NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

Early value assessment: CaRi-Heart for predicting cardiac risk in suspected coronary artery disease

Final scope

September 2022

1 Introduction

The topic selection oversight panel identified the CaRi-Heart for predicting cardiac risk in suspected coronary heart disease as potentially suitable for early value assessment by the Diagnostics Assessment Programme.

The purpose of this early value assessment evaluation would be to map the evidence that is available on the technology; assess the potential clinical and cost-effectiveness of CaRi-Heart software for predicting cardiac risk in suspected coronary artery disease (CAD); and identify evidence gaps to help direct data collection and further research.

The final scope was informed by discussions at the scoping workshop and assessment subgroup meeting held on 14 September 2022. A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technology

This section describes the properties of the diagnostic technology based on information provided to NICE by manufacturers and experts and information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

The current NICE guideline (CG95) for people with recent-onset chest pain of suspected cardiac origin recommends that people with stable chest pain undergo computed tomography coronary angiography (CTCA). CTCA is a non-invasive procedure used in the visualisation of coronary arteries. During the test, a dye may sometimes be injected through an intravenous line in the

hand or arm, and computed tomography (CT), a combination of X-rays and computer technology, is used to produce images of inside the body. The test can be used to identify plaque (fatty deposits that can form in the artery wall) and blockages or stenosis (narrowing) of the coronary arteries.

However, the risk of a heart attack is not only linked to the presence of plaque or 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. Currently used CTCA scans do not identify inflammation around arteries, only abnormalities such as plaque build-up and narrowing.

CaRi-Heart is a software device that can be used in addition to CTCA to quantify the extent of inflammation in the coronary arteries and provide additional information (such as risk of future cardiac mortality) to the patient. CaRi-Heart is non-invasive. It is claimed that it could help identify an individual's risk of cardiac mortality with greater discrimination than currently used risk factor-based models (such as QRISK3), improving patient outcomes by personalising prevention and treatment.

2.2 Product properties

2.2.1 Technology description and indications for use

The CaRi-Heart (Caristo diagnostics Ltd) is a class IIa medical imaging analysis software device that uses artificial intelligence (AI) technology to analyse images from CTCA scans to provide information on the extent of inflammation in the coronary arteries and plaque characteristics. CaRi-Heart then combines this information with a person's clinical risk factors (such as age, sex, smoking status, diabetes status, cholesterol) to estimate an individual's future risk of a fatal cardiovascular event.

CaRi-Heart CTCA analysis takes place by trained operators who are employed by the company. CTCA scans can be transferred directly to the company from the hospital PACS (picture archiving and communication system) via secure, cloud-based transfer for analysis. The analysis is performed on a standard CTCA image using technology that analyses fat tissue (known as perivascular fat) surrounding the coronary arteries. The company states that results from CaRi-Heart are presented in a report (see section 2.2.3 for details) sent to the originating PACS by secure data transfer (cloud-based). The turnaround time for a CaRi-Heart report is within 48 hours.

Information provided by CaRi-Heart is intended to be used by healthcare professionals alongside other clinical information (conventional CTCA interpretation, clinical history, symptoms, clinical risk factors, results of other diagnostic tests and clinical judgement) to make more informed patient management decisions.

The company states that the main output of a CaRi-Heart report is risk and that it uses similar information to widely used clinical risk scores such as QRISK3. Therefore, minimal training (30-minute training sessions at hospitals) may be required to interpret the report because clinicians (who are the intended users of the report) are familiar with using risk calculators. The company state that the technical failure rate of CaRi-Heart analysis is low (<3%).

The company has indicated that the CaRi-Heart analysis does not add benefit in people who have undergone coronary artery bypass grafting surgery (CABG) or people with congenital heart disease.

2.2.2 Imaging pre-requisite

The company has provided the following imaging pre-requisites:

- 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.

2.2.3 CaRi-Heart report

The company has indicated that the CaRi-Heart report provides the following information:

2.2.3.1 Fat attenuation index (FAI)

Fat Attenuation Index (FAI) (an imaging biomarker of coronary inflammation) is an unadjusted, visual representation of the extent of coronary inflammation in the 3 main epicardial (inner layer of the membrane enclosing the heart) coronary arteries (right coronary artery [RCA], left anterior descending artery [LAD], and left circumflex artery [LCX]). Inflammation is detected by analysing changes in CT attenuation (which shows differences in density of the tissue

reflected by darker or brighter areas on the image) from the tissue surrounding the coronary arteries.

