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Design and rationale of “a pragmatic approach to the investigation of stable chest pain: A UK, multicenter, randomized trial to assess patient outcomes, quality of life and cost effectiveness (CE-MARC 3)”

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ABSTRACT

Rationale The optimal noninvasive diagnostic imaging strategy for patients with suspected coronary artery disease (CAD) is widely debated. Computed Tomography Coronary Angiography (CTCA) and functional imaging are both guideline-recommended, although comparative effectiveness in patients with intermediate-high pretest likelihood (PTL) is limited. Primary Hypothesis: We aim to establish if a personalized investigation strategy compared to CTCA first-line for allcomers, leads to improved patient outcomes.

Design In a multi-center, randomized trial, 4,000 patients newly referred for the investigation of suspected cardiac chest pain will be recruited and randomized (1:1) to either personalized care (first-line CTCA or functional imaging based on PTL) or CTCA first-line for allcomers. The primary endpoint is time to a composite of cardiovascular death, myocardial infarction, or unobstructed coronary arteries on invasive angiography. Follow up will occur at 6 and 12 months and then annually for up to 4 years for symptoms, quality of life, and guideline directed medical therapy usage. A cost-effectiveness analysis will be performed capturing impacts on health, measured in quality adjusted life years (QALYs) using the EQ-5D-5L, and costs (including investigations, procedures, procedural complications, medical treatment costs and any future hospital admissions) calculated. It will be possible for the whole trial pathway to be conducted remotely with the option to perform non-face-to-face consent, randomization, and follow-up data collection including health-related quality of life.

Sites About 20 UK sites.

Enrolment First site opened April 2022 and recruitment is due to complete by July 2025, with an average recruitment of 135 patients a month to date.

Current status About 3,407 patients recruited and randomized by the end of February 2025

Conclusion This trial will address whether, in patients with suspected cardiac chest pain, a strategy of personalized investigation according to pretest likelihood (PTL), compared to CTCA for allcomers, leads to improved patient outcomes, quality of life and cost-effectiveness. (Am Heart J 2025;289:95–104.)

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Background

Approximately 60% of patients with stable chest pain that undergo invasive diagnostic coronary angiography do not proceed to revascularization. Serious complications of angiography are rare, but include risk of stroke and myocardial infarction at 0.1% to 0.5%, and vascular complications 0.5% to 1%.^{1,2} Furthermore, patient preference is clearly for noninvasive imaging rather than invasive coronary angiography, the latter being associated with more anxiety and pain.³

Computed Tomography Coronary Angiography (CTCA) has a very high sensitivity and negative predictive value making it an excellent rule-out test for coronary artery disease (CAD). Its specificity is, lower, raising questions about the rate of false positive results, especially in higher-risk populations, and also its generalizability in older patients and those with known cardiac disease, with the potential for poor image quality in those with obesity, coronary calcification or arrhythmia.^{4,5} Functional imaging for myocardial ischemia includes modalities such as stress echocardiography, myocardial perfusion scintigraphy (MPS) and stress cardiovascular magnetic resonance (CMR). These tests typically have higher specificity than CTCA but lower sensitivity, whilst all cardiac imaging tests are constrained by local availability and expertise.

The 2016 UK National Institute for Health and Care Excellence guidelines, based on a cost effectiveness analysis which only included the index test cost and no downstream investigation/treatment costs or assessment of benefit in terms of quality adjusted life years (QALYs), proposed a strategy of CTCA first-line for all-comers with suspected typical/atypical cardiac chest pain (angina) or with nonanginal chest pain but an abnormal ECG.⁶ In stark contrast, both the US (2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guidelines for the evaluation and diagnosis of chest pain) and European (2019 European Society of Cardiology Guidelines for the management of chronic coronary syndromes) are more pragmatic, particularly in patients with intermediate-high pretest likelihood (PTL).^{4,5} US guidelines recommend that in such patients, choice of test should be influenced by local availability and expertise, with a suggestion of CTCA in those age <65 years and functional testing in those age ≥65 years.⁴ European guidelines similarly recommend that either functional imaging or CTCA can be used first-line depending on pretest likelihood (PTL) of obstructive disease, local availability and expertise, with the suggestion of CTCA for those with lower PTL and functional imaging for those with higher PTL.⁵

