Early Value Assessment commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence – Final Protocol

Title of project

CaRi-Heart® for predicting cardiac risk in suspected coronary heart disease (CAD): A systematic review and conceptual economic model to inform Early Value Assessment (EVA)

Name of External Assessment Group (EAG) and project lead

Kleijnen Systematic Reviews Ltd. Assessment Group

Project lead: Marie Westwood
Second Contact: Nigel Armstrong
Kleijnen Systematic Reviews Ltd
[redacted]
Tel: [redacted]
Email: [redacted]

Health economics lead: Isaac Corro Ramos
Second contact: Eline Krijkamp
Institute for Medical Technology Assessment/Institute of Health Policy and Management
Erasmus University
[redacted]
Tel: [redacted]
Email: [redacted]

Plain English Summary

Coronary artery disease affects around 2.3 million people in the UK. It is caused by a build-up of fatty plaques on the walls of the blood vessels that supply the heart muscle. This can reduce the flow of blood to the heart and result in people experiencing chest pain (angina) especially when they exercise. Over time, the fatty plaques can grow and block more or all of the artery and blood clots can also form, causing blockage. A heart attack happens when the supply of blood to the heart muscle is blocked.

People who have episodes of chest pain, who's doctors think that they may have coronary artery disease, can have a type of imaging (CT coronary angiography) which shows whether there is any narrowing of their coronary arteries. When offering treatment, specialist heart doctors are likely to consider a person's symptoms and other risk factors (such as family history of heart disease, diabetes, and smoking history), as well as how much narrowing of the arteries has occurred, how long is the affected area, the location of the affected area. Medicines, such as statins or aspirin, can be used to reduce the risk of fatty plaques growing or blood clots forming. For more serious disease, procedures may be used to unblock the arteries (angioplasty) or to allow blood to flow round the blockage (bypass).

Some people, whose CT coronary angiography imaging results show that they have no or only a small amount of narrowing of their coronary arteries, go on to have heart attacks over the next ten years. For some people this will be because new coronary artery disease has developed during this time. However, it is thought that inflammation of the coronary arteries, which is not detected by CT coronary angiography, can also increase the risk of heart attack.

CaRi-Heart® is a computer programme that can be used, with CT coronary angiography imaging, to detect inflammation of the coronary arteries. The programme uses information about inflammation of the coronary arteries and other information (such as age, sex, smoking status, diabetes status, cholesterol) to estimate an individual's risk of dying from a heart attack in the next eight years.

This assessment will consider whether the information provided by the CaRi-Heart® software has the potential to change how patients are treated so that the numbers of deaths from coronary artery disease are reduced.

1 Background

The primary indication for this early value assessment (EVA) is the assessment of cardiac risk, specifically, the risk of cardiac death.

Coronary artery disease (CAD) and acute myocardial infarction (AMI) are a significant health burden in the UK, with Office of National Statistics (ONS) mortality data for 2021 showing 20,061 deaths from AMI (3.42% of all deaths recorded in 2021) and ischaemic heart disease being the leading cause of death in males (37,095 deaths, 12.4% of all male deaths).[1, 2]

Computed tomography coronary angiography (CTCA) is recommended, in NICE guideline CG95,[3] and in European Society of Cardiology guidelines,[4] for the investigation of CAD in people with stable chest pain. CTCA provides a visualisation of the coronary arteries, which is used to identify plaques (fatty deposits that can form in the artery wall), to quantify the extent of any stenosis (narrowing) of the coronary arteries and the length and location of the affected area, and to quantify the extent of coronary artery calcification (e.g. using the coronary calcium score [CCS]). Information provided by CTCA is structural rather than functional. However, it is well established that acute coronary events can arise from unstable, but anatomically non-significant atherosclerotic plaques.[5-7] The vascular inflammatory response is a modulator of atherogenesis and can be a factor in plaque rupture, leading to acute coronary events.[8] A recent prognostic modelling study (CRISP-CT), which included 3912 patients (1872 in the derivation cohort and 2040 in the validation cohort) who were undergoing clinically indicated CTCA, assessed mapping of the fat attenuation index (FAI), a marker of vascular inflammation, as a potential predictor of adverse cardiac events.[9] This study found that high perivascular FAI values (optimal cut-off ≥ -70.1 Hounsfield units) improved prediction of cardiac mortality, over and above clinical risk factors and CTCA parameters (such as extent of atherosclerosis and CCS).[9]

The early and accurate identification and characterisation (e.g. plaque burden, atheroma, CCS) of CAD is important to inform treatment decisions and reduce adverse cardiac outcomes. In addition, improvements in the assessment of individual cardiac risk in people being investigated for suspected CAD have the potential to further optimise prevention and treatment strategies.

