A cloud-based medical device for predicting cardiac risk in suspected coronary artery disease: a rapid review and conceptual economic model

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Scientific summary

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Background

Coronary artery disease (CAD) and acute myocardial infarction (AMI) are a significant health burden in the UK, with ischaemic heart disease being the leading cause of death in males.

Guidelines from the National Institute for Health and Care Excellence (NICE) and the European Society of Cardiology (ESC) recommend computed tomography coronary angiography (CTCA) 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, to quantify the extent of any stenosis of the coronary arteries and the length and location of the affected area, and to quantify the extent of coronary artery calcification. Information provided by CTCA is structural rather than functional. Acute coronary events can arise from unstable, but anatomically non-significant, atherosclerotic plaques. The vascular inflammatory response is a modulator of atherogenesis and can be a factor in plaque rupture, leading to acute coronary events.

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. The CaRi-Heart device uses this information to generate a perivascular fat attenuation index (FAI) score. It then estimates individual patient risk of 8-year cardiac death with a prognostic model, which includes the perivascular FAI score, as well as atherosclerotic plaque burden and clinical risk factors.

This Early Value Assessment (EVA) considers whether CaRi-Heart Risk has potential to provide an effective, safe and cost-effective adjunctive investigation for assessment of cardiac risk, in people with stable chest pain/suspected CAD, who are undergoing CTCA. This assessment does not include the development of an executable cost-effectiveness model but does include conceptual modelling which explores the structure and evidence about parameters required for model development.

Objectives

A series of research questions were defined 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:

1. 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 a major adverse cardiovascular event (MACE)?
2. 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?
3. 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?

4. What are the costs, from a UK NHS and Personal Social Services (PSS) perspective, using CaRi-Heart, as an adjunctive investigation for assessment of cardiac risk, in people with stable chest pain, who are undergoing CTCA?
5. 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?

Methods

Questions 1–4 were addressed using a rapid review process. Twenty-four databases were searched from inception to October 2022, using a variety of databases including MEDLINE, EMBASE, Cochrane, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Kleijnen Systematic Reviews Ltd (KSR) Evidence and Epistemonikos. One reviewer screened titles and abstracts of all reports identified by the searches, and a minimum of 20% were independently screened by a second reviewer. Full copies of all studies deemed potentially relevant, by either reviewer, were obtained and both reviewers independently assessed these for inclusion; any disagreements were resolved by consensus or discussion with a third reviewer. Data were extracted by one reviewer and checked by a second reviewer; any disagreements were resolved by consensus or discussion with a third reviewer. Study quality was assessed using appropriate risk-of-bias tools. Results were summarised by research question: prognostic performance; prevalence of risk categories; clinical effects; costs of CaRi-Heart.

In addition to the rapid review, evidence that might be required to inform parameterisation of a future cost-effectiveness model was explored, as part of the conceptual modelling process, using a pragmatic, iterative searching approach; model parameterisation questions, other than costs, were not included in the rapid review.

Results

Rapid review

The rapid review identified one relevant model development and validation study, which included a total of 3912 patients who were undergoing clinically indicated CTCA for the evaluation of stable coronary disease. The training/development (USA) cohort comprised 2040 patients, with a median (range) follow-up duration of 53.8 (4–105) months; a total of 85 deaths were reported during follow-up, of which 48 were cardiac. The validation (Germany) cohort comprised 1872 patients, with a median (range) follow-up duration of 72 (51–109) months; there were a total of 114 deaths during follow-up, of which 26 were confirmed cardiac deaths and 16 were deaths of unknown cause. Based on Prediction model Risk Of Bias ASsessment Tool (PROBAST), this study was rated as having high risk of bias and high concerns regarding its applicability to the decision problem specified for this EVA. Importantly, there has been no external validation of the CaRi-Heart Risk model, as the reported validation data set was used in a previous study to develop methods and thresholds for the main imaging predictors (FAI scores). With respect to applicability, the CaRi-Heart study evaluated CaRi-Heart Risk for the prediction of 8-year cardiac death; it did not consider prediction of cardiac risk, as specified in the scope for this EVA (i.e. including risk of non-fatal adverse cardiovascular events). In addition, it is unclear whether the clinical comparator model can be considered representative of standard of care in the UK NHS.

The included study provided information relevant to research question 1: 'What is the prognostic performance of CaRi-Heart, in people with stable chest pain, who are undergoing CTCA where: (1) the dependent variable is cardiac death? (2) the dependent variable is MACE?' The hazard ratio (HR) for 8-year cardiac death, per unit increase in CaRi-Heart Risk, adjusted for 'traditional risk factors' (smoking, hypercholesterolaemia, hypertension, diabetes mellitus, Duke index, presence of high-risk plaque

features and epicardial adipose tissue volume), was 1.05 [95% confidence interval (CI) 1.03 to 1.06] in the training/development cohort and 1.04 (95% CI 1.03 to 1.06) in the validation cohort. With respect to the subgroups of clinical interest, the predictive value of the CaRi-Heart Risk model was consistent across patients with and without obstructive CAD. In addition, the results of the included study indicated that the CaRi-Heart Risk model showed improved risk discrimination, when compared to a baseline clinical risk model, which included age, sex, hypertension, hypercholesterolaemia, diabetes mellitus and smoking (Δ *c*-statistic 0.149, $p < 0.001$, in the validation cohort). This improved discrimination appeared to be retained when the extent of coronary atherosclerosis (indicated by the modified Duke CAD index) was added to the baseline clinical risk model.

The included study also provided information relevant to research question 2: '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?' The prevalence of 'low' (< 5%), 'medium' (5–10%) and 'high' (> 10%) CaRi-Heart Risk scores, estimated from this study, was 3060/3912 (78.2%), 423/3912 (10.8%) and 429/3912 (11.0%), respectively.