The SCOT-HEART trial randomized 4,146 patients to standard care (exercise ECG) with or without CTCA and showed that use of CTCA improved the diagnostic certainty of angina and CAD, with a nonsignificant trend towards increased revascularization rates and reduction

in fatal and nonfatal myocardial infarction rates at 1.7 years.⁷ However, this study had important limitations by design: no imaging was undertaken in the control arm (i.e. no comparator) and a history of prior CAD was permissible (9% had prior CAD, including a history of coronary bypass surgery). Despite a strategy of coronary imaging noninvasively, CT-guided management was associated with an excess of 58 invasive coronary angiograms by 6 weeks and less improvement in symptoms and quality of life at 6 weeks and 6 months.⁸ The 5 year follow up did show reduced rates of nonfatal MI with a strategy of CTCA in addition to exercise ECG testing, possibly due to more aggressive primary prevention treatment in the CTCA arm, but it was confounded by the fact that clinical events were not independently nor blindly adjudicated.⁹ Finally, although a health economics analysis was prespecified, the results have not been published to date.

The PROMISE trial of 10,003 symptomatic patients, showed CTCA (compared to functional testing by exercise ECG, MPS, or stress echo) had a higher rate of coronary angiography (13.3% vs 5.1%), percutaneous coronary intervention (6.0% vs 1.8%) and coronary bypass surgery (2.9% vs 1.3%) without any difference in clinical outcomes at 2 years.¹⁰

Currently there are no published randomized trials demonstrating the diagnostic accuracy or comparative effectiveness of CTCA in patients with chest pain and high-risk of CAD.¹¹ One study of symptomatic patients with high PTL suggested CTCA provided no additional relevant diagnostic information.¹² Indeed, both UK and international¹³⁻¹⁵ data suggest higher down-stream resource utilization rates, especially invasive coronary angiography, following a CTCA-first strategy. For example, an observational study of Medicare beneficiaries showed higher costs after CTCA compared with functional testing¹³ and a Danish registry of >86,000 patients showed downstream costs after CTCA were 39% higher (\$995 vs. \$718; $P < .001$).¹⁵

In the PRECISE trial 2,103 patients with suspected CAD were randomized to CTCA with selective CT-derived fractional flow reserve (FFR_{CT}) or usual care. The intervention arm had lower rates of angiography with obstructive disease (2.6% vs 10.2%) but there was no difference in the clinical endpoint of death or myocardial infarction between trial arms.

In summary, CTCA has high sensitivity and negative predictive values, but with lower specificity than other cardiac imaging tests, resulting in more false positive results and hence additional down-stream testing, in particular increased rates of invasive angiography. Functional imaging has a higher specificity than CTCA, but much lower sensitivity, meaning that it is better at detecting more severe disease (ischemia), which may benefit from coronary revascularization, but it is less reliable as a rule-out test. Thus, an optimal and pragmatic strategy might

be one that utilizes the strength of each of the different cardiac investigations, targeted to individual patient needs, based upon their risk factors and co-morbidities.

Study objectives

The CE-MARC 3 trial will evaluate head-to-head, opposing strategies from internationally recognized clinical guidelines for the management of patients with chest pain, to determine if a patient-focused pragmatic choice of first-line cardiac test is superior to a one-size-fits-all strategy of CTCA for allcomers. The primary research question being ‘can we improve the management of patients with new onset chest pain, both from a patient perspective and payer perspective?’ CE-MARC3 will address this by answering whether, in patients with suspected cardiac chest pain, a pragmatic diagnostic pathway compared to CTCA as first-line test for all, results in:

1. Lower rates of cardiovascular death, myocardial infarction and unobstructed coronary arteries at invasive angiography.
2. Improved quality of life .
3. Improved cost effectiveness in terms of QALYs and decreased resource use

Methods

Study design

UK multi-center, 2-arm parallel group, superiority, open-label randomized controlled trial. A total of 4,000 patients in out-patient secondary care with de novo chest pain suggestive of typical or atypical angina will be randomized to receive either standard care (CTCA first-line) or pragmatic personalized care (where choice of test will be based on PTL, local expertise and availability). Randomization will allocate patients on a 1:1 basis to standard care and pragmatic care arms and the trial will not be blinded, as it is not possible to blind patients to their own management. Anticipated study duration is 60 months which includes 6 months setup and 36 months recruitment.

Patient population and recruitment

The inclusion/exclusion criteria are shown in [Table 1](#). The screening population is males ≥ 45 yrs or females ≥ 50 yrs (comparable to the PROMISE trial)¹⁰ with atypical or typical angina and at least one major cardiac risk factor (diabetes, peripheral arterial disease, cerebrovascular disease, current or past tobacco use, hypertension, dyslipidemia, or family history of premature CAD) referred to cardiology outpatient services, requiring further investigation and who are deemed suitable for coronary revascularization if required.

