Evidence overview: CaRi-Heart for predicting cardiac risk in suspected coronary artery disease (CAD)

This overview summarises the main issues the diagnostics advisory committee needs to consider. It should be read together with the final scope and the early value assessment report.

1 Aims and scope

Coronary artery disease (CAD) affects the arteries on the surface of the heart which supply blood to the heart muscle. Fatty plaques can build up on the walls of these arteries, leading to narrowing of the arteries. This reduces blood flow and can result in angina. Other complications of CAD include stroke, heart attack, and sudden cardiac death. It is thought the risk of a heart attack in people with CAD is not only linked to the presence of plaque or the degree of narrowing in the arteries. Inflammation in the wall of the artery can cause plaque formation and rupture, potentially causing a blockage leading to acute coronary syndrome or sudden death.

The current NICE guideline CG95 recommends people with recent-onset chest pain undergo computed tomography coronary angiography (CTCA). This is a non-invasive procedure used in the visualisation of coronary arteries. Currently used CTCA scans do not identify inflammation around arteries, only abnormalities such as plaque build-up and narrowing.

CaRi-Heart is class IIa medical imaging analysis software device that uses artificial intelligence (AI) to analyse images from CTCA scans to provide information on the extent of inflammation in the coronary arteries and plaque characteristics. Coronary inflammation is captured and quantified via fat attenuation index (FAI), an imaging biomarker. FAI is adjusted for various factors such as local anatomy, scan settings, age and sex to produce an FAI-score. This is expressed in percentile values for each major coronary artery

(right coronary artery [RCA], left anterior descending artery [LAD], and left circumflex artery [LCX]), allowing for comparison with people of the same age and sex. This is combined with a person's clinical risk factors (such as smoking status, diabetes status, cholesterol etc.) to estimate an individual's 8-year risk of having a fatal cardiovascular event. Results from CaRi-Heart are reported as low (CaRi-Heart risk ≤5% or FAI score ≤75th centile in LAD or RCA <95th centile in LCX), medium (CaRi-Heart risk 5 to 10%, FAI score 75 to 89th centile for LAD or RCA >95th centile in LCX), or high (CaRi-Heart risk >10% or 90th centile for LAD or RCA).

The company claims that CaRi-Heart could help identify an individual's risk of cardiac mortality with greater discrimination than currently used risk factor-based models, improving patient outcomes by personalising prevention and treatment.

Decision questions

- Does CaRi-Heart for predicting cardiac death in people with suspected coronary artery disease have the potential to be clinically and cost effective?

- What evidence is available to support the value proposition outlined in the scope and where are the evidence gaps?

Populations

CaRi-Heart is intended to be used for adults with stable chest pain who have been referred for CTCA.

Potential subgroups for consideration include:

- No CAD
- Non-obstructive (minor) CAD
- Obstructive CAD

Instructions for use state that CaRi-Heart is not intended to be used for people with unstable coronary syndromes, to guide revascularisation decisions, or for monitoring of CAD.

Interventions

CaRi-Heart software is used as an add-on to CTCA scans.

CaRi-Heart is intended to be used to aid clinical decision-making. However, there are no established guidelines on how patients should be managed following a CaRi-Heart result. The company state that it is not intended to de-escalate treatment. That is, if someone with obstructive CAD had a low CaRi-Heart risk score they should still receive appropriate medication such as statins.

Comparator

CTCA alongside clinical assessment of risk factors for CVD.

Healthcare setting

- Secondary care

Further details, including descriptions of the interventions, comparator, care pathway and outcomes, are in the final scope for CaRi-Heart for predicting cardiac risk in suspected coronary artery disease.

2 Clinical effectiveness evidence

The EAG did a systematic review using rapid review methods to identify evidence on the clinical effectiveness and prognostic performance of CaRi-Heart. Find further details on the methods and results of the review on pages 24 to 49 of the early value assessment report.

The clinical review aimed to find evidence on the following questions:

- 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?

The EAG also conducted pragmatic searches (not using systematic methods) to identify evidence relevant to the value proposition of CaRi-Heart. These searches were conducted to explore literature that might usually be explored to support the development of an economic model (which was outside the scope of this Early Value Assessment).