2 Decision problem

2.1 Population

The population of interest is people with stable, recent onset chest pain, of suspected cardiac origin, who are undergoing CTCA, in line with NICE guideline CG95.[3] The use of CaRi-Heart® in this population would represent opportunistic additional risk assessment, as an adjunct to current standard of care. The company have indicated that the CE-marked application for CaRi-Heart® is to guide preventative interventions NOT to guide or change

revascularisation decisions. However, the population specified for this assessment includes all patients undergoing CTCA for the investigation of recent-onset stable chest pain, irrespective of CTCA findings without CaRi-Heart®; this is because it is not clear whether a risk assessment based on CaRi-Heart® could be used to guide additional interventions in patients requiring revascularisation. Subgroups of interest are patients with no evidence of CAD on CTCA, patients with non-obstructive CAD and patients with obstructive CAD (requiring revascularisation).

2.2 Intervention technologies

CaRi-Heart® is a cloud-based CE-marked medical device (Caristo diagnostics Ltd, Oxford, UK) that analyses images from CTCA scans to provide information about inflammation in the coronary arteries.[10, 11] This analysis utilises the imaging biomarker perivascular FAI.[9] The main outputs of the CaRi-Heart® medical device are:[10]

- FAI for the proximal segments of each major coronary artery (right coronary artery [RCA], left anterior descending artery [LAD] and left circumflex artery [LCX]).
- FAI score (FAI weighted for scan parameters, un-specified anatomical parameters related to fat distribution around the arteries age *'basic demographics [age, sex]'*) for each major coronary artery. The FAI score is accompanied by vessel-specific nomograms to allow localised interpretation of the degree of inflammation.
- CaRi-Heart® Risk (calculated, individual patient risk of a fatal cardiac event in the next eight years). CaRi-Heart® Risk calculation uses a prognostic model, which includes FAI score, information about atherosclerotic plaque burden as indicated by the modified Duke index[12]and clinical risk factors (including diabetes mellitus, smoking, hyperlipidaemia and hypertension).

CaRi-Heart® analysis is undertaken centrally, by the company (Caristo diagnostics Ltd).[13] CTCA scans can be transferred directly to the company from the hospital PACS (picture archiving and communication system) using a gateway appliance installed in the healthcare provider's network and reports can be electronically transferred back to the originating PACS or sent by e-mail.[10] Segmentation of the epicardial adipose tissue and perivascular space is done by a deep learning network and the device includes a quality control step by a trained analyst.[10] The analysis is performed on a standard CTCA images; the minimum requirements, specified by the company, are:[13]

- Patients for CaRi-Heart® should be between 30 and 80 years old
- Images are acquired using a CTCA protocol on a 64-slice scanner or above
- Image scans should include the pulmonary artery bifurcation cranially and fully include the apex of the heart caudally

The company have stated that CaRi-Heart® risk uses similar information to widely used clinical risk scores such as QRISK3 and that no training is, therefore, required to interpret the report because clinicians (who are the intended users of the report) are familiar with using risk calculators.[13]

The company have also stated that the technical failure rate of CaRi-Heart® analysis is low (<3%).[13]

2.3 Potential alternative technologies

No commercially available alternative technologies were identified for this topic. Clinical experts highlighted that FAI can be estimated using other methods but that these methods are not standardised and are used in research only.

2.4 Comparator(s)

The comparator, for this EVA, is the current standard of care, which is CTCA without the addition of CaRi-Heart®, alongside clinical risk assessment and patient-appropriate risk factor management (see section 2.5).

2.5 Care pathway

Diagnostic assessment of people with stable chest pain of suspected cardiac origin

The NICE guideline on assessment and diagnosis of chest pain of recent onset, (CG95, updated 2016)[3] recommends diagnostic testing for people with stable chest pain, for whom initial clinical assessment (history taking and physical examination) cannot rule-out typical or atypical angina.

CG95)[3] recommends offering 64-slice (or above) CTCA, as the first-line diagnostic investigation, if:

- Clinical assessment indicates typical or atypical angina, or
- Clinical assessment indicates non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves

Additional, non-invasive, functional imaging for myocardial ischaemia is recommended if 64-slice (or above) CTCA has shown CAD of uncertain functional significance or is non-diagnostic.[3] Non-invasive functional testing is also recommended for people with a history of CAD, when there is uncertainty about whether chest pain is being caused by myocardial ischemia.[3]

Recommended options for non-invasive functional imaging for myocardial ischemia are:[3]

- myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT) or

- stress echocardiography or
- first-pass contrast-enhanced magnetic resonance (MR) perfusion or
- MR imaging for stress-induced wall motion abnormalities

Guidelines state that the choice of non-invasive functional imaging technique should consider locally available technologies and expertise, the person and their preferences and any contraindications (for example, disabilities, frailty, limited ability to exercise).[3]

CG95 recommends offering invasive coronary angiography (ICA) as a third-line investigation when the results of non-invasive functional imaging are inconclusive. [3]

Significant CAD, on CTCA or ICA, is defined as ≥70% stenosis of at least one major epithelial artery segment or ≥50% stenosis of the left main coronary artery (LMCA).[3]

A diagnosis of stable angina should be made when:[3]

- There is evidence of significant CAD on CTCA or ICA
- Reversible myocardial ischaemia is found during non-invasive functional imaging