CE-MARC 3 will be conducted in secondary care cardiology departments that have well-established clinical services for both CTCA and functional cardiac imaging.

Twenty UK high-volume, experienced research centers with geographical spread and with ethnically diverse populations have been selected.

As both arms of this trial are supported by international guidelines, it is considered very low risk to trial participants. The consent process has therefore been designed to be as accessible to patients and as inclusive as possible. Particularly in the post-COVID era with many outpatient appointments being virtual rather than face-to-face, flexibility in recruitment is required. As different hospitals have been dealing with COVID-recovery in different ways for elective outpatient consultations, patients will be able to choose from written paper consent, e-consent (via computer or smartphone) or telephone consent.¹⁶ For all modes of consent, the patient will be given a copy, a copy will be stored at hospital site and a copy stored at the Clinical Trials Research Unit, University of Leeds, UK.

Informed consent and eligibility

The research team or the clinical care team on the delegation log, will provide information (written/verbal) about the trial prior to or during the routine clinic appointment. Before discussion with potential participants a check will be made to establish that all the inclusion criteria are met and none of the exclusion criteria apply. The right of the patient to refuse consent without giving reasons will be respected. Trial information will be provided in a plain English video summary <https://www.youtube.com/watch?v=I9UdGQx2xjs> and in the non-English languages of Urdu, Bangla, Polish and Arabic to aid inclusivity of diverse populations and trial generalizability.

Randomization

Patients who fulfil the eligibility criteria and have provided documented informed consent will be randomized centrally using an automated web-based randomization system to one of the 2 trial arms and will be allocated a trial identification number. Randomization will allocate patients using Soares and Wu's Method (i.e. allocating randomly within a prespecified maximum tolerable imbalance), in a 1:1 ratio between standard care (CTCA for all) or a pragmatic management strategy, after taking account of the following stratification factors: age, sex and center, ([Figure 1](#)).

Investigation details

Standard care arm: CTCA will be first-line test for all patients in this arm, as per the 2016 UK National Institute for Health and Care Excellence guidelines. Following a negative test result, guideline directed medical therapy (GDMT) will be recommended. Following a positive result, GDMT will be recommended followed by invasive coronary angiography as clinically necessary, according to shared patient-physician decision-making.

Table 1. Inclusion and exclusion criteria

Inclusion criteria

- Male ≥ 45 years, female ≥ 50 years
- Typical or atypical angina (chest pain)
- At least one major cardiovascular risk factor (diabetes, peripheral arterial disease, cerebrovascular disease, current or past tobacco use, hypertension, dyslipidemia, or family history of premature CAD)
- Suitable for coronary revascularization if required, as determined by clinician/shared decision making
- Provided written informed consent to participate in the trial

Exclusion criteria

- Prior normal CTCA within the last 2-years or any prior CTCA with extensive calcification (Coronary Artery Calcium >400)
- Clinically unstable cardiac symptoms (clinician discretion)
- Known obstructive CAD (including previous myocardial infarction, acute coronary syndrome or coronary revascularization)
- Absolute contraindication to CTCA or functional cardiac imaging
- Pregnancy and/or breast feeding
- Chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m²)

Pragmatic care arm: The pragmatic investigation arm will personalize the first-line investigation, based on contemporary risk stratification, to either CTCA in the lower risk group or functional cardiac imaging in the higher risk group (lower/higher risk will be defined from the European Society of Cardiology 2019 guidelines using symptoms, sex and age; [Figure 2](#)).⁵ Patients in this arm will have their first test based on pretest likelihood (PTL), with those with a $PTL \geq 15\%$ getting a functional imaging test and those with $PTL < 15\%$ getting CTCA. A major strength of this updated risk model is that it was developed and validated using data from different hospitals, settings, and countries, and is less likely to overestimate risk compared to the older Diamond-Forrester model.¹⁹ The choice of functional imaging test in the pragmatic arm, be it stress echocardiography, MPS or CMR, will be made according to shared decision making and local availability/expertise. Following a negative test result, GDMT will be recommended. Following a positive result GDMT will be recommended, followed by invasive angiography as clinically necessary, according to shared decision-making.