Studies identified on CaRi-Heart are detailed first, followed by a discussion of the pragmatic searches and their findings.

Rapid review of CaRi-Heart studies

Overview of included studies

The EAG identified 2 publications reporting on 1 study (Oikonomou et al. 2021). Oikonomou et al. (2021) reported the development and validation of the CaRi-Heart risk prediction model. The study authors included founders, shareholders, employees, and directors of the company who developed CaRi-Heart.

Oikonomou et al. (2021) included a total of 3,912 people undergoing computed tomography coronary angiography (CTCA) for the evaluation of stable coronary disease. The study comprised 2 independent cohorts, one used for the development or training of the algorithm based in the USA (n= 2,040), and one used for validation based in Germany (n= 1,872). The USA cohort was followed up for a median of 53.8 months. During this time a total of 85 deaths (48 cardiac) were reported. The German cohort was followed up for a median of 72 months and 114 (26 cardiac) deaths were reported during that time. The baseline characteristics of the people included in the study are outlined in table 3 on pages 34 to 35 of the early value assessment report.

Study quality

The EAG used the PROBAST evaluation tool (find full details of the assessment in tables 4 to 7 on pages 34 to 43 of the early value assessment report) to assess the risk of bias and applicability of the 1 included study (Oikonomou, 2021).

The EAG noted the study reports external validation, but that the German validation dataset in the CaRi-Heart study was used in a previous study (Oikonomou, 2018) to develop methods and thresholds for the main imaging predictors (FAI scores). This, therefore, does not match the definition of external validation in PROBAST and the EAG considers this internal validation.

Risk of bias introduced by the selection of participants was assessed as unclear because people with poor image quality CTCA or anatomical anomalies were excluded which may result in over-estimation of the performance of CaRi-Heart. The risk of bias introduced by predictors was also assessed as unclear because it was unclear whether predictor assessments were made without knowledge of outcome data. Additionally, the risk of bias in applicability of predictors was assessed as high because the CaRi-Heart risk model does not appear to have included all imaging parameters that might be reported as part of standard CTCA such as maximum stenosis or presence of high-risk plaque. These parameters were recorded and included in the earlier modelling study which assessed the prognostic value of FAI (Oikonomou, 2018).

The EAG assessed applicability of the outcome as high risk of bias because the choice of the 8-year time point appears to have been data driven rather than being determined by clinical considerations. It also only assesses the ability to predict cardiac death.

Overall, the EAG assessed the study as high risk of bias and high concern for applicability.

Intermediate outcomes

Prognostic performance of CaRi-Heart

Cardiac death

The results of the study indicate that CaRi-Heart is predictive of a person's absolute 8-year risk of a fatal cardiac event when applied in a population undergoing clinically indicated CTCA for the investigation of suspected CAD. The hazard ratios (HRs), for 8-year cardiac death, per unit increase in CaRi-Heart® Risk (adjusted for smoking, hypercholesterolaemia, hypertension, diabetes mellitus, Duke index, presence of high risk plaque features and epicardial adipose tissue volume) were 1.05 (95% 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.When compared to a baseline clinical risk model, which included age, sex, hypertension, hypercholesterolaemia, diabetes mellitus and smoking, the CaRi-Heart® Risk model showed improved risk discrimination (Δ C-statistic 0.085, p=0.01, in the training/development cohort and 0.149, p<0.001, in the validation cohort). The improved risk discrimination with CaRi-Heart risk appeared to be retained when the extent of coronary atherosclerosis (indicated by modified Duke CAD index) was included in the clinical risk model (C-statistic for CaRi-Heart® Risk for the training and validation cohort combined was 0.863 (SE 0.029), the C-statistic for the clinical risk model + modified Duke CAD index was 0.733 (SE 0.057) and the delta (Δ) C-statistic was 0.130 (p<0.001).

The predictive value of CaRi-Heart risk was consistent across people with and without obstructive CAD. People without obstructive CAD were defined as those with maximum stenosis from none to 50%. No subgroup analysis was presented for people with no evidence of CAD.