2.2.3.2 Fat attenuation index (FAI) score

In order to interpret FAI it must be adjusted for various factors (such as local anatomy and scan settings). CaRi-Heart provides an FAI score which is an individualised assessment of the coronary inflammation in each major coronary artery. It is adjusted for age and sex and accompanied by vessel-specific nomograms for each coronary artery giving an individual's relative risk of a fatal cardiovascular event.

The FAI-Score is expressed in percentile values to allow for comparison with people of the same age and sex.

Figure 1: Example FAI score around the 3 main epicardial arteries

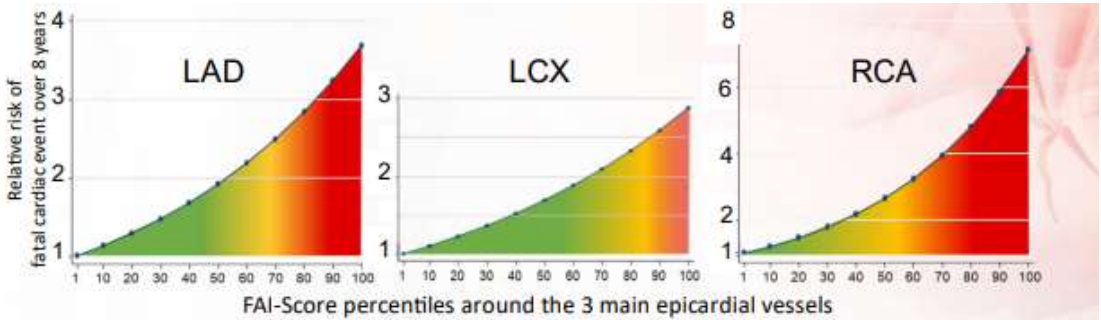


Figure 1 shows an example of FAI scores around the 3 main epicardial arteries. The interpretation of FAI score can be aided by the above risk curves, where centile values are shown on the x-axis and relative risk for a fatal cardiovascular event over 8 years on the y-axis. For example, if FAI score for LAD was on the 90th percentile then this correlates to a relative risk of around 3 meaning the patient has a 3-fold risk of a fatal cardiac event in their LAD artery compared with someone of the same age and sex in the general population.

2.2.3.3 CaRi-Heart risk

The CaRi-Heart risk is said to integrate detailed information on coronary inflammation (provided by FAI score), plaque characteristics and clinical risk factors (such as smoking status, hypercholesterolemia, diabetes status) into a single number to estimate an individual's 8-year risk of having a fatal cardiovascular event. Figure 2 illustrates the company's guide to interpretation of the CaRi-Heart risk.

Figure 2: Interpretation of the CaRi-Heart risk

2.3 Potential alternative technologies

No commercially available alternative technologies were identified for this topic.

3 Target conditions

3.1 Cardiovascular disease

Cardiovascular disease (CVD) affects 7 million people in the UK and is the leading cause of morbidity and mortality (NHS, England). People from the most deprived populations are nearly 4 times more likely to die prematurely from CVD, compared with those from the most affluent populations (NHS, England). Coronary artery disease (CAD) is one of the most common forms of CVD.

3.1.1 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 chest pain (angina). Overtime, the plaques in the coronary artery wall may become inflamed and can rupture, leading to blood clots which could potentially cause a heart attack or even sudden cardiac death. This coronary artery inflammation is not visible on the current tests used to diagnose CAD.

It is estimated that 2.3 million people are living with CAD in the UK (around 1.5 million men and 830,000 women) with around 64,000 deaths per year (BHF, UK).

Causes of CAD include lifestyle factors (such as excessive alcohol consumption or smoking) and family history of disease. The risk of developing

CAD is higher in those who have high cholesterol, high blood pressure (hypertension) or diabetes.

CAD may be suspected after symptoms such as stable angina (chest pain that is brought on by physical activity or emotional stress and goes away with rest), body pain, nausea and feeling faint are reported. Other symptoms of CAD may include heart palpitations and unusual breathlessness. Some people may not have any symptoms before they are diagnosed. CAD can lead to cardiovascular complications such as unstable angina (chest pain that is more unpredictable and can continue despite rest), myocardial infarction, heart failure and sudden cardiac death.

