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Conor P Bradley MBChB, MRCP , Vanessa Orchard MSc ,
Gemma McKinley BSc , Robert Heggie MA, MSc , Olivia Wu PhD ,
Richard Good MD, FRCP , Stuart Watkins MD, FRCP ,
Mitchell Lindsay MD, FRCP , Hany Eteiba MD, FRCP ,
James McGowan MD , Ross McGeoch MD , David Corcoran PhD ,
Peter Kellman PhD , Alex McConnachie PhD ,
Colin Berry PhD, FRCP

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The Coronary Microvascular Angina Cardiovascular Magnetic Resonance Imaging Trial: Rationale and Design

Brief Title: The CorCMR trial

Conor P Bradley MBChB MRCP[1,2], Vanessa Orchard MSc[2], Gemma McKinley BSc[3], Robert Heggie MA MSc[4], Olivia Wu PhD[4], Richard Good MD FRCP[1,2], Stuart Watkins MD FRCP[1,2], Mitchell Lindsay MD FRCP[2], Hany Eteiba MD FRCP[2], James McGowan MD[5], Ross McGeoch MD[6], David Corcoran PhD[1], Peter Kellman PhD[7], Alex McConnachie PhD[3], Colin Berry PhD FRCP[1,2]

Institutional Affiliations: [1]British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [2] NHS Golden Jubilee hospital, Clydebank, United Kingdom; [3]Robertson Centre for Biostatistics, University of Glasgow, Scotland, UK; [4]Health Economics and Health Technology Assessment, School of Health and Wellbeing, University of Glasgow, Glasgow, UK; [5]Department of Cardiology, University Hospital Ayr, Ayr, UK; [6]Department of Cardiology, University Hospital Hairmyres, East Kilbride, UK; [7]National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA;

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Correspondence: Professor Colin Berry, British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, 126 University Place, University of Glasgow, Glasgow, G12 8TA, Scotland, UK. Telephone: +44 (0) 141 330 1671 or +44 (0) 141 951 5180. Fax +44 (0) 141 330 6794. Email: <u>colin.berry@glasgow.ac.uk</u>

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Abstract

Background: Coronary microvascular dysfunction may cause myocardial ischemia with no obstructive coronary artery disease (INOCA). If functional testing is not performed INOCA may pass undetected. Stress perfusion cardiovascular MRI (CMR) quantifies myocardial blood flow (MBF) but the clinical utility of stress CMR in the management of patients with suspected angina with no obstructive coronary arteries (ANOCA) is uncertain.

Objectives: First, to undertake a diagnostic study using stress CMR in patients with ANOCA following invasive coronary angiography and, second, in a nested, double-blind, randomized, controlled trial to assess the effect of disclosure on the final diagnosis and health status in the longer term.

Design: All-comers referred for clinically indicated coronary angiography for the investigation of suspected coronary artery disease will be screened in three regional centers in the United Kingdom. Following invasive coronary angiography, patients with ANOCA who provide informed consent will undergo noninvasive endotyping using stress CMR within 3 months of the angiogram.

Diagnostic study: Stress perfusion CMR imaging to assess the prevalence of coronary microvascular dysfunction and clinically significant incidental findings in patients with ANOCA. The primary outcome is the between-group difference in the reclassification rate of the initial diagnosis based on invasive angiography versus the final diagnosis after CMR imaging.

Randomized, controlled trial: Participants will be randomized to inclusion (intervention group) or exclusion (control group) of myocardial blood flow to inform the final diagnosis. The primary outcome of the clinical trial is the mean within-subject change in the Seattle Angina Questionnaire summary score (SAQSS) at 6 months.

Secondary outcome assessments include the EUROQOL EQ-5D-5L questionnaire, the Brief Illness Perception Questionnaire (Brief-IPQ), the Treatment Satisfaction Questionnaire (TSQM-9), the Patient Health Questionnaire-4 (PHQ-4), the Duke Activity Status Index (DASI), the International Physical Activity Questionnaire- Short Form (IPAQ-SF), the Montreal Cognitive Assessment (MOCA) and the 8-item Productivity Cost Questionnaire (iPCQ). Health and economic outcomes will be assessed using electronic healthcare records.

Value: To clarify if routine stress perfusion CMR imaging reclassifies the final diagnosis in patients with ANOCA and whether this strategy improves symptoms, health-related quality of life and health economic outcomes.

Clinicaltrials.gov: NCT04805814

Keywords: Stress cardiac magnetic resonance imaging, angina and no obstructive coronary artery disease, coronary microvascular dysfunction, microvascular angina, stratified medicine

Background

Coronary microvascular dysfunction

Angina is the most common symptom of stable ischemic heart disease, a leading global cause of premature morbidity and death (1). The management of angina is traditionally focused on the detection and treatment of epicardial coronary artery disease (2). However, most patients with angina referred for coronary computed tomography angiography (cCTA) or invasive coronary angiography do not have obstructive coronary artery disease (3), leaving the cause of angina uncertain.

Some of these patients may have coronary microvascular dysfunction(4–6), a condition that is not benign. It is associated with increased risk of major adverse cardiovascular events(7,8), persistent anginal symptoms(9), impaired quality of life(10), and considerable health resource utilization due to recurrent hospitalizations and repeat invasive angiograms(7). The prevalence of coronary microvascular dysfunction in patients with angina and no obstructive coronary arteries (ANOCA) is uncertain.

Functional imaging for coronary endotype evaluation

In patients with ANOCA, functional imaging may identify endotypes of myocardial ischemia (INOCA). However, European guidelines identify the usefulness/efficacy of functional imaging as being less well established with a Class IIb ("may be considered" recommendation and a grade B Level of Evidence (Data derived from a single randomized clinical trial or large non-randomized studies) (2) due to a lack of evidence from randomized, controlled trials. The combination of invasive coronary angiography with adjunctive tests of coronary vascular function is described as 'functional coronary angiography'. This remains the reference method for the diagnosis of coronary microvascular dysfunction "Class IIa, Should be Considered" recommendation (2).

Contemporary advances in non-invasive imaging include automated, pixel-wise quantitative mapping of myocardial perfusion by CMR (Figure 1). This method generates pixel-encoded maps of myocardial blood flow (ml/min/g tissue) which are acquired during vasodilator (hyperemic) stress and resting conditions. Myocardial perfusion reserve is calculated in a similar way to PET(11–13). The novel CMR method has been validated against invasive measures of coronary function and PET(12,14). Furthermore, myocardial blood flow and myocardial perfusion reserve measured using this method are independent predictors of adverse cardiovascular outcomes(15).