Management
Options for the management of CAD include:[4, 14]

- Risk modifying lifestyle advice (e.g. exercise, dietary, smoking cessation and limiting alcohol consumption)
- Risk modifying pharmacological interventions (e.g. aspirin, statins, anti-hypertensives, anti-anginal drugs)
- Revascularisation (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG])

The choice of appropriate intervention(s) is multi-factorial and is likely to include consideration of: the burden of disease (extent, location and length of stenosis, CCS, and atheroma), in patients with CAD detected on CTCA or ICA; history of coronary events; presence of modifiable risk factors; adequacy of symptom control.[14]

Risk modifying interventions may also be offered, for primary prevention, to patients in whom CTCA or ICA show no evidence of CAD, but where significant risk factors are present.[15]

Guidelines for the management of CAD[4, 14] do not currently include any recommendations for the use of formal risk assessment tools and specific risk thresholds, either for risk of cardiac death or risk of major adverse cardiac event (MACE), to guide intervention decisions.

Proposed position of CaRi-Heart® in pathway

The company have indicated that CaRi-Heart® could be used as an adjunctive investigation for all people with stable chest pain/suspected CAD who have been referred for CTCA.[13] The flow chart in Figure 1 provides an illustration of current practice and Figure 2 illustrates the potential position of CaRi-Heart® in the care pathway (including possible changes to management based on CaRi-Heart® Risk), and is based on discussions with clinicians during the NICE scoping workshop (14/09/2022).

Figure 1: Current care pathway for people with stable chest pain/suspected CAD who have been referred for CTCA

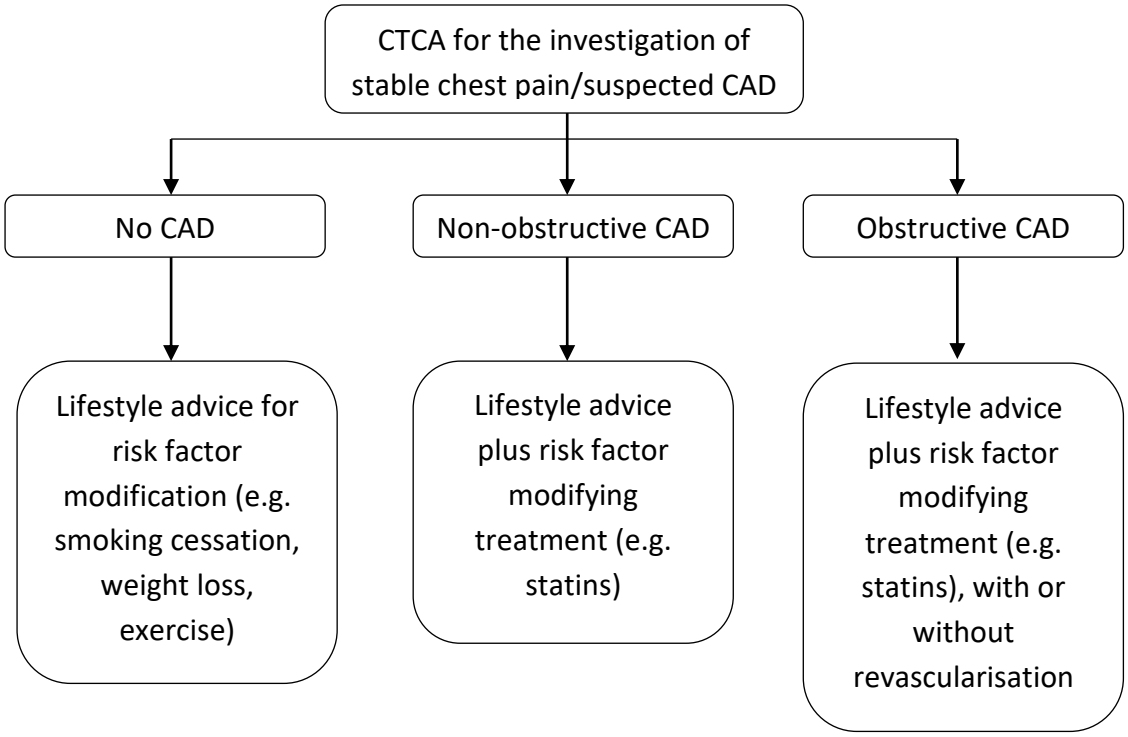
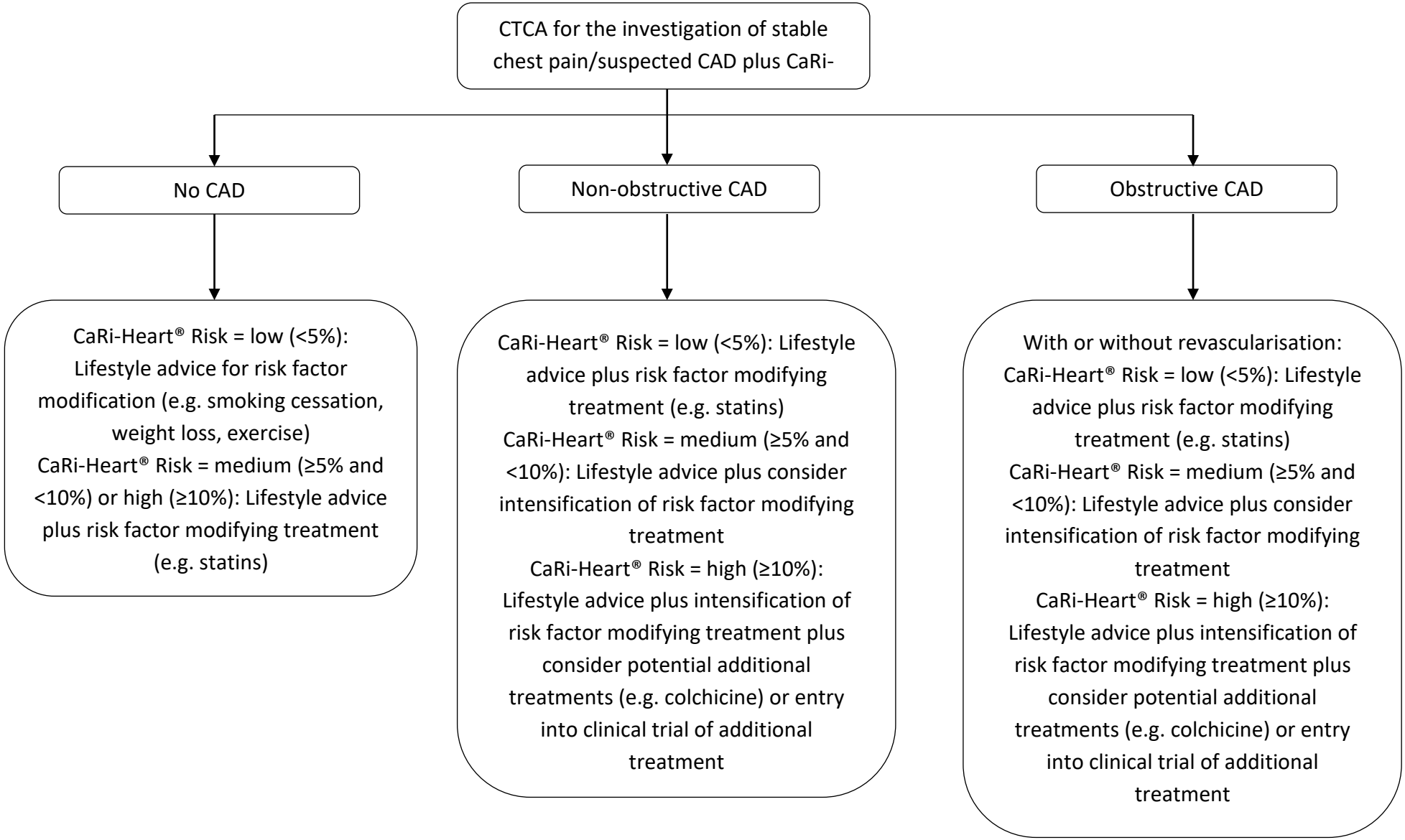