The predictive value of CaRi-Heart risk also appeared consistent across other characteristics such as age and sex in the validation cohort. HRs were only presented by race/ethnicity for the training/development cohort and appeared

consistent for people of black family origin and white family people but the effect was not statistically significant for people reported as ‘other’ family origin (Asian, multi-ethnic). . Find more details in Table 8 of the early value assessment report.

The study also reported HRs for cardiac mortality per unit increase in FAI score for each of the 3 major coronary arteries (RCA, LAD and LCX). Find more details in Table 9 of the early value assessment report.

Major adverse cardiac events

Oikonomou et al. (2021) did not assess the ability of CaRi-Heart to predict other major adverse cardiac event (MACE) outcomes (including stroke, MI, heart failure, or cardiac hospitalisation).

Prevalence of ‘low’, ‘medium’ and ‘high’ CaRi-Heart Risk

The EAG found no studies reporting the prevalence of ‘low’, ‘medium’ and ‘high’ CaRi-Heart risk for people in the specified subgroups (no evidence of CAD, people with evidence of non-obstructive CAD and people with evidence of obstructive CAD) based on findings on conventional CTCA imaging. However, Oikonomou et al. (2021) reported the numbers of people in CaRi-Heart Risk categories versus risk categories derived from a clinical risk model (which included age, sex, hypertension, hypercholesterolaemia, diabetes mellitus and smoking). The EAG used this data to calculate the prevalence of ‘low’, ‘medium’ and ‘high’ CaRi-Heart Risk scores in the overall study population (see Table 1).

Table 1: Prevalence of CaRi-Heart risk

	USA training/development cohort, n (%) n=2040	**German validation cohort, n (%) n=1872**	**Overall study population, n (%) n=3912**
Low CaRi-Heart risk (<5%)	1415 (69.4%)	1645(87.9%)	3060 (78.2%)
Medium CaRi-Heart risk (5% to 10%)	302 (14.8%)	121 (6.5%)	423 (10.8%)
High CaRi-Heart risk (>10%)	323 (15.8%)	106 (5.7%)	429 (11.0%)

Table 2 summarises the rates of reclassification using CaRi-Heart compared with the clinical risk model. The percentages show the proportion of the total cohort in each risk category. Overall, 11.9% of the patients in the training/development cohort and 3.3% of patients in the validation cohort were reclassified to a lower risk category with CaRi-Heart. Reclassification to a higher risk category occurred in 10.8% of people in the training/development cohort and 8.3% in the validation cohort with CaRi-Heart. The rate of reclassification from 'low' (<5%) to 'high' (>10%) risk was 17/1,354 (1.3%) in the training/development cohort and 36/1,712 (2.1%) in the validation cohort.

Table 2: Reclassification of risk using CaRi-Heart

Cohort analysed	**Clinical risk model**	**CaRi-Heart® Risk model**		
		<5%	**5 to 10%**	**>10%**
Training/Development (USA) cohort, n=2040	**<5%**	1230 (60.3%)	107 (5.2%)	17 (0.8%)
	5 to 10%	167 (8.2%)	138 (6.8%)	96 (4.7%)
	>10%	18 (0.9%)	57 (2.8%)	210 (10.3%)
Validation (Germany) cohort, n=1872	**<5%**	1595 (85.2%)	81 (4.3%)	36 (1.9%)
	5 to 10%	44 (2.4%)	28 (1.5%)	38 (2.0%)
	>10%	6 (0.3%)	12 (0.6%)	32 (1.7%)

Clinical outcomes

The EAG did not identify any studies reporting on whether or how CaRi-Heart might affect treatment decisions or how people take medication. They also did not identify any studies reporting on the clinical effects of using CaRi-Heart.

Health-related quality of life outcomes

No study reported on health-related quality of life outcomes.

On-going studies

ORFAN study

The EAG's rapid review searches identified an ongoing trial (NCT05169333), the oxford risk factors and non-invasive imaging (ORFAN) study. This is a prospective, multi-centre, multi-ethnic observational study in the UK which is expected to complete in 2030. The study includes consecutive patients undergoing CT scans (coronary CT angiograms (CCTA), CT chest, abdomen and pelvis scans) and collects their data on computed tomography (CT) scans, biological material, and outcomes such as disease progression and mortality.