Advances in the accuracy and availability of quantitative stress perfusion CMR is reflected in the North American 2021 ACC/AHA Guideline for the Evaluation and Diagnosis of Chest pain guideline which accords stress CMR with myocardial blood flow/myocardial perfusion reserve a IIa recommendation for the diagnosis of coronary microvascular dysfunction in patients with stable chest pain and suspected INOCA(16).

CMR presents other advantages. CMR is noninvasive, safe, does not involve ionizing radiation, is undertaken on an outpatient basis, and is less expensive than invasive coronary angiography. CMR is a multiparametric method revealing cardiovascular structure, function, myocardial scar, inflammation and extracellular volume, whilst stress CMR may quantify microvascular dysfunction. The field-of-view may reveal incidental findings in the chest and upper abdomen. On the other hand, CMR has limitations: the absolute cost is relatively high and claustrophobia may preclude imaging.

Stratified medicine

Stratified medicine is the identification of key sub-groups of patients within a heterogeneous population; these being distinguishable groups with differing mechanisms of disease, or responses to treatments. Stratification can be used to improve mechanistic understanding of

disease processes and enable: the identification of new targets for treatments; the development of biomarkers for disease risk, diagnosis, progression and response to treatment; and treatments to be tested and applied in the most appropriate patient groups(17).

The Coronary Microvascular Angina (CorMicA) trial introduced stratified medicine in ischemic heart disease(4). The CorMicA investigators prospectively enrolled 391 patients referred for clinically indicated coronary angiography during a 12-month period in a regional cardiac center in Scotland. Almost half of this population (n =185; 47%) had no obstructive coronary artery disease and one hundred and fifty-one of these patients entered the randomized trial. CorMicA involved a 1:1 randomized, blinded, parallel-group clinical trial of stratified medicine versus standard angiography-guided management. The intervention involved disclosure of adjunctive tests of coronary vascular function to identify disease endotypes with linked medical therapy. Compared to angiography-guided standard care, the intervention changed the initial diagnosis in half of the participants in the intervention group and was associated with improvements in angina, health-related quality of life, and treatment satisfaction at 6- (4) and 12- months (18).

Rationale

Tests of coronary vascular function are uncommonly used during invasive angiography, meaning the diagnosis may be inaccurate and the management and clinical outcomes may be suboptimal. On the other hand, the lack of randomized, controlled trials present gaps in the clinical evidence, stimulating this research. Anatomical tests, including cCTA and invasive angiography, do not provide information on vasomotor endotypes and without noninvasive functional imaging, a diagnosis of INOCA is uncertain.

CorCMR is a diagnostic strategy trial that addresses this evidence gap. Among patients with chest pain without obstructive coronary artery disease defined by invasive angiography and

fractional flow reserve (FFR >0.80), we aim to assess whether endotype diagnosis informed by noninvasive functional imaging using stress CMR (myocardial blood flow disclosed to inform endotyping) versus no functional assessment (myocardial blood flow measured but not disclosed), with endotype specific-treatment algorithms applied to all patients, affected the final diagnosis, health status and treatment satisfaction.

We propose that a prospective study involving novel, noninvasive diagnostic tests of myocardial perfusion will increase accuracy for clinical subgroups (endotypes) not identified by standard invasive management. We aim to provide information on endotype prevalence. Stress CMR will be undertaken in patients without obstructive coronary disease. These patients will be randomized 1:1 to disclosure of the myocardial blood flow findings to the imaging cardiologist reporting the CMR scan (intervention group) or non-disclosure (control group). Patients and treating clinicians will be blinded to the randomized group and the myocardial blood flow findings. They will be provided with a final diagnosis post-CMR and they will be unaware of the randomized group and the myocardial blood flow findings. The clinical significance of disclosure of the stress CMR findings results versus non-disclosure will be assessed in a nested randomized, controlled trial collecting patient reported outcome measures.

Methods

Aim

The first aim is to use quantitative stress perfusion CMR in a near-consecutive series of patients with clinically-suspected ANOCA following recent (<3 months) invasive coronary angiography to assess for coronary endotypes, including microvascular dysfunction and obstructive coronary artery disease, and clinically-significant incidental findings not detected by standard care involving invasive management.

The second aim is to assess the reclassification effect on the final diagnosis of coronary endotype classification based on disclosure of the myocardial perfusion assessment and, finally, to assess the effect of the intervention on health status during follow-up.

Hypotheses

1) In patients with ANOCA confirmed by invasive coronary angiography ± FFR, microvascular angina is prevalent.

2) Disclosure of coronary microvascular function using quantitative stress perfusion CMR will be associated with improvements in well-being as compared to decisions based on coronary angiography alone.

3) The intervention will improve health care resource utilization.

Study Design

A prospective observational cohort study and a nested double-blind, randomized, controlled clinical trial.

Objectives

The study includes two distinct primary objectives.

Primary objective of the diagnostic study

To systematically assess the prevalence of abnormal myocardial perfusion in patients with known or suspected angina in whom other causes of angina, e.g., obstructive coronary artery disease (>70% stenosis), systemic or cardiovascular problem that would cause angina, have been ruled out and medical management is intended.

The primary outcome reflects the reclassification of the initial diagnosis based on use of multiparametric, quantitative stress perfusion CMR at 1.5 Tesla. The diagnostic groups include endotypes for angina and clinically-significant incidental findings:

1) Angina due to obstructive coronary artery disease

2) Microvascular angina

3) Vasospastic angina

4) Incidental finding that is actionable e.g. aortic stenosis, cardiomyopathy, lung cancer; or

5) Non-cardiac chest pain.

The primary outcome is the between-group difference in the reclassification rate of the initial diagnosis based on invasive angiography versus the final diagnosis after noninvasive imaging. This outcome i.e. a change in diagnosis after CMR, is intended to be meaningful for patients and physicians.

Primary objective of the randomized trial

The primary objective of the clinical trial is to determine whether disclosure of myocardial blood flow revealed by stress CMR imaging benefits patients. The primary outcome is the within-subject change at 6 months from baseline in the Seattle Angina Questionnaire summary score; range 0 – 100, a higher score represents less angina).

Secondary objectives

The pre-specified secondary objectives are described in Table 1.

Implementation

The diagnostic study involves enrolling patients with symptoms suggestive of angina and who have undergone invasive coronary angiography within 3 months at three hospitals. Patients without obstructive coronary artery disease on invasive angiography will be eligible to participate and following informed consent they will be invited to return for a CMR scan at the NHS Golden Jubilee hospital, a regional cardiac center.

The design includes a nested prospective, double-blind, randomized, controlled trial of routine disclosure vs. non-disclosure of quantitative stress perfusion CMR findings.