Figure 2: Potential position of CaRi-Heart® in the care pathway for people with stable chest pain/suspected CAD who have been referred for CTCA



3 Objectives

The overall aim of this project is to provide a comprehensive summary of all available evidence that may be relevant to the evaluation of CaRi-Heart®, as an adjunctive investigation for assessment of cardiac risk, in people with stable chest pain/suspected CAD, who are undergoing CTCA. This assessment will not include the development of an executable cost effectiveness model, but will include conceptual modelling to explore the structure and evidence about parameters required for model development.

Current guidelines do not include recommendations about the use of formal risk assessment tools, or intervention(s) based on specific risk thresholds, in this patient group. The potential clinical consequences of the availability of additional risk information from CaRi-Heart® are, therefore, unclear.

Given the anticipated limitations of the evidence base, the NICE scope for this assessment[13] is broad and includes some evidence about secondary outcomes (see Table 1). These outcomes may be used to inform consideration of the potential benefits of implementing CaRi-Heart®, as specified in the scope, and to guide further research to enable full assessment of clinical efficacy and safety.

Based on the NICE scope,[13] we have defined a series of research questions that could inform both a full assessment of the clinical- and cost-effectiveness of using CaRi-Heart®, as an adjunctive investigation for assessment of cardiac risk, in people with stable chest pain/suspected CAD, who are undergoing CTCA and consideration of the potential of this technology to be cost effective:

- What is the prognostic performance of CaRi-Heart®, in people with stable chest pain, who are undergoing CTCA, where:
    a) the dependent variable is cardiac death?
    b) the dependent variable is MACE?

- What is the prevalence of 'low', 'medium' and 'high' CaRi-Heart® Risk in people with no evidence of CAD, people with evidence of non-obstructive CAD and people with evidence of obstructive CAD, based on currently available CTCA imaging?