No studies were identified which addressed research question 3 ('What are the clinical effects of using CaRi-Heart to assess cardiac risk?) or research question 4 ('What are the costs, from a UK NHS and PSS perspective, using CaRi-Heart®, as an adjunctive investigation for assessment of cardiac risk, in people with stable chest pain, who are undergoing CTCA?').

Exploratory searches to inform model parameterisation

Additional exploratory searches were conducted to inform the conceptual cost-effectiveness modelling, focusing on changes to treatment that might be made based on CaRi-Heart Risk and potential alternative technologies to CaRi-Heart. The results of these searches indicated that there is a deficiency with respect to evidence about the effects of changing existing treatments or introducing new treatments, based on assessment of cardiac risk (by any method), or on measures of vascular inflammation, such as perivascular FAI. However, the evidence is broadly supportive of a positive relationship between FAI and risk of adverse coronary events and hence of the future inclusion of FAI as an alternative technology (in evaluations of the CaRi-Heart device) should a method of measurement become commercially available in the UK NHS. The evidence also supports the efficacy of colchicine for secondary prevention of adverse cardiac events in unselected patients with CAD but does not provide unequivocal evidence about the mechanism by which this effect is mediated. Importantly, for the aims of this EVA, the evidence identified does not provide any indication of the efficacy of targeting colchicine treatment using CaRi-Heart Risk or separate measures of coronary inflammation, such as FAI. It should also be noted that colchicine is not currently recommended by NICE, or licensed in the UK, for this indication. Finally, the evidence suggests some uncertainty about whether and to what extent the efficacy of statins, for the secondary prevention of MACE in people with CAD, may vary with baseline risk assessed using currently available methods. In addition, there is currently no information about the effects of introducing statin treatment or changing the dose of existing statin treatment, based on CaRi-Heart Risk or on any assessment of coronary artery inflammation.

Conceptual modelling

A de novo conceptual decision-analytic model that could be used to inform an early assessment of the cost effectiveness of CaRi-Heart has been described. A combination of a short-term diagnostic model component and a long-term model component that evaluated the downstream consequences is anticipated to capture the diagnosis and the progression of CAD, respectively. It is expected that for the CaRi-Heart strategy, the initial diagnostic groups based on CTCA only would be, in turn, further split by the CaRi-Heart information into groups of low, medium or high CaRi-Heart Risk. If other competing alternatives are identified, those could be added to the model, if there is sufficient available evidence.

Conclusions

The rapid review methods and pragmatic approach to additional exploratory searches used to inform this EVA mean that, although areas of potential uncertainty have been described, our findings cannot be used to definitively state where there are evidence gaps. The evidence about the clinical utility of CaRi-Heart Risk is, as yet, sparse and is subject to considerable limitations, both in terms of risk of bias and applicability to UK clinical practice. There is some evidence to indicate that CaRi-Heart Risk may be predictive of an individual patient's 8-year risk of cardiac death, for patients undergoing CTCA for suspected CAD. However, whether and to what extent CaRi-Heart represents an improvement relative to current standard of care remains unclear.

Currently available data are insufficient to fully inform cost-effectiveness modelling. A large (*n* = 15,000) ongoing study, NCT05169333, the Oxford risk factors and non-invasive imaging (ORFAN) study, with an estimated completion date of February 2030, may address some of the uncertainties identified in this EVA.

Suggested research priorities

- External validation of the CaRi-Heart Risk model should be considered a high priority. The external validation process could also be used to address some of the applicability concerns, for example, the ability of CaRi-Heart Risk to predict non-fatal adverse cardiovascular events (in addition to cardiac death) could be considered.
- It remains unclear whether and to what extent CaRi-Heart represents an improvement relative to current standard of care; this is largely because the definition of standard of care and hence the applicability of the comparator used in the CaRi-Heart study are uncertain. If a consensus could be reached, among clinical experts, as to what should constitute standard of care, then the prognostic performance of CaRi-Heart Risk could be compared to this standard.
- There is currently a lack of information about the costs, from a UK NHS and PSS perspective, using CaRi-Heart, as an adjunctive investigation for assessment of cardiac risk, in people with stable chest pain, who are undergoing CTCA. The company have indicated that the ORFAN study will collect data on costs to the NHS of adding CaRi-Heart to CTCA, including cardiologists' time in training to interpret CaRi-Heart analyses, and the implementation costs per CTCA (if any) added to the price of a CaRi-Heart analysis to estimate the total cost per CTCA of introducing CaRi-Heart into the NHS.
- There is also a lack of information about the clinical effects of any changes to treatment/management that may be made as a result of adding assessment using CaRi-Heart Risk to current standard of care, in patients undergoing CTCA for suspected CAD. The optimum study design would be a randomised controlled trial (RCT) or cluster RCT, where patients or study centres are randomised to receive CTCA with or without the addition of CaRi-Heart Risk assessment, and information about changes to treatment/management and long-term clinical effects is collected. Observational study designs, including 'before and after' implementation studies or using matching techniques to provide a control, could provide an alternative approach.
- Acknowledging that the collection of data about the long-term clinical effects of using CaRi-Heart Risk will take a number of years, alternative, pragmatic approaches to populating this component of a full cost-effectiveness model may be considered useful. Such approaches could include estimation of the potential effects of treatment changes based on risk-stratified effects of treatment (e.g. statins), where risk stratification has been based on methods other than CaRi-Heart Risk and/or estimation of the potential effects of introducing new treatments (e.g. colchicine) where the 'target condition' (coronary inflammation) has been assessed by methods other than CaRi-Heart Risk (e.g. FAI alone).

Study registration

This study is registered as PROSPERO CRD42022366496.

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This article

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