A medical management plan is prespecified for each clinical endotype (Table 2). The endotype-specific treatment guidance will be provided to inform downstream care providers of the final diagnosis and provide a management plan for the endotype informed by practice guidelines. These guidance documents will be used for all patients with the plan provided for individual patients according to the final diagnosis, regardless of randomization group. In the intervention group the final diagnosis is informed by the endotype determined using the stress CMR imaging and other standard care information. In the control group, the final diagnosis is informed by the standard care information but not the stress CMR findings. The randomized group will not be disclosed to the patient or the attending clinicians with responsibilities for ongoing care. As the same guidance documents will be used in the intervention and control group to inform downstream clinicians of the endotype diagnosis and management guidelines, blinding will be maintained. Clinically significant incidental findings revealed by the CMR scan will be disclosed and actioned regardless of the randomized group. In an ancillary study, brain MRI will be acquired when feasible (Figure 2).

Setting

The participating sites include three hospitals in West and Central Scotland (NHS Golden Jubilee Hospital, University Hospital Hairmyres, University Hospital Ayr) (Figure 3). The sites include a regional cardiothoracic center, a large urban hospital, and a district general hospital. These hospitals serve a socially and geographically diverse population of approximately 2.5 million people drawn from urban and rural areas. Stress CMR imaging will be acquired the NHS Golden Jubilee hospital, a single reference center.

Population

Electronic health records for patients referred for assessment of coronary artery disease by invasive coronary angiography at the three hospitals in Scotland will be screened. Out-patients with a diagnosis of known or suspected stable angina (typical or atypical) will be eligible to participate. The Rose angina questionnaire(19) will be used to assess anginal symptoms at baseline and define them as typical, atypical, or non-anginal. It defines typical angina as pain/discomfort affecting the center/left anterior chest or left arm which is precipitated by exertion and relieved by rest or nitroglycerin within 10 minutes. Anginal symptoms will further be assessed, including intensity and severity, using the Seattle Angina Questionnaire(20). Information about the study be provided to patients before and/or after the standard of care coronary angiogram.

Baseline demographic information will be collected for all patients. This will include preceding investigations such as ischemia testing (e.g. treadmill exercise electrocardiography, myocardial perfusion imaging) and coronary imaging (e.g. cCTA).

Eligibility

Inclusion criteria

The decision to enroll patients will be made after the angiogram when obstructive disease in the main epicardial coronary arteries has been excluded and a medical management plan has been established by the treating cardiologist. Enrolment may occur up to three months after the angiogram.

Inclusion criteria:

The inclusion criteria are: age ≥18 years; symptoms of angina or angina-equivalent informed by the Rose Angina questionnaire; coronary angiography ≤3 months with a plan for medical management.

Exclusion criteria

The exclusion criteria are: obstructive coronary artery disease i.e. a stenosis >70% in a single segment or 50 – 70% in 2 adjacent segments in an artery >2.5 mm, or FFR ≤0.80; coronary revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery following the index angiogram; prior coronary artery bypass graft surgery; a diagnosis that would explain the angina e.g. anemia, aortic stenosis, hypertrophic cardiomyopathy; contra-indication to contrast-enhanced CMR e.g. eGFR<30mL/min/1.73m^2; contra-indication to intravenous adenosine, i.e. severe asthma; long QT syndrome; second- or third-degree AV block and sick sinus syndrome; lack of informed consent.

A history of PCI or coronary function testing prior to the index angiogram is not an exclusion criterion.

Enrolment and randomization

The Study Information Sheet and Consent form will be provided to patients before or after the standard care coronary angiogram. After the angiogram, eligibility will be reconfirmed. Following written informed consent, study participants will be invited to return for stress CMR.

In order to minimize bias, randomization will be performed before the scan and neither the participants, the CMR technologists nor the treating clinicians responsible for on-going care will be informed of the randomized group allocation. Randomization will be performed using a web-based randomization system provided by the Robertson Centre for Biostatistics in the University of Glasgow. The randomization sequence involves block lengths randomized in blocks of length of four, that is, every twenty allocations consists of four blocks, two of length four and two of length six, in a random order. The allocation sequence is on a 1:1 basis between the intervention group and the control group. The sequence is concealed electronically. Patients are randomized as soon as the allocation is assigned on the web-based portal.

The randomization involves whether or not the myocardial perfusion findings are disclosed to inform the final diagnosis. The scan will be acquired and reported by a Level 3 accredited imaging cardiologist (C.B.) blind to randomized group. Since the imaging clinician, the treating clinicians and the participants will be blind to the randomized group the design is double-blind. The radiology report will be established and communicated in the same way for all participants. The report will not include the stress CMR findings (all patients, both groups); instead, the report will include the final diagnosis (informed by the stress CMR (intervention group) or not (control group) and any clinically significant incidental findings (all patients, both groups).

The treatment plan based on angiography alone is established during standard care. This will be recorded by the researcher in the Case Report Form at the time of the angiogram. The management plan will be retained by the clinicians until the CMR scan is performed. Once done, the management plan will be communicated in the usual way.

Myocardial perfusion will be quantified in all randomized participants. In the intervention group, the stress perfusion CMR findings will be used to inform the final diagnosis. The control group follows standard, angiography-guided care and the myocardial perfusion findings will not be used to inform the final report. The final CMR report will state the diagnosis but the perfusion MRI findings will not be disclosed (all patients).

Since CMR may disclose prognostically important findings e.g. aortic valve disease, hypertrophic cardiomyopathy, lung mass, then clinically relevant incidental findings will be disclosed in all patients (independent of the randomized group) and actioned as would normally be done after a CMR scan and in line with standard care. This approach will not lead to unblinding.

CMR Protocol and analysis

Stress Perfusion CMR

CMR imaging will be performed at 1.5 Tesla (Siemens MAGNETOM Avanto, Erlangen, Germany), using a standardized CMR protocol (Figure 4). All patients will be invited to abstain from caffeine-containing beverages or foodstuffs for 24 hours and vasoactive medications for 48 hours prior to the CMR examination.

The imaging protocol will include localizers, cine imaging for cardiovascular dimensions and function including long axis left ventricular imaging e.g. 4 and 3 chamber acquisitions, aortic cine and flow sequences, short-axis planes through the left ventricle (basal, mid-ventricular and apical) for T1-mapping and T2 mapping (mid-LV only) pre- contrast, adenosine stress-

and rest- perfusion imaging, short axis cine for LV function, late gadolinium enhancement imaging and post- contrast myocardial T1 mapping.

Vasodilator stress will be achieved by intravenous infusion of adenosine at a dose of 140μg/kg/min for 4 min (increased to 210μg/kg/min for a further 2 minutes if no symptoms or less than 10% heart rate increase). Splenic switch-off will retrospectively be confirmed during image analysis to assess for adequate stress. At peak stress, a gadolinium-based contrast agent (Gadovist®, Bayer Healthcare) will be injected at 4 ml/s at a dose of 0.05 mmol/kg. Resting first-pass myocardial perfusion will be performed at least 10 minutes later.