- What are the clinical effects of using CaRi-Heart® to assess cardiac risk?
    a) How does CaRi-Heart® Risk affect treatment decisions and patient adherence in people with no evidence of CAD, people with evidence of non-obstructive CAD and people with evidence of obstructive CAD, based on currently available CTCA imaging?
    b) What are the clinical effects of any changes to treatment, based on CaRi-Heart® Risk, in people with no evidence of CAD, people with evidence of

non-obstructive CAD and people with evidence of obstructive CAD, based on currently available CTCA imaging?

- What are the costs, from a UK NHS and Personal Social Services perspective, using CaRi-Heart®, as an adjunctive investigation for assessment of cardiac risk, in people with stable chest pain, who are undergoing CTCA?

- How might a conceptual model be specified in terms of structure and evidence required for parameterisation in order to estimate the cost effectiveness of CaRi-Heart® in people with stable chest pain, who are undergoing CTCA?

The above questions have been defined in-line with the NICE scope[13] and have been used to inform the inclusion criteria for the systematic review component of this assessment (see Table 1). Evidence that may be required to inform parameterisation of a future cost effectiveness model will be explored, as part of the conceptual modelling process (see section 5), using a pragmatic, iterative searching approach; model parameterisation questions will not be included in the systematic review.

The available evidence will be summarised, with consideration of its relevance to the above research questions, and a detailed description of evidence gaps where further research is needed will be provided.

4 Methods for assessing clinical effectiveness

Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,[16] the NICE guide to methods of technology appraisal,[17] and the Cochrane Rapid Reviews group's interim methods guidance.[18]

4.1 Inclusion criteria

Separate inclusion criteria were developed for each of the research questions listed in section 3. These are summarised in Table 1.

Table 1: Inclusion criteria

Question	What is the prognostic performance of CaRi-Heart®?	What is the prevalence of 'low', 'medium' and 'high' CaRi-Heart® Risk?	What are the clinical effects of using CaRi-Heart® to assess cardiac risk?	What are the costs, from a UK NHS and Personal Social Services perspective, using CaRi-Heart® for assessment of cardiac risk?
Participants:	People undergoing CTCA for the investigation of stable chest pain/suspected CAD Subgroups of interest: people with no evidence of CAD, people with evidence of non-obstructive CAD and people with evidence of obstructive CAD, based on currently available CTCA imaging			
Setting:	Secondary or tertiary care			
Intervention:	CaRi-Heart®			
Comparators:	Current standard of care, for cardiac risk assessment	NA	Current standard of care, which is CTCA without the addition of CaRi-Heart®, alongside clinical risk assessment and patient-appropriate risk factor management	
Outcomes:	Any reported measure of model performance, e.g. HR or OR for prediction of cardiac death or MACE Secondary outcomes:[a] Test failure rate Time to results	Number (%) of patients undergoing CTCA who are classified as 'low', 'medium' and 'high' CaRi-Heart® Risk and, if reported, number of cases (cardiac events) in each risk category[a]	Cardiac mortality, MACE, HRQoL Secondary outcomes:[a] Change to treatment/management Patient adherence to treatment	Secondary outcomes:[a] Costs of CaRi Heart testing (including test cost, time to interpret results, and staff training/implementation costs) Costs of treatment/ additional testing/other management, including treatment/additional testing/other management of MACE[b]
Study design:	Prediction model development and validation studies	RCTs, CCTs and comparative or non-comparative observational studies	RCTs, CCTs or observational before and after (implementation) studies	RCTs, CCTs, comparative or non-comparative observational studies and cost effectiveness analyses

CAD: coronary artery disease; CCT: controlled clinical trial; CTCA: computed tomography coronary angiography; HR: hazard ratio; HRQoL: health-related quality of life; MACE: major adverse cardiovascular event; OR: odds ratio; RCT: randomised controlled trial

[a]Outcomes which are not sufficient to inform decision making about routine use in UK NHS clinical practice, in the absence of higher-level outcomes data, but which may inform consideration of the potential benefits of the intervention and future research decisions

[b]Outcomes which will be explored, in order to inform conceptual modelling, but which will not form part of the systematic review

4.2 Search strategy

Searches will be undertaken to identify studies evaluating CaRiHeart (as described in Table 1), as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[16]

Candidate search terms will be identified from target references, browsing database thesauri (e.g. Medline MeSH and Embase EMTREE), and existing reviews identified during the initial scoping searches. Strategy development will involve an iterative approach, testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies will be developed specifically for each database and the keywords and thesaurus terms will be adapted according to the configuration of each database.