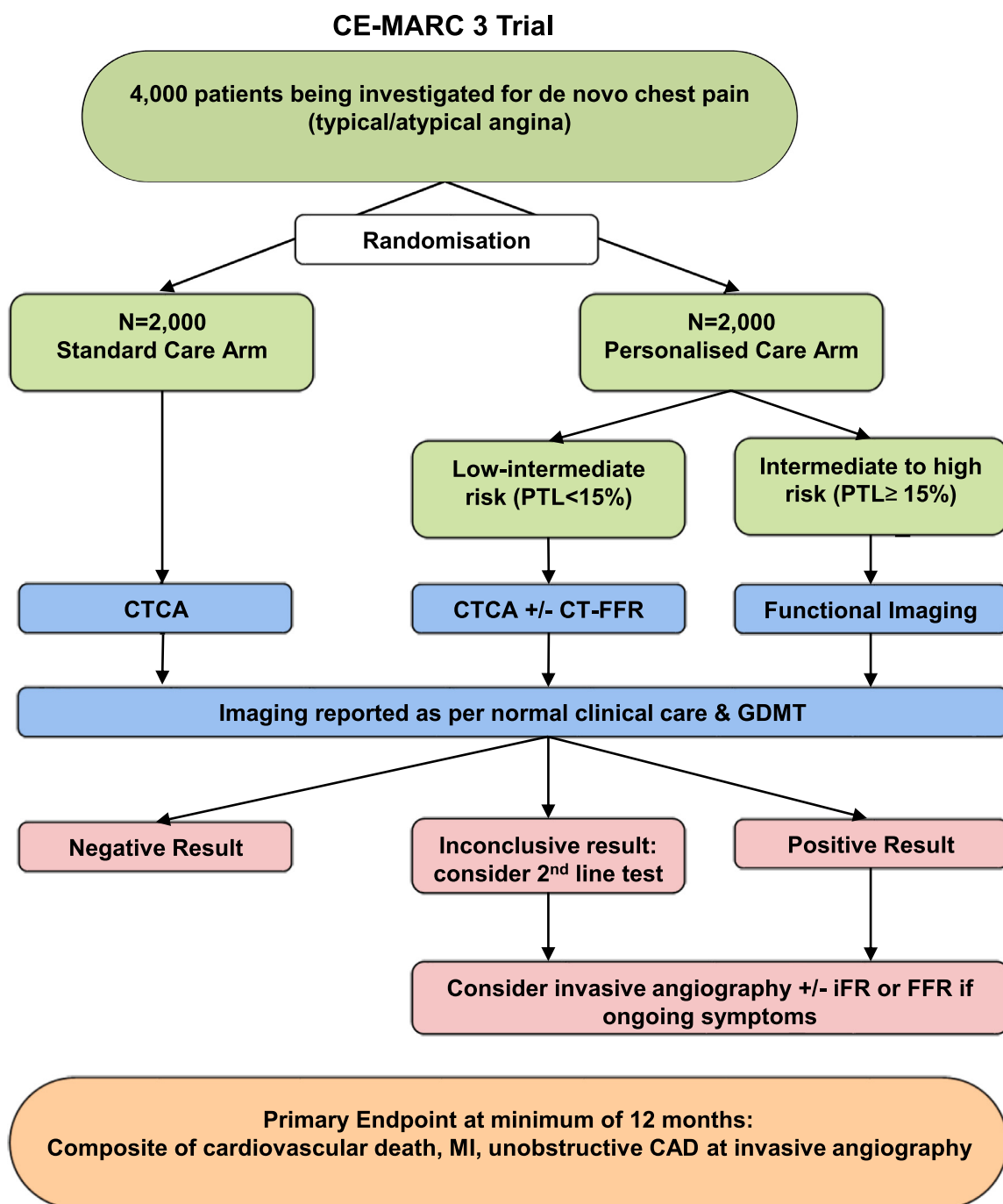
Test reporting (both arms): In keeping with the pragmatic design, all imaging tests will be reported on-site by independent cardiology or radiology consultants with certified accreditation and experience in the respective imaging modality. Where additional adjudication of test results is required, anonymized images may be securely transferred for secondary core-lab analysis. As a guide, the following reporting criteria will be recommended:

- a) CTCA: A positive result will be recorded as the presence of any luminal stenosis $\geq 70\%$ ($\geq 50\%$ LMS) in an epicardial coronary artery ≥ 2.5 mm diameter. Lesions that are of uncertain functional signifi-

cance, lower-risk, or nondiagnostic will be considered for functional testing (see below). FFR_{CT} is performed as an adjunct to CTCA, and the threshold for its performance will follow the recommendations in the FORECAST trial.¹⁷ That is, those patients with a coronary stenosis of $\geq 40\%$ in at least one major epicardial vessel of stentable/graftable diameter will be considered for FFR_{CT} (NB, lesions in distal vessels or vessels of a diameter not suitable for stenting/grafting will not qualify for FFR_{CT} if there are no other more significant lesions). FFR_{CT} will be performed by HeartFlow, independently of clinical assessment. As per normal practice, a secure web transfer portal will be established with each site allowing transfer of the raw CTCA DICOM data to HeartFlow where analysis according to their published FFR_{CT} protocol will be undertaken. The FFR_{CT} output will be returned to the investigating site within 24 hours.