The study combines individuals' imaging data with their demographics and clinical information to inform the development and/or validation of new or existing image analysis algorithms and software tools to improve diagnosis, clinical risk discrimination and prediction. The study intends to recruit 250,000 participants who will be followed up for 15 years prospectively.

NHS AI award

Caristo has also been awarded an NHS AI Stage 3 award. This includes a model-based early economic evaluation alongside implementation of CaRi-Heart in NHS trusts with data from around 800 people. This is expected to complete in early 2023. The following outcomes will be collected:

- Mapping of the referral patient pool for CaRi-Heart analysis
- Patient risk reclassification to model costs of changes to medication and effect size of CaRi-Heart analysis on downstream consequences
- Costs to the NHS of adding CaRi-Heart to CTCA (including cardiologists time for training/interpretation, implementation costs).

Pragmatic searches

Pragmatic searches to find literature that might usually support the development of an economic model were conducted to explore the evidence around the:

- link between fat attenuation index (FAI) and adverse cardiac events,
- efficacy of treatments that are not currently part of standard care for the treatment or prevention of CAD but that target coronary inflammation (such as colchicine),
- effects of changing or introducing treatments that are currently part of standard care for the treatment or prevention of CAD (such as statins).

Colchicine is not currently licensed in the UK or recommended by NICE for the treatment of coronary inflammation but was suggested during scoping as a potential treatment option.

These searches were not specific to CaRi-Heart. The EAG prioritised meta-analyses and systematic reviews in these pragmatic searches and only reported single studies if they were not already included in another review.

Evidence on FAI and cardiac events

The EAG identified 2 systematic reviews on the association between FAI and adverse cardiac events (Kato et al. 2022 and Antonopoulos et al. 2022). They also identified an additional study, Chattergee et al. 2022 which was not included in either systematic review. Antonopoulos et al. (2022) included

studies with a range of different populations and the included population was not limited to people undergoing CTCA for suspected CAD. Kato et al. (2022) included 4 studies in people with suspected CAD and 1 study in people with end-stage renal disease.

Kato et al. (2022) showed a positive association between FAI and the risk of adverse cardiac events. The 'predictive ability' of FAI was quantified by the Hazard Ratio (HR) a:b, where a = the hazard of an adverse cardiac event for people with FAI values above a cut-off value, and b = the hazard of an adverse cardiac event for people with FAI values below that cut-off value. When using the coronary artery with the highest FAI value within each study a HR of 2.23 (95% CI: 1.80 to 2.77) was reported.

Antonopoulos et al. (2022) included 39 studies that evaluated the association between various biomarkers of vascular inflammation including 3 studies (n=5,507) looking at CT angiography-derived biomarkers of vascular inflammation (CT-PVAT) on cardiac events. CT-PVAT is equivalent to the measure of FAI. The results suggested that CT-PVAT had the highest prognostic value and had good accuracy for predicting MACE and all-cause mortality (%Δ c-index 8.2 [95% CI: 4.0 to 12.5]).
The EAG assessed both reviews as being at high risk of bias using the ROBIS tool. Full details of the quality assessment can be found in Table 11 and 12 in the early value assessment report.

Chattergee et al. (2022) included 381 stable patients undergoing invasive coronary angiography. Pericoronary adipose tissue attenuation (PCAT) measurements were made, which are a type of FAI. PCAT values were reported to have poor ability to predict MACE. The authors suggested that the results were less favourable than previous findings because of more severe disease. This could indicate that FAI measures may be most useful in low to intermediate risk patients.

The EAG summarised that overall, the evidence is supportive of a positive relationship between FAI and risk of MACE.

See pages 51 to 53 of the early value assessment report for further details.

Evidence on treatments that are not currently part of standard care

The EAG did not identify any evidence on the effects of introducing potential treatments which target coronary inflammation based on assessment using CaRi-Heart® Risk or measurements of coronary inflammation such as FAI.However, 27 systematic reviews were identified assessing the efficacy of colchicine for preventing MACE in unselected patients with CAD. These studies provide an indication of the general efficacy of colchicine in the population of interest but do not provide any indication of the efficacy of targeting colchicine treatment using CaRi-Heart or FAI. Only 1 of the systematic reviews, Bytyci et al. (2022) reported on the effects of colchicine on inflammatory markers as well as clinical outcomes.