The following databases will be searched for relevant studies:

- MEDLINE (Ovid)
- MEDLINE In-Process Citations (Ovid)
- MEDLINE Daily Update (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- EMBASE (Ovid)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (Internet) (https://www.crd.york.ac.uk/CRDWeb/)
- Health Technology Assessment Database (HTA) (Internet) (https://www.crd.york.ac.uk/CRDWeb/
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO)
- KSR Evidence (KSR Ltd)
- Epistemonikos (Internet) (https://www.epistemonikos.org/)
- International HTA database (INAHTA) Publication (Internet) (https://www.inahta.org/hta-database/)
- NIHR Health Technology Assessment Programme (Internet) (https://www.nihr.ac.uk/)
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet)
- (http://www.crd.york.ac.uk/prospero/)
- International Platform of Registered Systematic Review and Meta-analysis Protocols (Internet) (Home - INPLASY)
- Latin American and Caribbean Health Sciences Literature (LILACS) (Internet) (http://regional.bvsalud.org/php/index.php?lang=en)
- Directory of Open Access Journals (DOAJ) (https://doaj.org/)

Completed and ongoing trials will be identified by searches of the following resources:

- NIH ClinicalTrials.gov (Internet) (http://www.clinicaltrials.gov/)
- EU Clinical Trials Register (Internet) (https://www.clinicaltrialsregister.eu/ctr-search/search)
- WHO International Clinical Trials Registry Platform (ICTRP) (Internet) (http://www.who.int/ictrp/en/)
- ScanMedicine (Internet) (https://scanmedicine.com/)

An example search strategy is presented in Appendix 1. Strategies may be adapted following consultation with clinical experts.

To identify conference proceedings, searches in Embase will not be restricted to exclude conference abstracts. In addition, a search will be undertaken of the following conference proceedings resource:

- Northern Light Life Sciences Conference Abstracts (Ovid)

Key conference proceedings, not indexed in either Embase or Northern Light and identified in consultation with clinical experts may also be screened for the last five years.

An additional search of the medRxiv PrePrint server will be undertaken. All results retrieved from this resource will be treated with due caution as these are preliminary reports of work that have not been certified by peer review.

- MedRxiv (Internet) (https://www.medrxiv.org)

No restrictions on language, publication status or date will be applied. Searches will include generic and other product names for the intervention.

The main Embase strategy for each search will be independently peer reviewed by a second Information Specialist based on the CADTH Peer Review checklist.[19]

References in retrieved articles will be checked for additional studies to identify any additional relevant papers not retrieved by the searches and clinical experts will be consulted to identify ongoing or un-published studies.

4.3 Review strategy

One reviewer will screen titles and abstracts of all reports identified by the searches, and a minimum of 20% will be independently screened by a second reviewer;[18] discrepancies will

be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details, participant characteristics (e.g. demographic characteristics, clinical history, cardiac risk factors, subgroup [no CAD, non-obstructive CAD or obstructive CAD on CTCA]), details of the implementation of CaRi-Heart® (protocol for use, definition of risk categories, method of reporting output, experience and training of healthcare professionals using the CaRi-Heart® report), measures of prognostic performance (e.g. hazard ratio [HR] for cardiac death or MACE) and test technical performance outcome measures (e.g. failure rate and reasons for failure, time to result), changes to treatment decision, patient adherence to treatment, cardiac outcomes (MACE and cardiac death), HRQoL, costs. Data will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

4.4 Quality assessment strategy

The methodological quality of any included RCTs will be assessed using the Cochrane Risk of Bias Tool.[20] Prediction model studies will be assessed using PROBAST.[21] The methodological quality of other study designs will be assessed using topic-specific criteria or published tools, as appropriate. The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

4.5 Methods of synthesis

We do not anticipate that the number and type of studies included in this assessment will be suitable for meta-analysis; we will, therefore, employ a narrative synthesis. This will involve the use of text and tables to summarise data and will be structured to allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies will be organised by research question addressed. A discussion of the relevance/applicability of study results to the overall aim of this EVA will be provided. A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results.

A detailed description of evidence gaps will be provided, in the context of the requirements for a full diagnostic assessment (including cost effectiveness modelling). Recommendations

for further research will be made based on any gaps in the evidence or methodological flaws.

4.6 Exploration of Intervention Technology-Specific Parameters

Pragmatic exploration of the literature, to inform parameterisation, is part of the process of developing a full, executable cost effectiveness model. This process is used to inform those parameters that fall outside the scope of the clinical effectiveness systematic review; it is designed to identify studies that can be used to support the development of a health economic model and to estimate the model input parameters, but not to perform a systematic review or define evidence gaps.

When developing cost effectiveness models for diagnostic technologies, using a 'linked evidence' approach, the additional parameters required can be broadly classified into two groups:

1. Those which relate to the mapping of the disease state, and which are not specific to the diagnostic technology being assessed (e.g. utilities, effects of current treatments)
2. Those which are specific to the diagnostic technology being assessed (e.g. costs, effects of any new treatments that may be introduced as a result of information provided by the diagnostic technology)

There will usually, though not always, be evidence available to inform group 1 parameters. When assessing a new diagnostic technology, evidence gaps are more likely in respect of type 2 parameters.