CMR Analysis

The CMR scan will be reviewed and reported by an imaging cardiologist (C.B.) at the NHS Golden Jubilee hospital, as per local standards of care. The CMR analyses will be performed as per standard reporting guidelines (21) using commercially available software (CVI42, Circle Cardiovascular Imaging, Calgary, Canada). Left ventricular volumes and function will be analyzed using manual planimetry. Late gadolinium enhancement will be reported (17 segment model) with scores of 0 (no hyperenhancement), 1 (1–25% extent), 2 (26–50%), 3 (51–75%), or 4 (>75%). A positive result will be taken as ≥2 adjacent segments (or 60○ arc-equivalent if the defect crosses segmental boundaries) with ≥50% transmural extent of ischemia, scar, or ischemia-scar combination) by protocol. Incidental findings identified during this review will be referred for interpretation by a radiologist with further action according to standard care.

Automated quantitative perfusion mapping will be performed using the method described by Kellman et al, including the Gadgetron framework(11). The method involves a dual sequence approach for myocardial perfusion acquisition and arterial input function acquisition simultaneously, allowing for quantification of myocardial blood flow (ml/min/g) for each

pixel of myocardium. The software allows for automated endocardial and epicardial contouring and segmentation using the American Heart Association 16- and 32- segment model. Automated endocardial and epicardial sub-segmentation is achieved by offsetting the epicardial border to 50%. The global myocardial blood flow is automatically calculated by the average of all the pixels and is measured at stress and rest. Global myocardial perfusion reserve (MPR) is the ratio of stress to rest myocardial blood flow. MPR can also be calculated specifically for the subendocardial layer (MPR_{ENDO}) (calculated by stress MBF_{ENDO}/ rest MBF_{ENDO}).

Automated contouring will be reviewed and quality-checked by the reporting cardiologist (C.B.). If errors are noted, automated contouring will be removed and replaced by manual contours.

In keeping with prior studies, in the absence of a regional or visual perfusion defect, a threshold of global stress myocardial blood flow <2.25ml/min/g, MPR<2.2 or MPR_{ENDO}<2.41 will be consistent with a diagnosis of coronary microvascular dysfunction(22,23).

CMR imaging to inform clinical management

The CMR perfusion results will be used to classify patients according to coronary endotypes including 1) Angina due to obstructive coronary artery disease 2) Microvascular angina, and 3) Non-cardiac chest pain (normal myocardial perfusion).

Clinical management

The intervention arm involved acquisition and use or non-use of the stress perfusion CMR findings.

Clinical management, intervention group

17

Perfusion CMR findings will be used by the blinded research cardiologist to establish a final diagnosis, which may involve reclassification of the initial diagnosis based on coronary angiography alone. In the intervention group, medical therapy will be mechanistically linked to the endotype, reflecting stratified medicine. If the initial diagnosis based on coronary angiography is revised then the management plan will be revised to align with the final diagnosis.

The medical management plan is pre-specified, and standardized informed by practice guidelines. The management plan will be provided to the downstream care providers and this approach will be the same for all patients, regardless of the randomized group.

Acetylcholine testing is not part of the study protocol, nor is it usually included in standard care although it is supported by a IIb guideline recommendation (2). Nonetheless, the clinician may still make a presumptive diagnosis of vasospastic angina based on the clinical history. If the clinician suspects vasospastic angina then therapy can be appropriated accordingly.

On rare occasions obstructive coronary artery disease may be 'missed' at the time of the standard care coronary angiogram, and the imaging findings revealed by stress perfusion CMR, by protocol, may disclose a regional myocardial perfusion deficit that is indicative (or diagnostic) of obstructive coronary artery disease.

Clinical management, control group

In the control arm, the stress CMR findings were acquired but not used to reclassify the initial diagnosis. The final diagnosis and related treatment were guided by the angiogram only. The same endotypes, including microvascular angina and vasospastic angina, could be empirically diagnosed but without access to the stress perfusion CMR results.

At the end of the stress CMR scan, following determination of the final diagnosis, the research cardiologist selected a pre-specified medical management plan customized for each endotype. This plan was provided for the endotype regardless of the randomized group. The plan involved medical therapy and non-pharmacological (lifestyle) measures to control cardiovascular risk factors according to guideline targets (2). This information was also provided to the primary and secondary care staff with responsibilities for ongoing care.

The treating clinician is encouraged to titrate medications to address persistent symptoms during the follow-up period. The treatment plan will be led by the blinded usual care teams rather than the research team and medication changes were at the discretion of the usual care clinicians. Standardized letters with customized medical management guidelines will be sent to the general practitioner and cardiologist with advice on treatment optimization to relieve anginal symptoms. Standard care for patients in the control group consists of guideline-directed medical therapy. Referral for cardiac rehabilitation will be prioritized for patients with a new diagnosis of ischemic heart disease.

Any clinically significant incidental findings (cardiac, extra-cardiac) will be disclosed. Any protocol deviations will be prospectively documented. This design aligns with the BHF CorMicA and CorCTCA studies (4,24).

Questionnaires and follow-up

The Seattle Angina Questionnaire (SAQ) is a self-administered, validated, disease-specific questionnaire that quantifies limitations caused by angina, the frequency of angina, treatment satisfaction, and subjective perception of quality of life(25). Each domain is transformed to a score of 0 to 100 where higher scores indicate better function (e.g. less angina). The summary score averages the domains of angina limitation, frequency, and quality of life to provide an overall metric of angina severity.

Health status will be assessed using the validated, self-administered EUROQOL EQ-5D-5L questionnaire, Brief Illness Perception Questionnaire (Brief-IPQ)(26–30). The Treatment Satisfaction Questionnaire (TSQM-9, which includes 9 questions and a scale from 0 to 100) will provide information regarding medication side effects, effectiveness, convenience, and overall satisfaction(31). The Patient Health Questionnaire-4 (PHQ-4) will be used to screen patient for depression and anxiety(32). The 8-item Productivity Cost Questionnaire (iPCQ) to estimate productivity loss and time lost from work(33). The Montreal Cognitive Assessment (MOCA) will be used to assess cognition(34).

The questionnaires will be administered at baseline, 6 months, and 12 months. Follow-up assessments for adverse events will be performed by the clinical research staff by telephone or in person (e.g., outpatient clinic review), as appropriate. Medical records will also be checked. Follow-up contact will occur at 6 monthly intervals until the last patient has achieved a minimum of 6 months of follow-up. Follow-up in the longer term (i.e., ≥3 years) will be supported by electronic record linkage with central government health records. Follow-up procedures will be the same for patients in both groups. The adherence to blinding will be prospectively recorded and monitored. The participants' knowledge of their randomized group assignment will be checked at 12 months.