Bytyci et al. (2022) evaluated 12 RCTs comprising 13,073 people with CAD. Results of the evaluation showed that colchicine treatment, compared with control, was associated with reduced risks for recurrent MI (risk ratio (RR) 0.78 [95% CI: 0.65 to 0.93]), stroke (RR 0.47 [95% CI: 0.29 to 0.76]), hospitalisation (RR 0.32 [95% CI: 0.12 to 0.87]), and MACE (RR 0.67 [95% CI: 0.55 to 0.83]). It also showed a significant reduction in some inflammatory markers using the ‘before and after’ change in each treatment arm after a mean follow up of 19 days. However, the results of meta-analyses indicated no effect on all-cause mortality (RR 1.05 [95% CI: 0.71 to 1.53]) or cardiovascular mortality (RR 0.75 [95% CI: 0.40 to 1.43]).

The EAG assessed the quality of the review as being at low risk of bias using the ROBIS tool. Full details of quality assessment can be found in Table 12 and Appendix 4 of the early value assessment report.

The EAG also identified a small (40 adults undergoing CTCA), ongoing randomised, placebo-controlled trial (NCT05347316) which aims to assess the effects of colchicine treatment on FAI (primary outcome), and all-cause mortality, cardiovascular mortality, AMI, stroke and need for revascularisation (secondary outcomes). The study is being conducted in Brazil and is expected to complete in March 2025.

Evidence on changing or introducing treatments that are part of standard care

The EAG did not identify any evidence about the effects of introducing or changing treatments that are currently part of standard care such as statins based on CaRi-Heart risk of on any measure of coronary artery inflammation.

They reported systematic literature reviews that investigated the effects of statins on MACE and death where results were stratified by baseline cardiovascular risk. The studies did not report any coronary inflammation outcomes. Fulcher et al. (2015) and Mihaylova et al. (2011) reported on the benefit of statins for preventing major vascular events. The results suggest that people at all levels of baseline cardiovascular risk (according to CTCA) may benefit from statins. See pages 57 to 59 of the early value assessment report for further details.

The EAG assessed the quality of the reviews on the efficacy of statins as being at high risk of bias using the ROBIS tool. Full details of the quality assessment can be found in Table 13 and Appendix 4 of the early value assessment report.

3 Conceptual model

Rapid review of cost studies

The EAG did a rapid review to identify any published economic evaluations or studies reporting on the costs of CaRi-Heart. No studies were found in the search. But the EAG identified a model that was in development by the University of Oxford, and the work is expected to be completed by March 2023. For further details see Appendix 3 of the early value assessment report.

Conceptual economic model

Model structure

The EAG described a de novo conceptual model which combines a short-term model (e.g., decision tree) to capture the diagnostic part of the care pathway and a long-term model to evaluate the downstream consequences (e.g., decision tree or cohort state-transition model). The model compares CTCA alone with CTCA plus CaRi-Heart.

In the short-term model, people in the comparator arm would be diagnosed as having either 1) no CAD, 2) non-obstructive CAD or 3) obstructive CAD based on the CTCA results. People in the intervention arm would be further grouped into low, medium, or high CaRi-Heart risk. Treatments such as statins or colchicine would be guided by these results and any other risk assessment done in standard practice.

Following this, people would enter the long-term model which aims to capture the impact of potential treatment strategies and simulate relevant CAD-related events based on their risk over their lifetime.

The EAG noted that the main differences between the EVA conceptual model and the ongoing Oxford model are:

- the Oxford model stratifies patients based on CaRi-Heart Risk but not by CAD status

- the Oxford model consists of a decision tree only with time horizon of 8 years.

Model inputs

Risk stratification

No studies reporting the prevalence of 'low', 'medium' and 'high' CaRi-Heart risk scores for people in the specified subgroups (no CAD, non-obstructive CAD, obstructive CAD) according to CTCA were identified. Therefore the conceptual model could not be informed with the currently available evidence.