3.2 Diagnostic and care pathway

3.2.1 Diagnostic pathway for recent-onset stable chest pain

The NICE guideline on assessment and diagnosis of chest pain of recent onset, (CG95, updated 2016) recommends diagnostic testing for people with recent-onset stable chest pain if clinical assessment indicates typical or atypical angina (Figure 3). It recommends offering 64-slice (or above) CT coronary angiography (CTCA) as the first-line diagnostic test 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

Clinical experts indicated that the 'coronary artery disease reporting and data system' (CAD-RADS) can be used following CTCA. CAD-RADs is a standardized reporting system for CTCA results to score the severity of CAD from 0 (documented absence of CAD) to 5 (total coronary occlusion). CAD-RADs is used to improve communication between clinicians, interpretation of results for CTCA, and guide management of patients.

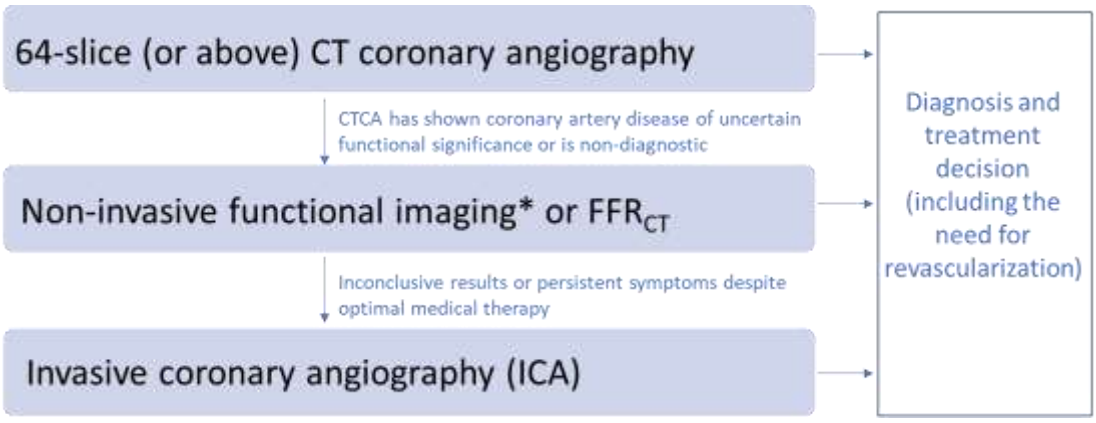
Experts further noted the use of coronary artery calcium scoring (a measurement of the amount of calcium in the walls of the arteries that supply the heart muscle which gives an indication of how much plaque may be present) in clinical practice but indicated that it is not routinely used across the NHS.

NICE guideline CG95 recommends that for people in whom CTCA has shown CAD of uncertain functional significance, or is non-diagnostic, non-invasive functional imaging for myocardial ischaemia should be offered. This includes:

- myocardial perfusion scintigraphy with single-photon emission CT (MPS with SPECT) or
- stress echocardiography or
- first-pass contrast-enhanced magnetic resonance (MR) perfusion or
- MR imaging for stress-induced wall motion abnormalities, or
- NICE's medical technologies guidance 32 recommends that HeartFlow FFR_{CT} should be considered as an option for patients with stable, recent onset chest pain who are offered 64-slice (or above) CTCA. This software provides a non-invasive method of estimating fractional flow reserve (FFR) using standard CTCA image data. FFR is the ratio between the maximum blood flow in a narrowed artery and the maximum blood flow in a normal artery.

Invasive coronary angiography (ICA) should be offered as a third-line investigation when the results of CTCA and non-invasive functional imaging are inconclusive. ICA should also be offered to guide treatment strategy for people with a confirmed diagnosis of stable angina whose symptoms are not satisfactorily controlled with optimal medical treatment. ICA is an invasive anatomical imaging technique used to visualise coronary arteries. It shows whether the arteries are blocked or narrowed (stenosis), and the degree of stenosis. ICA can also be used as a second-line investigation (following non-invasive functional imaging) for people who are not suitable for CTCA, or in centres where 64-slice (or above) CTCA is not available, and for people with a confirmed diagnosis of stable angina who have persistent symptoms despite optimal medical therapy.

Figure 3: Diagnostic pathway for recent-onset stable chest pain



*Non-invasive functional imaging includes:

- myocardial perfusion scintigraphy with single photon emission computed tomography (MPS with SPECT),
- stress echocardiography,
- first-pass contrast-enhanced magnetic resonance (MR) perfusion,

- MR imaging for stress-induced wall motion abnormalities.

A diagnosis of stable angina should be made when:

- significant coronary artery disease is found during ICA or CTCA. This is usually defined as 70% or more diameter stenosis of at least one major epicardial artery segment or 50% or more diameter stenosis in the left main coronary artery.
- reversible myocardial ischaemia is found during non-invasive functional imaging.