Adjudicated adverse events

Follow-up assessments for adverse events will be performed by research staff who will be blind to the baseline data and randomized groups. The contacts will involve in-person visits, telephone follow-up, or review of electronic health records. Clinical events identified as potentially relevant were assessed by a Clinical Event Committee according to a pre-specified charter. This committee will be blind to the baseline data and randomized groups. The committee will be independent of the investigators, funder, and sponsor.

Statistical considerations

Primary outcome

The primary outcome of the randomized trial is the reclassification of the initial diagnosis based on findings from the CMR scan. This will be reported as a percentage with a 95% confidence interval. Logistic regression models will be used to assess factors associated with the likelihood of diagnostic reclassification.

The primary outcome of the randomized clinical trial is the SAQ summary score. This will be analyzed with a baseline-adjusted linear regression model, reported as the estimated mean difference between randomized groups. Alternative imputation approaches will be used to assess the sensitivity of the main results to missing outcome data.

Secondary outcome

Continuous outcomes will be analyzed using baseline-adjusted linear regression models. Where data are clearly not normally distributed (e.g. laboratory variables) standard transformations will be applied to improve model fit. Binary outcomes will be analyzed using logistic regression models. Clinical events will be presented with Kaplan-Meier time-to-event curves and compared where appropriate using Cox regression models.

Models will be extended to assess associations between baseline characteristics, including angiographic parameters, and study outcomes. Subgroup analyses will use interaction tests within regression models to assess intervention effect heterogeneity.

Sample size calculation for the diagnostic study

The primary outcome is the reclassification of the initial diagnosis based on invasive management following multi-parametric stress perfusion CMR. The intention-to-treat analysis will be the between-group comparison of the reclassification rate using logistic

regression, adjusted for baseline factors associated with the likelihood of reclassification of the initial diagnosis with a sample size of 250, the 95% confidence interval of the estimate will have a width of no more than ±6.2%. This should be sufficiently precise to inform the utility of the test.

Sample size calculation for the randomized trial

The sample size was determined based on the power to detect a clinically relevant difference in the Overall SAQ summary score. If 6-month outcomes can be obtained from 200 patients, the trial will have 80% power to detect a mean between-group difference in SAQ summary score of 0.40 standard deviation (SD) units. This is a small difference but we anticipate that not all patients will have their therapy changed as a result of disclosure. Using the coronary function data for the control (non-disclosure) group, we will carry out focused analyses of the sub-group of patients whose therapy might have been altered based on abnormal results. For example, if therapy would be altered in 50% of patients, the study will have 80% power to detect a difference in SAQ score of 0.57 SD units for these patients; if therapy is altered in 30% of patients, there will be 80% power to detect a between-group difference of 0.74 SD units. Allowing for 20% loss-to-follow-up, we would require 250 patients to undergo stress perfusion CMR. Allowing for an additional 10% of randomized patients not undergoing CMR, we aim to randomize 280 participants.

Trial Management and Governance

Trial management

The study will be conducted according to observational (STROBE)(35), GCP(36), and CONSORT guidelines(37). The study will be coordinated by the Study Management Group which will include those individuals responsible for the day-to-day management of the study including the Chief Investigator, Co-Investigators, and Research Nurse. This group will

coordinate the progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself.

Study monitoring will be conducted by monitors on behalf of NHS Golden Jubilee National Hospital Research Management Office. During monitoring assessments, Informed Consent Forms will be reviewed and source clinical data as appropriate.

Ethics

The CorCMR study is approved by the UK National Research Ethics Service (Reference 20/WS/0159).

Sources of funding

The study is funded by the British Heart Foundation (PG/19/28/34310; RE/18/6134217). The Chief Scientist Office funded the CMR scans. The funders had no other involvement in the study.

Registration

The ClincalTrials.gov registration is NCT04805814.

Discussion

This multicenter, double-blind, randomized, controlled trial is designed and powered to determine whether use of stress perfusion CMR in patients with suspected ANOCA improves diagnosing the cause of angina. The study should provide new information on the prevalence of microvascular angina and clinically-significant incidental findings in this post-angiography population. The trial will clarify whether the intervention might be associated with improvements in angina, health status, treatment satisfaction and healthcare resource utilization. The results should be useful to inform evidence-gaps on the role of noninvasive functional imaging in patients with suspected ANOCA. The results may be informative to future clinical guidelines.

Novel design features include multicenter recruitment in a wide geographic area, use of validated questionnaires, noninvasive estimation of myocardial blood flow using CMR acquired in a single reference center, randomization before stress CMR, a control procedure, blinding, and stratified medical therapy. The study presents ethical considerations in relation to the use, or not, of the myocardial perfusion findings. In our healthcare system, stress perfusion CMR is not available for clinical use (research indication only) and the protocol was approved by the ethics committee on this basis. Clinically-significant incidental findings will be disclosed, in line with standard radiology care, and blinding for the randomized group will be preserved.

Advances in noninvasive quantitative stress perfusion CMR imaging potentially improve identification of coronary microvascular dysfunction. In a study of 51 patients (n=27 and n=23 with obstructive and no obstructive coronary artery disease, respectively) Kotecha et al observed that when compared against invasive coronary physiology, global stress myocardial blood flow measured by pixel-wise quantitative myocardial perfusion mapping identified coronary microvascular dysfunction(22). However, this nonrandomized study lacked

longitudinal follow-up or clinical correlation and unlike the 2021 ACC/AHA Guideline for the Evaluation and Diagnosis of Chest pain (16), European guidelines have given a IIb recommendation for functional imaging for the assessment of coronary microvascular disease.