The Oikonomou 2021 study reported information about the number of people in the CaRi-Heart risk categories versus clinical risk categories. The EAG noted that these data can be used to calculate the prevalence of 'low', 'medium' and 'high' CaRi-Heart risk scores in the overall study population in the Oxford model. The comparator arm in the Oxford model is either real-world practice or patient stratification based on their phenotyping, CTCA, and other risk scores such as QRISK3 or ESC risk.

Treatment change

In the comparator arm the distribution of treatments given would need to be in line with clinical practice for each CTCA subgroup (no CAD, non-obstructive CAD and obstructive CAD). These data are being collected as part of the NHS Artificial Intelligence (AI) award study and will be used to populate the Oxford model.

The same approach could be used to populate treatment distribution for the CaRi-Heart arm. These data are also being collected as part of the NHS AI award study and will be used to populate the Oxford model.

The current evidence available for long term modelling of treatment effects suggests there is uncertainty about whether and to what extent the efficacy of statins may vary with baseline risk according to CTCA. No information about

the effects of introducing or changing the dose of statin treatment based on any measure of inflammation was identified.

Resource use and costs

The EAG did not identify any studies that reported information about the costs associated with using CaRi-Heart for predicting cardiac risk. However, these data have been collected for the Oxford model via the ORFAN study (group 4 cohort) where individual level hospital records are available up to 8 years after initial cardiac assessment. Costs of CaRi-Heart will include cardiologists' time for training and interpretation, implementation costs, and the cost of the CaRi-Heart analysis. The cost of CaRi-Heart is per scan and covers performing the analysis and returning the report to the requesting clinician. These costs were not available to the EAG but the company provided a list price for CaRi-Heart analysis per scan of £495.

Utility values

The EAG considered that utility values would be derived from literature sources to be incorporated in the economic model for the various health states to calculate quality-adjusted life years (QALYs). The EAG's pragmatic literature searches were conducted to identify utility values associated with MACE, and an overview of the utilities for MACE that were identified is presented in Appendix 7 of the early value assessment report.

4 Issues for consideration

Prognostic performance of CaRi-Heart

The EAG's rapid review found 1 study on using CaRi-Heart in people who were undergoing CTCA which reported improved risk discrimination versus a clinical risk model (Oikonomou et al. 2021). Model performance was consistent across people with and without obstructive CAD but no data was presented for people with no evidence of CAD. The EAG considered the study to have high risk of bias and noted a lack of external validation. The comparator in the study was a clinical risk model which is not consistent with

the comparator in the scope (CTCA alongside clinical assessment of risk factors for CVD). Therefore, the extent to which such increases represent improvements to the current standard of care in the UK is uncertain.

No data on CaRi-Heart's performance to predict other MACE outcomes was identified. It should be noted that the decision question and aim of the device for this assessment relates to predicting cardiac death. However, other MACE outcomes were noted to be of interest to the assessment during scoping because treatments for CAD could also impact on other MACE outcomes. The EAG did pragmatic searches and found evidence to support the positive relationship between FAI and the risk of MACE.

Is further data or external validation needed on prognostic performance of the CaRi-Heart device for cardiac death?

If yes, are there any considerations for the generation of this evidence such as subgroups of interest, for example, to address inequality issues (people of African and South Asian heritage have higher rates of CAD).

Risk reclassification

No studies were identified that provided information on how people might be reclassified from current risk categories using CTCA alongside clinical assessment of risk factors into different risk categories based on CaRi-Heart.

Data reported in the Oikonomou (2021) study comparing CaRi-Heart with a clinical risk model showed the majority of people classified as low risk using the clinical risk model were still classified as low risk with CaRi-Heart, but that reclassification to a higher risk category occurred in around 8% of the European cohort. Around 2% of people in the European cohort were reclassified from low risk to high risk with CaRi-Heart.

Is further data needed on how risk stratification might change with implementation of CaRi-Heart in UK clinical practice?

What/how should the comparator be defined?

No evidence on clinical outcomes

No evidence was identified which looked at the impact of CaRi-Heart on clinical decision making or clinical outcomes.