3.2.2 Management

The aim of CAD management is to stop or minimise symptoms, and to improve quality of life and long-term morbidity and mortality. Management options, as described in the NICE guideline on management of stable angina (CG126) and the 2019 European Society of Cardiology guidelines for the diagnosis and management of chronic coronary syndromes (Knuuti et al. 2019). include:

- Lifestyle advice (to encourage lifestyle changes such as exercising more, eating healthier, stopping smoking, and diet and weight control)
- Drug treatment (such as beta blocker or a calcium channel blocker) as first-line treatment for stable angina plus drugs for secondary prevention of CVD (aspirin, angiotensin-converting enzyme (ACE) inhibitors, statins)
- Revascularisation using percutaneous (stent placement during percutaneous coronary intervention) or surgical techniques (such as coronary artery bypass surgery)

The choice of appropriate management option depends on correctly detecting and characterising coronary obstructions (stenoses). Clinical experts noted that appropriate assessment and management of CVD risk factors should be undertaken for all patients regardless of their CTCA scan result. Clinical risk assessment tools such as QRISK3 (recommended in NICE clinical guideline CG181) may be used to assess patient risk.

3.3 Proposed position of the technology in the diagnostic pathway

The company's proposed position of CaRi-Heart within the diagnostic pathway for people with suspected CAD and management options before/after CaRi-Heart is presented in Figure 4. The diagram was provided

by the company but has been amended to incorporate comments from clinical experts on the current care pathway. The company has indicated that this could be used to assess all people with stable chest pain/new onset chest pain who have been referred for CTCA. However, the instructions for use indicate that CaRi-Heart should not be requested for patients with unstable coronary syndromes or in patients where urgent or timely workup and evaluation is critical. Additionally, NICE guideline CG95 only recommends CTCA for people with stable new onset chest pain (rather than acute new onset chest pain). Therefore, people with acute new onset chest pain have been considered to be outside the scope of this assessment.

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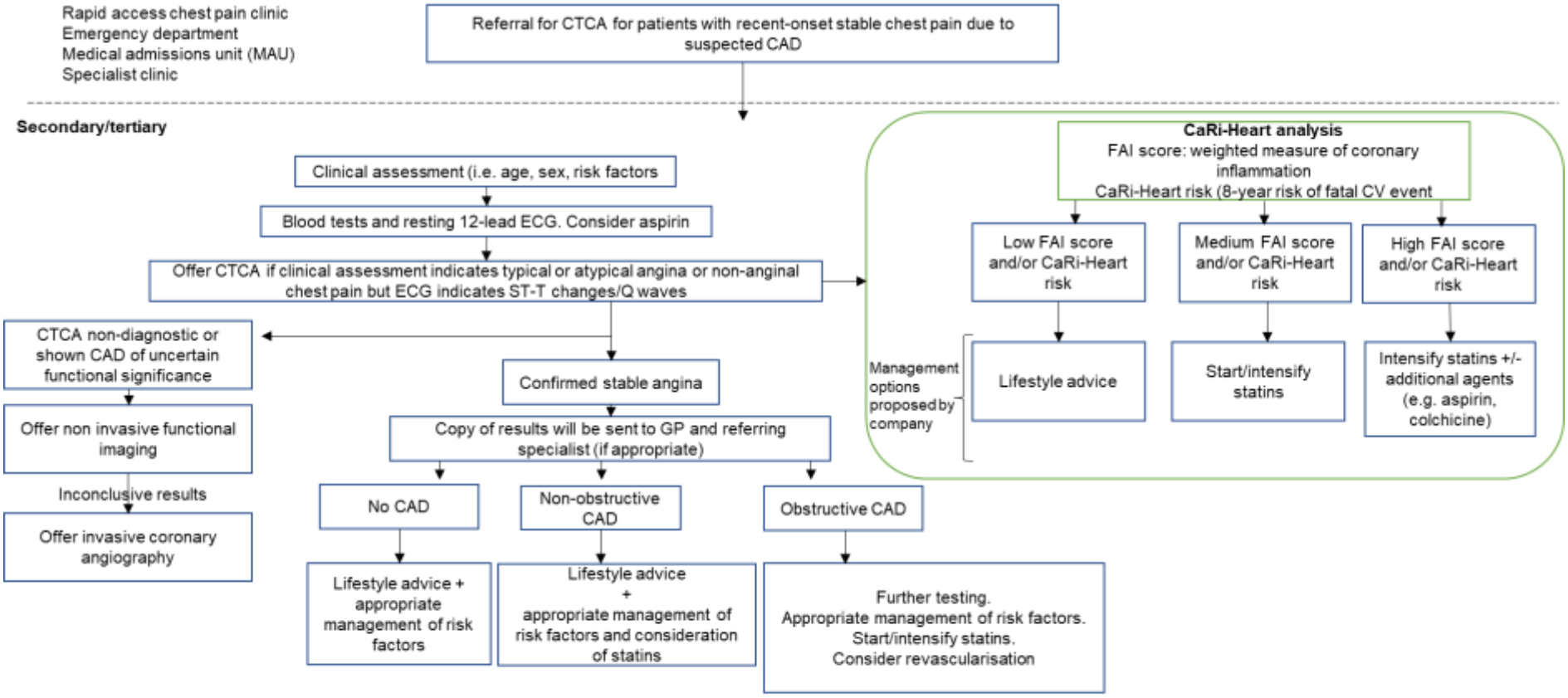
Figure 4: The company's proposed position of CaRi-Heart technology within the current CG95 guidelines