Stress perfusion CMR imaging has limitations including contraindication in certain patient groups e.g. severe renal disease, claustrophobia, implantable devices. Furthermore, the diagnostic gap for coronary vasospasm is a major limitation compared with coronary vasomotor testing using intracoronary infusion of acetylcholine.
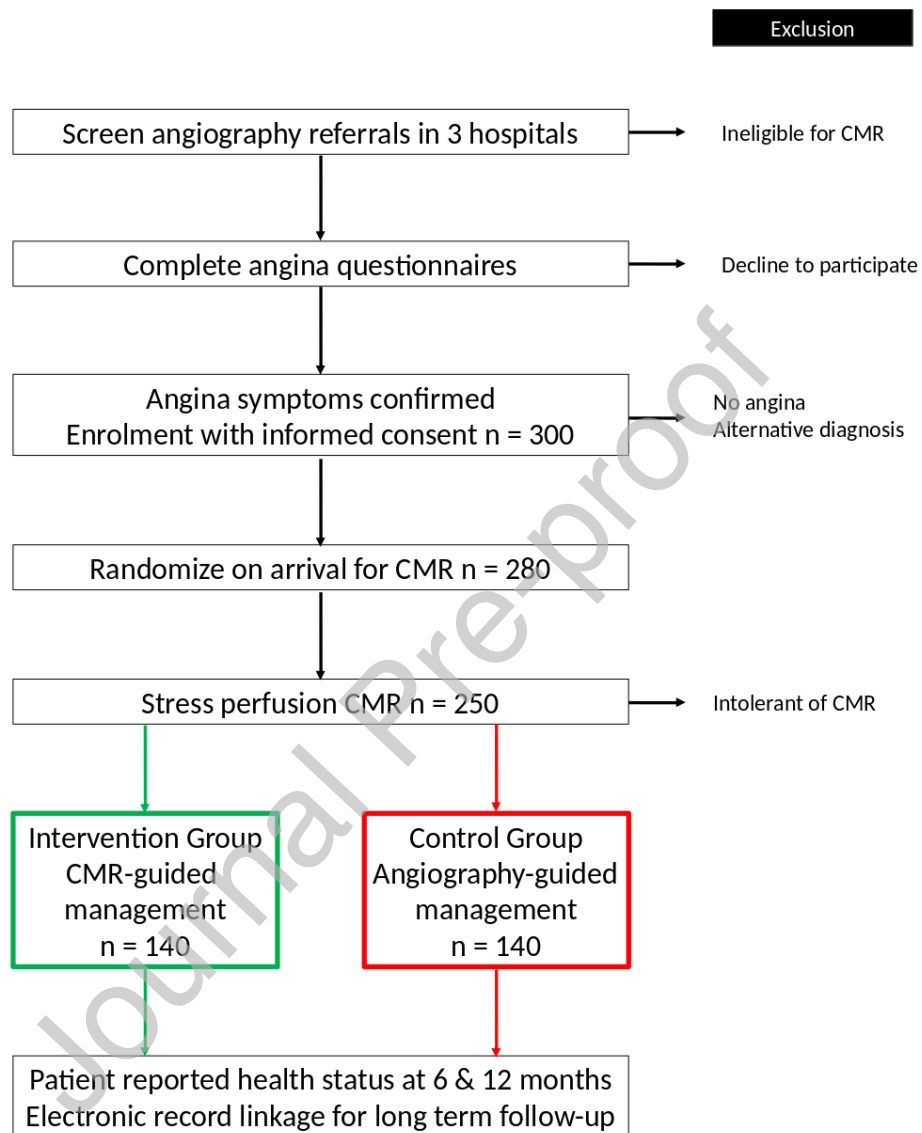
Acknowledgement

Figures

Figure 1. Myocardial perfusion maps revealing normal perfusion and microvascular dysfunction.
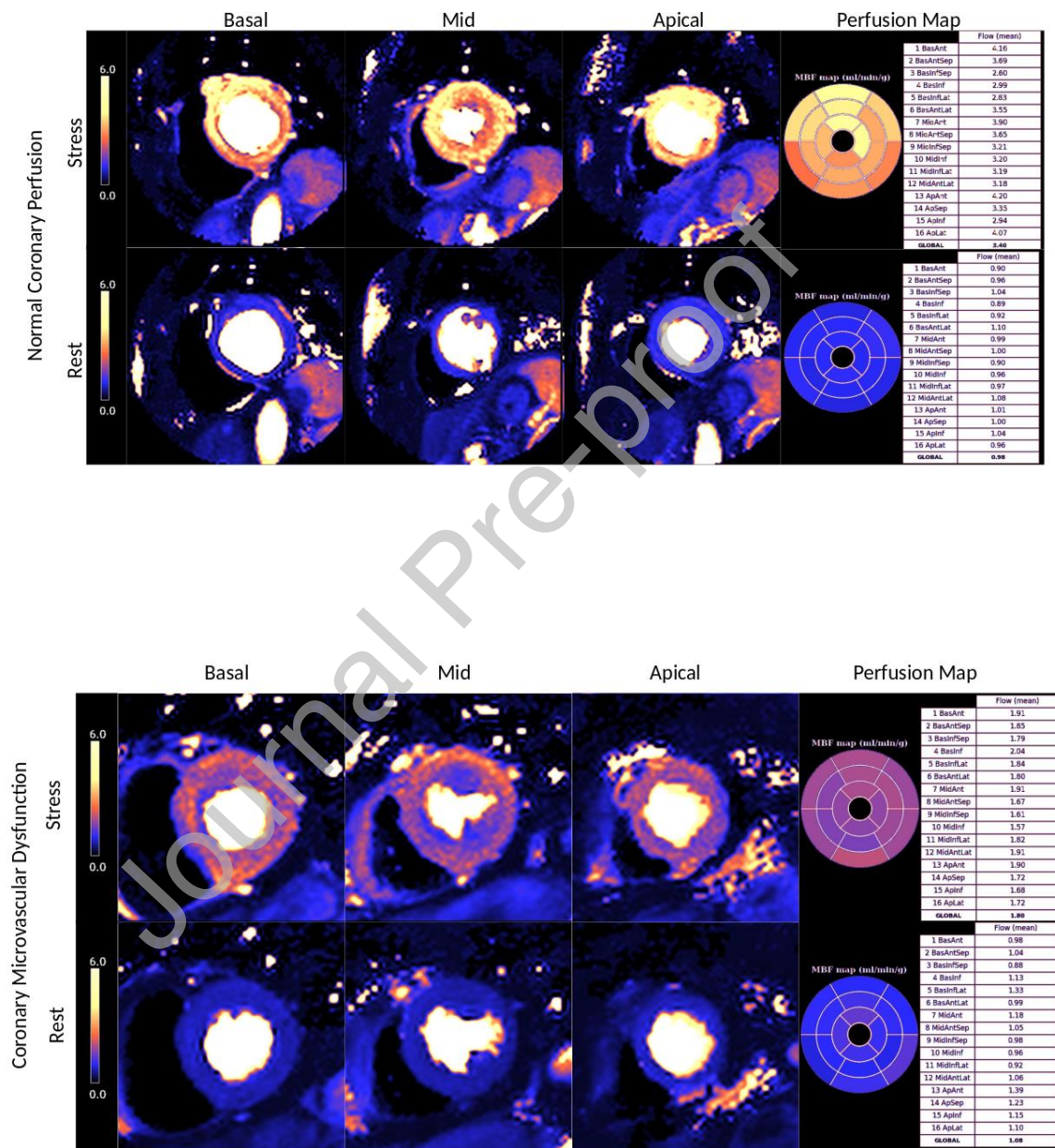
Figure 2. Study design.

