (CorMicA) stratified medicine clinical trial, *Am. Heart J.* 201 (2018) 86–94, <https://doi.org/10.1016/j.ahj.2018.03.010>.
- [7] T. Ford, B. Stanley, N. Sidik, R. Good, P. Rocchiccioli, M. McEntegart, et al., 1-year outcomes of angina management guided by invasive coronary function testing (CorMicA), *J. Am. Coll. Cardiol. Intv.* 13 (1) (2020 Jan) 33–45.

- [8] Henry A. Glick, Jalpa A. Doshi, Seema S. Sonnad, Daniel Polsky, *Economic Evaluation in Clinical Trials*. OUP Catalogue, Oxford University Press, 2007 number 9780198529972.
- [9] NICE, Guide to the Methods of Technology Appraisal, Available at www.nice.org.uk/process/pmg9/chapter/the-reference-case 2013 Accessed on 2nd September 2020.
- [10] J.F. Committee, British National Formulary (online), BMJ Group and Pharmaceutical Press, London, 2020, Available at www.medicinescomplete.com Accessed on 2nd September 2020.
- [11] Personal Social Services Research Unit (PSSRU), Available at <https://www.pssru.ac.uk/> Accessed on 2nd September 2020.
- [12] National Schedule of Reference Costs, Available at <https://improvement.nhs.uk/resources/reference-costs/> 2017/18 Accessed on 2nd September 2020.
- [13] A. Manca, N. Hawkins, M. Sculpher, Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility, *Health Econ.* 14 (5) (2005) 487–496.
- [14] S. Ramsey, R. Willke, A. Briggs, R. Brown, M. Buxton, A. Chawla, et al., Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report, *Value Health* 8 (5) (2005 Sep-Oct) 521–533, <https://doi.org/10.1111/j.1524-4733.2005.00045.x>16176491.
- [15] T.J. Ford, E. Yii, N. Sidik, R. Good, P. Rocchiccioli, M. McEntegart, et al., Ischemia and no obstructive coronary artery disease: prevalence and correlates of coronary vasomotion disorders, *Circ. Cardiovasc. Interv.* 12 (12) (2019), e008126.
- [16] A. Szende, B. Janssen, J. Cabases, *Self-Reported Population Health: An International Perspective Based on EQ-5D* [Internet], Springer, Dordrecht (NL), 2014 PMID: 29787044.
- [17] R. Al-Lamee, D. Thompson, H.M. Dehbi, S. Sen, K. Tang, J. Davies, et al., Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial, *Lancet* 391 (10115) (2018 Jan 6) 31–40, [https://doi.org/10.1016/S0140-6736\(17\)32714-9](https://doi.org/10.1016/S0140-6736(17)32714-9).
- [18] J.A. Spertus, P.G. Jones, D.J. Maron, S.M. O'Brien, H.R. Reynolds, Y. Rosenberg, et al., Health-status outcomes with invasive or conservative care in coronary disease, *N. Engl. J. Med.* 382 (15) (2020 Apr 9) 1408–1419, <https://doi.org/10.1056/NEJMoa1916370>.
- [19] L.J. Shaw, C.N. Merz, C.J. Pepine, S.E. Reis, V. Bittner, K.E. Kip, et al., Women's Ischemia Syndrome Evaluation (WISE) Investigators. The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health – National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation, *Circulation* 114 (9) (2006 Aug 29) 894–904, <https://doi.org/10.1161/CIRCULATIONAHA.105.609990> Epub 2006 Aug 21. PMID: 16923752.
- [20] C.L. Schumann, R.C. Mathew, J.L. Dean, Y. Yang, P.C. Balfour Jr., P.W. Shaw, et al., Functional and economic impact of INOCA and influence of coronary microvascular dysfunction, *JACC Cardiovasc. Imaging* (2021 Apr 7) <https://doi.org/10.1016/j.jcmg.2021.01.041> S1936-878X(21)00179-0. Epub ahead of print. PMID: 33865784.
- [21] NICE, Recent-Onset Chest Pain of Suspected Cardiac Origin: Assessment and Diagnosis, Clinical guideline [CG95], Available at <https://www.nice.org.uk/guidance/CG95> Accessed on September 2nd 2020.
- [22] J. Knuuti, W. Wijns, A. Saraste, D. Capodanno, E. Barbato, C. Funck-Brentano, et al., 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes, *Eur. Heart J.* 41 (3) (2020) 407–477, <https://doi.org/10.1093/eurheartj/ehz425>.
- [23] M. Poon, J. Lesser, C. Biga, ESC Guidelines for the diagnosis and management of chronic coronary syndromes, *Eur. Heart J.* 41 (3) (2020 Jan 14) 407–477, <https://doi.org/10.1093/eurheartj/ehz425>.
- [24] N.P. Sidik, M. McEntegart, G. Roditi, T.J. Dord, M. McDermott, A. Morrow, et al., Rationale and design of the British Heart Foundation (BHF) coronary microvascular function and CT Coronary Angiogram (CorCTCA) study, *Am. Heart J.* 221 (2020) 48–59, <https://doi.org/10.1016/j.ahj.2019.11.015>.