- b) CMR: A positive result will be recorded as: 1) Presence of ≥ 2 adjacent segments (or 60-degree arc-equivalent if the defect crosses segmental boundaries) with $\geq 50\%$ transmural extent of ischemia, scar, or ischemia-scar combination. 2) Wall motion Score ≥ 1 in 2 or more adjacent segments, or ≥ 2 in one or more segments (wall motion in each segment [17-segment model] scored poststress [0 = normal, 1 = mild-moderate hypokinesis, 2 = severe hypokinesis, 3 = akinesis, 4 = dyskinesis]).
- c) Stress Echo: A positive result will be recorded as: 1) A definitive myocardial scar at rest (wall thickness <0.5 mm). 2) A new/worsening wall motion abnormality in 2 or more contiguous myocardial segments. 3) A transient for dobutamine or persistent (into recovery) for supine bike exercise, drop

Figure 1. CE-MARC 3 trial flow diagram. CAD, coronary artery disease; CTCA, computed tomography coronary angiography; PTL, pretest likelihood; GDMT, guideline directed medical therapy.



in global left ventricular function. 4) An increase in wall motion score index to greater than >1.2. 5) A change in myocardial activation (postsystolic thickening) felt to be highly significant by the operator. A negative stress echo will be defined as >85% target

HR with no wall motion abnormalities and normal augmentation of myocardial function.

d) MPS-SPECT: A positive result will be recorded as: 1) Presence of a reversible or fixed perfusion defect by visual assessment (a reversible defect = a decrease

Figure 2. Pretest likelihood of obstructive CAD. Pretest likelihood of obstructive CAD in 15,815 symptomatic patients according to age, sex, and the nature of symptoms in a pooled analysis of contemporary data.³⁰ Patients in the pragmatic arm have their first test based on PTL, with those with PTL $\geq 15\%$ (red) getting a functional test and those with PTL $< 15\%$ (purple) getting CTCA $\pm$ FFR_{CT}.

Age	Typical		Atypical	
	Men	Women	Men	Women
40 - 49	22%	Not eligible	10%	Not eligible
50 - 59	32%	13%	17%	6%
60 - 69	44%	16%	26%	11%
≥ 70	52%	27%	34%	19%

in perfusion score between rest and stress ≥ 2 in any segment, or ≥ 1 in each of 2 adjacent segments. Fixed defect = any fixed score ≥ 1). 2) Presence of a reversible or fixed perfusion defect by semi-automated assessment (as an adjunct to, and not a substitute for, visual analysis), using QPS software, SSS ≥ 4 or SDS > 0 (segmental scores summed to give SSS and SDS [SSS minus SRS]). 3) Wall motion Score ≥ 1 in 2 or more adjacent segments, or ≥ 2 in one or more segments (wall motion in each segment [17-segment model] scored poststress [0 = normal, 1 = mild-moderate hypokinesis, 2 = severe hypokinesis, 3 = akinesis, 4 = dyskinesis]). 4) Transient ischemic dilatation (TID) (ratio > 1.15). 5) Increased RV myocardial uptake at stress.

Inconclusive/uninterpretable test results (both arms): Patients with inconclusive first-line test results could have second line noninvasive cardiac imaging or invasive coronary angiography, based upon shared decision-making. If invasive angiography is performed at a later stage, fractional flow reserve (FFR) or nonhyperemic pressure ratio (NHPR) would be encouraged in borderline cases (intermediate stenosis severity) to confirm the hemodynamic severity of any stenosis prior to a revascularization decision.²⁰ The prescriptive management of patients with ongoing symptoms despite negative tests is not mandated in the protocol, in keeping with a pragmatic trial design, and patients can be managed with additional tests or medical therapy as per local clinical practice and shared decision making. All additional tests and the reasons for them will be captured in the trial database.

Primary endpoint

Time to first composite endpoint or censoring measured from randomization for a minimum of 12 months to a maximum of 48 months of:

- Cardiovascular death: due to myocardial infarction, heart failure, acute unexpected death, stroke,

pulmonary embolism, cardiovascular procedure-related, other cardiovascular cause, or unknown cause of death.