Figure 3. Recruitment sites for the CorCMR trial. Three recruiting hospitals with a catchment area which covers West and Central Scotland (labeled in orange).
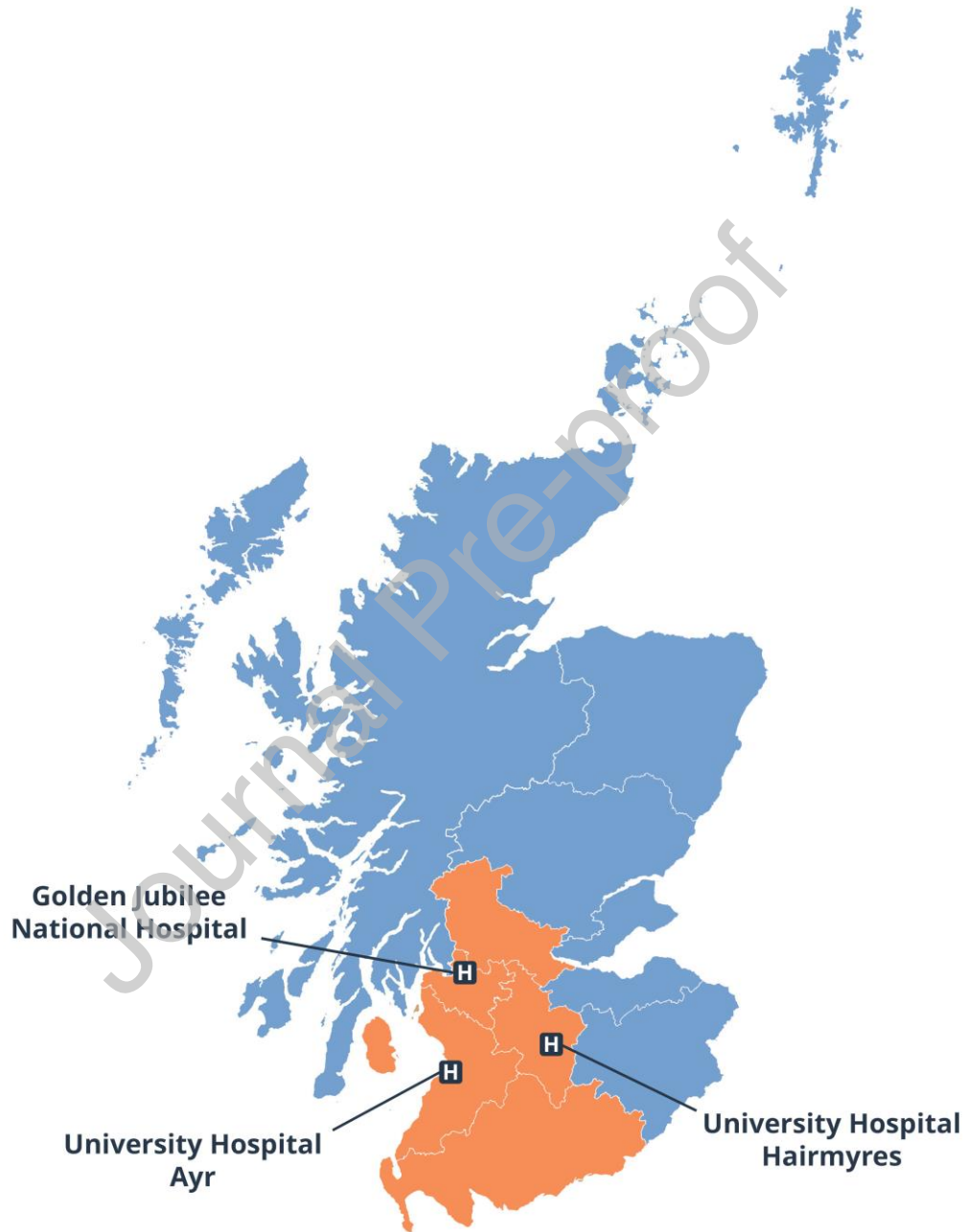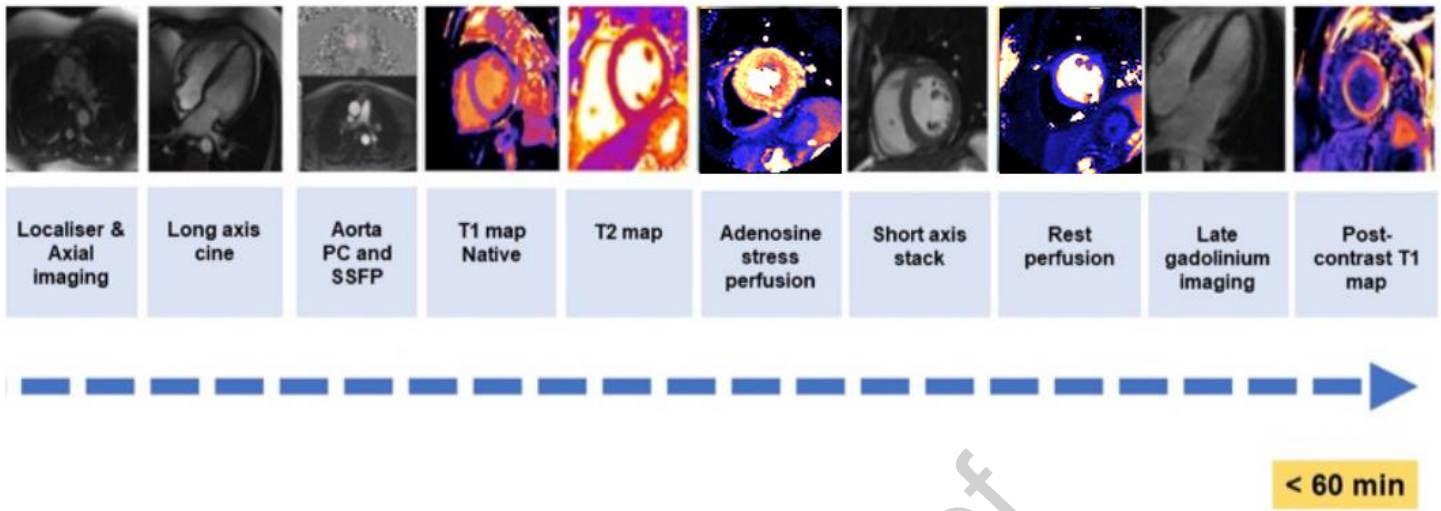
Figure 4. CorCMR CMR protocol

Tables

Table 1. Secondary objectives

1. Assess compliance with the protocol, reflected by the rate of enrolment, % of patients who withdraw, and % of patients who complete the MRI scan.