No evidence was identified via the EAGs pragmatic searches which looked at targeting treatments used in standard care, such as statins, using any measure of coronary inflammation. Studies were identified that suggested that statins may be beneficial for people in all risk groups but there is uncertainty about how the treatment effect may vary with baseline risk (according to CTCA). These studies were also assessed as having high risk of bias.

No evidence was identified evaluating the effects of introducing new treatments, such as colchicine, based on any assessment of coronary inflammation. But studies suggested treatments such as colchicine may be effective at reducing the risk of cardiac events. However, they indicated there was no effect on all-cause mortality. One systematic review was identified that suggests that treatment with colchicine may reduce some inflammatory markers (Bytyci 2022). The EAG also identified a small ongoing study (n=40) which aims to assess the effects of colchicine treatment on FAI, all-cause mortality, cardiac mortality, acute myocardial infarction, stroke and need for revascularisation.

The EAG notes that a linked evidence approach could be an alternative option to a clinical outcome study but that this would require studies targeting treatments using a measure of FAI or inflammation. Data on how the introduction of CaRi-Heart impacts clinical decision making would also be required. No such studies were identified in the EAGs pragmatic review. They also noted that evidence showing differential treatment effects of statins for risk groups identified by CTCA (such as no CAD, non-obstructive CAD and obstructive CAD) may be beneficial. Otherwise, if a ‘flat’ treatment effect was assumed then it may be difficult to demonstrate any benefit of CaRi-Heart because treating more people regardless of their risk would appear to be more effective.

Is a clinical outcome study needed in which treatments are targeted using CaRi-Heart?

Would a more pragmatic approach be possible/sufficient using a linked evidence approach or surrogate outcomes?

Are there any considerations for the generation of this evidence such as risk subgroups (no CAD, non-obstructive CAD, obstructive CAD)?

Costs

The EAG's searches found no cost studies reporting costs or cost-effectiveness estimates of CaRi-Heart. But there is an economic model being developed by the University of Oxford. The EAG described a conceptual model in the assessment, in which people are stratified by their CAD status and the CaRi-Heart risk and are observed over a lifetime time horizon. This model is expected to differ slightly from the Oxford model (at the time of writing this report) which uses the CaRi-Heart risk score only and has an 8-year time horizon.

The only cost available to the EAG is the list price of the CaRi-Heart analysis (£495) which is priced per scan. Information provided to the EAG about the Oxford model suggests additional costs of CaRi-Heart would relate to implementation, and costs of cardiologists' time to be trained and to interpret each CaRi-Heart report. There would also be costs related to downstream consequences such as costs of treatments (which are likely to increase if CaRi-Heart is only used to 'escalate' treatment) and costs related to MACE events (which may decrease if CaRi-Heart is successful in identifying those at higher risk and encouraging access to earlier treatment). However, there is uncertainty about how many people would be reclassified using CaRi-Heart and therefore have their treatment changed.

Should any cost and resource use outcomes be prioritised for data collection?

5 Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Angina and coronary artery disease can sometimes have a substantial and long-term adverse effect on a person's ability to carry out normal day-to-day activities. Therefore, people with these conditions may be covered under the disability provision of the Equality Act (2010).

The risk of CAD is more common in people who are older, live in deprived areas, and men, however women are often underdiagnosed. People of African and South Asian heritage have higher rates of CAD than people who are white and East Asian. Sex, race, and age are protected characteristics. An objective measure of cardiac risk could help address this and promote equality.

6 Implementation

CaRi-Heart analyses CTCA results and access to CTCA is needed. Service provision for CTCA is variable across the UK and there may be limited availability of CT in some areas.

There were also concerns about the capacity of existing IT systems to transfer images to a remote site, and whether this could be subject to a risk to data protection and information governance.

It was also noted that the skill/experience of the person reading the report may affect how it is interpreted and how risk is defined.

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Glossary

C-index/C-statistic

The probability a randomly selected person who experienced an event had a higher risk score than a person who had not experienced the event. A value of 0.5 means the model is no better at predicting an outcome than random choice. Values over 0.8 indicate a strong model and a value of 1 means the model perfectly predicts those who will experience a certain outcome and those who will not.

Hazard ratio

The probability of an event in a treatment group relative to the probability of an event in the control group over a unit of time.