- Myocardial infarction: Spontaneous myocardial infarction (Type 1), myocardial infarction secondary to ischemic imbalance (Type 2) or myocardial infarction related to stent thrombosis (Type 4b).
- Unobstructive CAD at invasive angiography (defined by the invasive reference standard of FFR > 0.80 [or NHPR ≥ 0.90 ¹⁸]), i.e. no functional ischemia, at the time of coronary angiography (or no coronary stenosis $> 70\%$ on quantitative coronary angiography should FFR/NHPR be deemed clinically inappropriate/unsafe to perform). Analysis of quantitative coronary angiography (i.e. those without subsequent revascularization or FFR/NHPR), will be performed in a central core-lab by the University of Glasgow.

Primary endpoints will be determined by review of medical records according to standard definitions within the protocol. Unobstructive CAD was included in the primary endpoint as it is marker of clinical effectiveness encompassing both false positive from the imaging strategy and exposure of patients to an unneeded test.

Secondary endpoints

- 1) Individual components of the composite primary endpoint.
- 2) Usage of the following cardiac medications or specific drug classes (ignoring any requirements for dosing), each at 0, 6 and 12 months: Antiplatelet agents; Statins/other lipid lowering medications; Beta-blockers; Angiotensin Converting Enzyme Inhibitor/Angiotensin II Receptor Blockers (ACEi/ARB); Nitrates; Calcium antagonists; Nicotinic; Ivabradine; Ranolazine.
- 3) Patient-reported quality of life from EQ-5D-5L, SAQ (5 domains) and SF12v2 (8 domains, and 2 summary scores) at 0, 6 and 12 months (sub-study).

- 4) Cost effectiveness: Resource use, costs and cost effectiveness analysis. Costs based on diagnostic evaluations undertaken, revascularization procedures, cardiovascular outpatient appointments, any hospitalizations and cardiovascular medication, outcomes measured in quality-adjusted life-years using the EQ-5D-5L.

Exploratory analyses

- 1) Total radiation dose from tests per patient in the 12 months since randomization.
- 2) Longer-term clinical outcomes for up to 10 years.

Statistical considerations

Sample size

A total of 4,000 participants will be randomized on a 1:1 basis to standard of care or pragmatic care arms. The 12-month primary outcome event rate in current standard care is assumed to be 8% (based on a hard cardiac death/MI rate of 1-2%/year and specificity of CTCA across the risk spectrum, which is similar to PROMISE).¹⁰ A large effect size (hazard ratio [HR] = 0.75) is required to standardize practice, and the potential for higher specificity with FFR_{CT} and functional imaging in the pragmatic arm, equates to a clinically relevant increase in event free survival from 92% to 94% at 12 months, requiring a sample size of at least 1,600 patients per group (nQuery Advisor v7.0 and PS v3.0). Calculations assume time to event follows an exponential distribution, 2-sided 5% level of significance, 90% power, 36-month recruitment and minimum 12-month follow-up of all patients. The sample size is sensitive to small changes in rates, hence a recruitment target of 4,000 patients will allow at least 80% power to detect a 25% reduction in risk of event (HR = 0.75) assuming the underlying standard of care event rate ranges between 5% and 10%.

Sample size for quality-of-life sub-study

The CE-MARC 3 Quality of Life sub-study has a recruitment target of 1,300 patients. For EQ-5D-5L, the minimum important difference in the utility score in cardiovascular trials is 0.05 points.¹⁹ In CE-MARC 2, a SD of 0.18 was observed.²⁰ To detect a 0.05-point difference with an assumed SD = 0.18, 1% 2-sided type-1 error and a 10% type-2 error requires 388 patients in each randomized group to complete and return questionnaires for comparison. CE-MARC 2 demonstrated a large questionnaire attrition rate of 40% at 12 months, as is often observed in quality-of-life studies, hence the target recruitment is inflated to 650 patients/arm, providing powered analysis.

Analysis plan

Statistical analysis will follow a predetermined plan by a certified independent clinical trials unit (Leeds Institute

of Clinical Trials Research, University of Leeds, Leeds, UK).²¹ All analyses will be conducted on the Intention-to-treat population where a patient's diagnostic pathway will be that allocated at randomization. A per-protocol population will also be defined for planned sensitivity analysis of the primary outcome and will include all participants according to the treatment randomized to, excluding participants who did not have sufficient exposure to their randomized investigation. This population will be defined in agreement with the external Trial Oversight Committee members. Final analysis of the primary outcome measure will be following a minimum 12-month follow-up of all patients. Analysis of long-term outcomes is planned based on electronic health records.