2. Document the integrity of the blinding.

3. Diagnostic utility: Assess the level of diagnostic certainty, as reported by the attending imaging cardiologist.

4. Clinical Utility: To assess impact of disclosure of the cardiac MRI results on clinical management (including treatment and investigations).

5. Myocardial perfusion: Assess the prevalence of abnormal myocardial blood flow, as defined by a minimum of 2 adjacent cardiac segments each with ≥50% deficit in myocardial perfusion at peak stress revealed by (1) visual assessment of the dynamic stress perfusion CMR scan and (2) pixel mapping of myocardial blood flow (< 2.0 ml/min/g tissue).

6. Sub-study: Assess the associations between myocardial perfusion (ml/min/g) and invasive measures of coronary function (where available) that might be implicated in the pathophysiology of abnormal coronary vascular function.

7. Assess the relationships between myocardial perfusion (ml/min/g) and myocardial tissue characteristics e.g., native T1- and T2- relaxation times, as revealed by MRI.

8. Assess the relationships between cardiovascular risk factors, reflected by validated risk scores (e.g., ASSIGN, JBS3 or QRisk), and myocardial perfusion (ml/min/g) in medically managed patients.

9. Assess the within-subject change in CMR findings during 12-months.

10. In patients who undergo repeat CMR, assess the between-group, within-subject change in CMR over 12 months.

11. Assess health status reflected by the EQ-5D-5L at baseline and during follow-up.

12. Assess components of the Seattle Angina Questionnaire at baseline and during follow-up.

13. Assess illness perception using the Brief Illness Perception Questionnaire (BIPQ) at baseline and during follow-up.

14. Assess the Treatment Satisfaction for Medication Questionnaire (TSQM-9) at baseline and during follow-up.

15. Assess the Duke Activity Status Index (DASI) at baseline and during follow-up.

16. Assess functional statusy using the International Physical Activity Questionnaire - Short Form (IPAQ-SF) at baseline and during follow-up.

17. Assess cognition using the Montreal Cognitive Assessment (MoCA) tool at baseline and during follow-up.

18. Assess the correlation between myocardial blood flow (ml/min/g) and health status, as measured by validated questionnaires.

19. Assess longer term prognosis and association with myocardial perfusion at baseline.

20. Assess major adverse cardiovascular events (MACE) including death, re-hospitalisation for cardiovascular events including myocardial infarction, heart failure, stroke/ transient ischemic attack, unstable angina and coronary

revascularization. Unscheduled hospital visits for chest pain that have not led to hospital admission will also be documented.

21. Assess anginal episodes based on completion of a chest symptoms log and adjudicated by a clinical event committee.

22. Assess the associations between myocardial perfusion (ml/min/g) and health status, as measured by validated questionnaires.

23. Assess the long-term prognostic significance of myocardial perfusion (ml/min/g) at baseline.

24. Undertake a health economic analysis including use of the Productivity Cost Questionnaire (iPCQ).

25. Assess longer term health outcomes, episodes of care and prescriptions, using electronic record linkage without patient contact and assess the associations with myocardial perfusion (ml/min/g) at baseline.

Table 2: Coronary endotypes with management guidance for health care provider

Endotype	Pharmacological Management	Non Pharmacological lifestyle and risk factor control
Microvascular angina	- Calcium antagonists (e.g. **Verapamil** 40mg BD up-titrated weekly according to response); NB do not combine a rate limiting calcium channel blocker (verapamil, diltiazem) with a beta blocker. - Or Beta-blockers (e.g. 1.25mg **Bisoprolol** up-titrated or alternatively 3.125 mg of carvedilol twice daily with up-titration if feasible and appropriate, see Summary of Product Characteristics; https://www.medicines.org.uk/emc/medicine/27714) **Aspirin, Statin** or **ACEI** may be reasonable (depending on patient characteristics) - Short-acting PRN nitrate (e.g. **Sublingual GTN**) **Nicorandil** if refractory symptoms (e.g. 5mg BD up-titrated weekly according to response) - Xanthine inhibitors (aminophylline) – if refractory to all above	**Smoking** "Smoking is a strong and independent risk factor for CVD and all smoking, including environmental smoking exposure, must be avoided in all patients with CVD" **Diet** "A healthy diet reduces CVD risk... Energy intake should be limited to the amount of energy needed to maintain (or obtain) a healthy weight—that is, a BMI <25 kg/m2." **Exercise** "moderate-to-vigorous intensity aerobic exercise training ≥3 times a week" (30 min) **Weight** "Weight reduction in overweight and obese people is recommended in order to achieve favorable effects on BP, dyslipidemia and glucose metabolism" **Lipids** – "The goals of treatment are LDL-C below 1.8 mmol/L" **Hypertension** – "Blood pressure to values within the range 130–139/80–85 mmHg" **Diabetes** "good control of glycated haemoglobin (HbA1c) to <7.0%...based on individual considerations." **Psychosocial** "Patients should be assessed for psychosocial distress and appropriate care offered… Refer for psychotherapy, medication or collaborative care in the case of clinically significant symptoms of depression, anxiety and
Vasospastic angina	- Non-dihydropyridine calcium channel blocker (e.g. **Verapamil** initially 40mg BD increasing at weekly intervals as tolerated up to 240-360 mg daily) +/- **Long-acting nitrates** if symptoms ongoing (scheduled to cover the period of the day in which ischaemic episodes most frequently occur, in order to prevent nitrate tolerance. - β-Blockers should be avoided. **Aspirin, statin and ACE-I** therapy may be reasonable, and is recommended if coronary disease is revealed by coronary angiography (CTCA or invasive)	

| Obstructive coronary artery disease | • Angina medication
  o Beta-blockers (e.g. 2.5mg **Bisoprolol** uptitrated or 3.125 mg of carvedilol twice daily with up-titration if feasible and appropriate, see Summary of Product Characteristics; https://www.medicines.org.uk/emc/medicine/27714)
  o Isosorbide mononitrate
  o Calcium antagonist e.g. **Verapamil** 40mg BD uptitrated weekly according to response; NB do not combine a rate limiting calcium channel blocker (verapamil, diltiazem) with a beta blocker.
• **Aspirin, Statin** or **ACEI** may be reasonable (depending on patient characteristics)
• Short-acting PRN nitrate (e.g. **Sublingual GTN**)
• **Nicorandil** if refractory symptoms (e.g. 5mg BD uptitrated weekly according to response) | hostility."
• **Cardiac rehabilitation** "A comprehensive risk-reduction regimen, integrated into comprehensive cardiac rehabilitation, is recommended." |
| Non-cardiac chest pain | • Anginal medication may not be needed and may be discontinued. | |

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