Development and parameterisation of a full, executable cost effectiveness model is outside the scope of an EVA, as currently defined. However, in order to provide as much information as possible about those areas where evidence gaps are most likely, a pragmatic exploration of type 2 parameters will be undertaken. For the current EVA, this will include:

- Exploration of evidence about the link between FAI and cardiac events
- Exploration of evidence about the efficacy of treatments (e.g. colchicine) which target coronary artery inflammation (e.g. as indicated by FAI) and which are not currently part of standard care for the treatment or prevention of CAD
- Exploration of evidence about the effects of changing or introducing treatments which are currently part of standard care for the treatment or prevention of CAD (e.g. statins) based on measures of coronary artery inflammation (e.g. FAI)

It should be noted that this part of the EVA will be informed by pragmatic searching and cannot be used to make definitive statements about evidence gaps.

5 Conceptual cost effectiveness modelling

This section describes a process for the development of a conceptual decision analytic model that could be used to inform a future full assessment of the cost-effectiveness of CaRi-Heart® in addition to CTCA in patients with stable, recent onset chest pain, of suspected cardiac origin, who are undergoing CTCA, in line with NICE guideline CG95[3] as described in Section 2.1. The comparator technology is, is the current standard of care, which is CTCA without the addition of CaRi-Heart®, alongside clinical risk assessment and patient-appropriate risk factor management.

The perspective will be that of the UK NHS and a time horizon of lifetime will be used, as CAD is a condition where the relevant outcomes are spread throughout the lifetime. Model assumptions and parameter values should reflect reality as well as possible and must be supported by the literature whenever possible, or otherwise informed by expert opinion.

Consideration of model structure

The model structure is closely linked to the described decision problem and, in particular, the proposed position of the technology in the care pathway (see e.g. Figure 1 and Figure 2). Therefore, any changes to the decision problem that arise from the EVA process (including consideration by the DAC) may have consequences for the draft model structure. In addition, the final proposed model structure may be subject to changes depending on data availability. Given the current information about the care pathway as described in Figure 1 and Figure 2 from Section 2.5, a model structure as described below is anticipated.

A combination of a (short-term) decision tree and a (long-term) cohort/patient-level state-transition model will be used to capture the diagnosis and the progression of CAD, respectively. The choice between a cohort (Markov) and patient-level (microsimulation) state-transition model is to be made depending on the type of data that is available. A schematic representation of the model should be based on the clinical pathway (see Figure 1 and Figure 2, Section 2.5). The model begins with a patient population with stable, recent onset chest pain, of suspected cardiac origin, who are referred for CTCA. The alternatives that will be compared for this cohort are, as a minimum: 1) CTCA only (the comparator) and 2) CTCA + CaRi-Heart®. If other competing alternatives are identified, those could be added to the model, if there is sufficient available evidence. The following is a brief description of a potential model structure and its implications for parameterisation (e.g. baseline risks, treatments effects, etc). This is presented for illustrative purposes only and is likely to change during the EVA process. However, it should be noted that this process cannot provide definitive information about evidence gaps. The process of identifying additional data required for model parameterisation is outside the scope of the systematic review and will be informed by supplementary, pragmatic searching, which would only be performed once construction of an executable model begins as part of a full diagnostic review.

Short-term model (diagnostic decision tree)

The first part of the model will be a short-term decision tree that is used to simulate the diagnostic part of the strategies.

In the comparator strategy (CTCA only) the patient population is diagnosed as either having 1) No CAD, 2) non-obstructive CAD or 3) obstructive CAD.

For the CaRi-Heart® strategy, the patient population is first diagnosed as either 1) No CAD, 2) non-obstructive CAD or 3) obstructive CAD based on the CTCA results. Those diagnostic groups are in turn further split by the CaRi-Heart® information into groups of low, medium or high CaRi-Heart® Risk. There will also be a group where CaRi-Heart® was not able to estimate the risk score; for those patients, only the CTCA results are available, and these results would be used to guide treatment.

The risk group/health state of the patient determines the type of treatment/intervention that is offered to the patient. The consequences of treatment/intervention decisions will be considered in developing the structure of the long-term model.

Long term model (alive, dead, with/out cardiac event)

The aim of the long-term model will be to simulate the effects of the potential treatment strategies that could be implemented, based on risk category. It should be noticed that, in general, the CTCA procedure, with or without CaRi-Heart®, is not expected to be repeated over time. Therefore, it is anticipated that the model will assume that patients do not change CAD status through the simulation.

Based on a cycle length relevant to capture CAD events (e.g., one year, but to be defined based on the literature and/or clinical experts), patients are simulated through the model to observe relevant (CAD) events based on their associated risks. For example, if one year was selected as cycle length, the model could estimate the annual probability of experiencing a cardiac event (including death) based on patients' risk factors.

In the strategy for the current management based on CTCA only, the CAD status (no CAD, non-obstructive CAD, obstructive CAD) will determine the type of long-term treatment that patients will receive.

Development of the conceptual model will require consideration of what additional questions (outside the scope of the systematic review) need to be addressed. The following are examples of questions of this type (this list is for illustrative purposes only and is not intended to be complete and final):

- What proportion of patients are classified as having no CAD, non-obstructive CAD and obstructive CAD, based on CTCA only?

- What is the baseline risk, of MACE and cardiac mortality, for patients in each CAD status (no CAD, non-obstructive CAD, obstructive CAD)?