Health-related quality of life

EQ-5D-5L utility, SAQ domain scores and SF12v2 domain and summary scores over 12-months will be analyzed longitudinally using multi-level regression. The estimate of the treatment effect will be reported with 95% confidence intervals from a multi-level model adjusted the baseline domain score value and for stratification factors at randomization: center, age and sex. Each multi-level model for each outcome will account for the nested structure of the data (repeated questionnaires within patients as well as patients within centers). Secondary analyses will consider other important baseline key covariates based on a predetermined statistical selection strategy. Patient and patient by time interaction effect will be included as random effects. Goodness of fit will be explored graphically based on residual plots. Analyses will include all randomized participants in their randomized groups, using the multi-level mixed model or multiple imputation under the 'Missing At Random' assumption.²²

Since patients may drop out due to death, then the EQ-5D-5L utility, SAQ domain scores and SF12v2 domain and summary scores may be used in a quality-adjusted survival analysis simultaneously analyzing longitudinal Quality of Life and time to event survival, pertinent to address censoring in both the quality and survival functions and informative drop-out due to death.³² Estimates of life-months and quality adjusted life months will be compared across randomized groups.

Economic evaluation

Analysis will be conducted at the Centre for Health Economics, University of York, York, UK. Resource use will be collected as part of the trial and used to estimate costs from a health care perspective using UK national costs.²³⁻²⁵ Outcomes will be estimated in QALYs based on the EQ-5D-5L and appropriate tariffs at the time of analysis. Any differences in costs and outcomes between the 2 management arms will be estimated and compared using incremental cost-effectiveness ratios and incremental net health benefits. incremental cost-effectiveness ratios will be compared to widely used es-

imates of health opportunity cost thresholds of £13,000 per QALY,²⁶ £20,000 per QALY and £30,000 per QALY²⁷ (i.e. estimates of how much it costs to generate a QALY elsewhere in the National Health Service at the margin), where a management strategy is regarded as cost-effective if its incremental cost-effectiveness ratio falls below this threshold (i.e. it generates health at a lower cost than is forgone elsewhere). Incremental net health benefits will be assessed using the same 3 thresholds. Decision uncertainty (i.e. the probability of the recommended management strategy being cost-effective) will be estimated using probabilistic sensitivity analysis.²⁸ One-way deterministic sensitivity analysis and scenario analyses will also be used to explore other uncertainties. The analysis will be conducted using appropriate statistical techniques to account for issues with economic data (e.g. non negative, skewed).²⁹ Initially the impacts will be estimated over the trial period, however, if there is evidence that differences in costs and/or benefits will persist beyond the trial period, extrapolation of results over the patients remaining lifetimes will be explored using a decision analytic model.²⁸

Recruitment targets

The first patient was recruited to CE-MARC 3 on April 26, 2022. There are presently 20 sites actively recruiting (Appendix A). By end of February 2025, 3,407 patients have been randomized (~135/month) with the trial on target to complete recruitment by July 2025.

Discussion

CE-MARC3 is a multicenter, randomized controlled trial of initial cardiac imaging strategy in patients presenting with typical/atypical suspected cardiac chest pain. It will test whether a personalized, pragmatic investigation strategy compared to CTCA first-line for allcomers leads to improved patient outcomes. In addition, this study will address whether either strategy is more cost effective or leads to improved patient reported quality of life.

Very few clinical practice guidelines in cardiology, or medicine in general, are subjected to the rigors of a randomized controlled trial, either before or after their implementation. In this regard, CE-MARC 3 is unique, in that it subjects internationally recognized guideline recommendations head-to-head in a clinical trial for the first time, in an area with quite divergent interpretations of the published clinical trial data. The 2016 UK National Institute for Health and Care Excellence guidelines⁶ are very prescriptive, recommending CTCA first-line for all comers with typical/atypical angina (with a few exclusions), whereas the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guidelines⁴ and the 2019 European Society of Cardiology guidelines,⁵ are much more pragmatic. Although the ESC Chronic coronary syndrome guidelines were updated in

2024 to include a more complex “Risk-Factor-weighted Clinical Likelihood” to decide the choice of initial imaging strategy, the “pragmatic arm” in CE-MARC 3 is still compatible with ethos of personalized care in these updated guidelines.