- What is the effect of lifestyle interventions in (reducing) the risk of experiencing cardiac events?

- What is the effect of combined treatment of lifestyle interventions plus medical treatment in (reducing) the risk of experiencing cardiac events?

- What is the effect of treatments (e.g. colchicine) that target coronary artery inflammation?

- If interventions target (and change) patient characteristics (like blood pressure or body mass index) over time, do these changes need to be simulated and use prediction models in turn to get personalized risks?

- How will the benefit and harms of symptomatic relief, lifestyle changes and statins be incorporated?

In the intervention strategy, CaRi-Heart® in addition to CTCA, the CAD status (no CAD, non-obstructive CAD, obstructive CAD) and the CaRi-Heart® risk (low, medium, high) will determine the type of long-term treatment that patients will receive. Development of the conceptual model, with respect to this strategy, will require a similar process of consideration of additional questions that need to be addressed. The following are examples of additional questions related to the intervention strategy:

- How will interventions (e.g., lifestyle choice or statin treatment) be affected given each risk category (low, medium and high)?

- How might the effect of those lifestyle and statin therapy changes be modified given each risk category (low, medium and high)?

- How should CaRi-Heart® technical failure be modelled?

Irrespective of the treatment strategy, questions such as the following will also need to be addressed:

- What type of cardiac events are relevant for this patient population?

- Are patients with a previous history of cardiac events at a higher risk of experiencing further cardiac events in the future?

- Are there any events (e.g. cardiac events, changes in personal characteristics) that can change the risk category (low, medium, high) of a patient and therefore the offered intervention?

- What might the effect be on uptake/compliance with existing interventions?

- What modelling approach (e.g., cohort or patient-level) is more appropriate to assess the cost effectiveness of CaRi-Heart®?

Health outcomes

Utility values, based on literature or other sources, should be incorporated in the economic model for the various health states to calculate QALYs. QALYs are calculated by multiplying the time patients spend in each health states by the associated utility. If applicable, disutility's are subtracted from the QALY estimation to reflect a temporary reduction of the utility value in case of an intervention or clinical event (like cardiac event). Additionally, consequences may also be expressed in terms of e.g., the number of cardiac events (including death) avoided or correctly treated patients (avoided under treatment in patients with high risk and avoided unnecessary treatment in low-risk groups). The development of our conceptual model will consider what approach should be used for the estimation of QALYs in the context of the current decision problem (e.g. EQ5D data, if available, or use of an algorithm to transform other measures into EQ5D).

Costs

The resources utilised for all aspects of the CaRi-Heart® implementation will need to be considered. Although, the CTCA procedure is part of the current standard of care (CTCA only) and the CaRi-Heart® intervention (and therefore equal in both strategies), the resource utilisation associated with the CTCA procedure, and with any potential adverse events associated to CTCA, need to be included in the model to make a fair comparison between both strategies. Costs associated with long-term care after diagnosis/risk stratification with either CTCA or CTCA + CaRi-Heart® will need to be considered. This may include the interventions (e.g., lifestyle, medicine, medical procedures) as well as costs associated with events (e.g., cardiac arrest, hospitalisation, GP visits, care).

Consideration will be given to which cost data should be obtained from existing studies (if any), routine NHS sources (e.g., NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)), and discussions with individual hospitals and/or with the manufacturers of the technologies included in the model.

6 Handling of information from the companies

All data submitted by the manufacturers, sponsors or other stakeholders will be considered if received by the ERG no later than 07/11/2022. Data arriving after this date will be considered if practicable and at the discretion of the ERG. If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report.

7 Competing interests of authors

None

8 Timetable/milestones

Milestones	Completion data
Draft protocol	22/09/2022
Final protocol	27/09/2022
Progress report	27/10/2022
Draft assessment report	03/11/2022
Final assessment report	30/11/2022

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Appendix 1: Example clinical effectiveness search

The following search strategy is for illustrative purposes only and will be amended in line with input from clinical experts and the agreed final scope.

Embase (Ovid): 1974-2022/09/19
Searched 20.9.22

1 ((CaRi adj3 heart) or CaRi-Heart or CaRiHeart).af. (8)
2 (Caristo or CariCloud).ti,ab,ot. (1)
3 (CRD42020181158 or CRD42021229491 or CRD42021297228 or NCT05169333).af. (2)
4 1 or 2 or 3 (11)
5 (Fat adj2 Attenuation$).ti,ab,ot. (435)
6 (FAI adj3 (Scor$ or Index$ or indic$ or measure$ or map$)).ti,ab,ot. (1359)
7 (FAITM or pFAI).ti,ab,ot. (26)
8 or/5-7 (1755)
9 4 or 8 (1763)
10 animal/ (1586871)
11 animal experiment/ (2867401)
12 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (7339217)
13 or/10-12 (7339217)
14 exp human/ (24097488)
15 human experiment/ (594047)
16 or/14-15 (24099614)
17 13 not (13 and 16) (5541647)
18 9 not 17 (1721)