This is important as taking a CTCA first-line for all approach, has potential implications for patient choice, shared decision-making, quality of care and patient quality of life. Equally important are the implications for global healthcare systems and resources, if just one modality is recognized as the only recommended first-line test. Ultimately this might be appropriate, but before chest pain investigation pathways are systematically restructured across multiple healthcare jurisdictions, it is essential that this is an evidenced based decision, rather than just based upon a few expert opinions. Thus, whatever the outcome of CE-MARC 3, it will have a direct impact on patient care and the use of healthcare resources, internationally.

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The main trial is charity funded by Heart Research UK (TRP13/19) and the Quality-of-Life sub-study by the British Heart Foundation (PG/21/10724). HeartFlow® is providing complimentary FFR_{CT} when performed. The authors are solely responsible for the design and conduct of this trial, all analyses, and the drafting, editing and content of all publications arising.

Conflict of interest

CB: Employed by the University of Glasgow which holds consultancy and research agreements for his work with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, CorFlow, Coroventis, HeartFlow, Menarini, Merck, Novartis, Siemens Healthcare, Xylocor, Zoll, and Valo Health. GM: Research support from Circle CVi, Resonance Health. CBD: Chief Executive Officer (Part-time) for the Society for Cardiovascular Magnetic Resonance; speaker fees from Circle Cardiovascular Imaging, Siemens Healthineers, Philips, GE Healthcare, Bayer. NC: Grants from Haemonetics, Boston Scientific, HeartFlow, Beckmann Coulter; consultancy from Abbott, HeartFlow; speaker fees from Abbott, HeartFlow. GL: Consultancy from GE Healthcare; speaker fees from Bayer. JPG: Advisory work for Bayer; speaker fees from Bayer, Edwards Lifesciences.

Appendix A. Recruitment centers

1. Leeds Teaching Hospitals NHS Trust
2. Mid Yorkshire Teaching NHS Trust
3. Northumbria NHS Foundation Trust
4. University Hospitals of Leicester NHS Trust
5. Oxford Health NHS Foundation Trust
6. NHS Greater Glasgow and Clyde

7. Guy's and St Thomas NHS Foundation Trust/ Harefield Hospital
8. Royal Devon University Healthcare NHS Foundation Trust
9. South Tees Hospitals NHS Foundation Trust
10. Barts Health NHS Trust
11. University Hospital Southampton NHS Foundation Trust
12. Manchester University NHS Foundation Trust
13. Bradford Teaching Hospitals NHS Foundation Trust
14. Kettering General Hospital NHS Foundation Trust
15. The Royal Wolverhampton NHS Trust
16. Norfolk and Norwich University Hospitals NHS Foundation Trust
17. Nottingham University Hospitals NHS Trust
18. Kings College Hospital NHS Trust, London
19. North Bristol NHS Trust
20. Mid and South Essex NHS Foundation Trust

Appendix B. Trial management structure

Trial Management Group, comprising the Chief Investigator, Clinical Trials Unit team, grant co-applicants and a CE-MARC 3 clinical research nurse, will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically this group will be responsible for (1) protocol completion, (2) Clinical Report Form development, (3) obtaining approval from the main REC and supporting applications for Site Specific Assessments, (4) completing cost estimates and project initiation, (5) nominating members and facilitating the Trial Oversight Committee, (6) reporting of serious adverse events, (7) monitoring of screening, recruitment, treatment and follow-up procedures, (8) auditing consent procedures, data collection, trial end-point validation and database development.

Trial Oversight Committee will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, no fewer than 2 other independent members including a statistician and a patient/consumer representative. The Chief Investigator and other investigators may attend these meetings and present and report progress. The Committee will meet (virtually or face to face) yearly as a minimum.

CRedit authorship contribution statement

Peter P. Swoboda: Project administration, Methodology, Funding acquisition, Conceptualization. **Colin Berry:** Methodology, Funding acquisition, Concep-

tualization. **Gerry P. McCann:** Methodology, Funding acquisition, Conceptualization. **Andrew Kelion:** Methodology, Funding acquisition, Conceptualization. **Chiara Bucciarelli Ducci:** Methodology, Funding acquisition, Conceptualization. **Nick Curzen:** Methodology, Funding acquisition. **Guy Lloyd:** Methodology, Funding acquisition, Conceptualization. **Laura Jones:** Project administration, Methodology. **Myka Ransom:** Methodology, Investigation. **Simon Walker:** Methodology, Funding acquisition, Conceptualization. **Deborah Stocken:** Methodology, Funding acquisition, Conceptualization. **John P. Greenwood:** Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

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