- **FAI:** Fat attenuation index
- **Cardiovascular risk factors**: a history of smoking, diabetes, hypertension, dyslipidaemia, family history of CVD

Figure 3 shows people with stable chest pain/new onset chest pain due to suspected CAD being referred from the rapid access chest pain clinic, emergency department, medical admissions unit, or specialist unit for CTCA. The company propose using CaRi-Heart in people with:

- No CAD
- Non-obstructive CAD
- Obstructive CAD

The company noted that CaRi-Heart is not intended to indicate 'de-escalation' of treatment. That is, if someone with obstructive CAD had a low CaRi-Heart risk score they should still receive appropriate medication such as statins. CaRi-Heart is also not intended to guide revascularisation decisions. Clinical experts indicated that management of people in the obstructive CAD group is unlikely to change based on CaRi-Heart risk and noted use in this group may be less beneficial. They commented that additional anti-inflammatory drugs such as Colchicine could be considered for people with a high CaRi-Heart risk but that these are not currently recommended by NICE or licensed in the UK in this indication.

Experts also noted that there is variation in clinical practice on how these groups of people are currently managed (particularly in the no CAD and non-obstructive CAD).

3.4 Patient issues and preferences

The CaRi-heart risk is calculated based on analysis of images from CTCA scans, therefore its use does not require people to undergo any additional testing. It provides personalised prognostic information on future cardiovascular risk so that the most appropriate treatment can be provided.

Management of patients after a CaRi-Heart result is unclear. If an individual's coronary arteries are normal, that could be reassuring to the person. If the results show an elevated risk, it may cause anxiety associated with knowing future risk of an adverse cardiovascular event. Some people may be motivated to initiate treatment and comply with lifestyle changes.

Clinical experts noted that careful consideration should be given to how risk results estimated by CaRi-Heart should be communicated to people because interpretation of risk can vary widely and depend on many factors.

4 Comparator

The current standard of care is a non-invasive CTCA alongside clinical assessment of risk factors for CVD (such as hypertension, diabetes, dyslipidaemia, smoking, family history of CVD).

5 Scope of the assessment

Table 1 Scope of the assessment

Decision question	• 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	Adults with stable chest pain who undergo a CTCA Potential subgroups for consideration: • No CAD • Non-obstructive (minor) CAD • Obstructive CAD
Intervention	CaRi-Heart software used as an add-on to CTCA scans.
Other alternative interventions	None identified.
Comparator	Standard care: • CTCA alongside clinical assessment of risk factors for CVD
Healthcare setting	Secondary care
Outcomes	Intermediate measures for consideration may include: • Prognostic accuracy • Proportion of patients requiring lifestyle changes/drug treatment • Changes to clinical management • Test failure rate • Time to test results • Patient adherence to lifestyle changes/drug treatment
	Clinical outcomes for consideration may include: • Rate of major adverse cardiac events • Cardiac and all-cause mortality

	Patient-reported outcomes for consideration may include: • Health-related quality of life • Anxiety associated with knowing future risk of an adverse cardiovascular event
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Costs of CaRi Heart testing (including implementation cost, test cost, time to interpret results and staff training costs) • Costs of lifestyle changes • Costs of drug treatment (optimal medical therapy) • Costs of revascularisation (percutaneous and surgical) • Costs of managing major adverse cardiac events • Costs of repeat imaging tests

6 Other issues for consideration

6.1 Possible alternative technologies

Clinical experts highlighted that fat attenuation index (FAI) can be estimated using other methods but that these methods are not standardised and are used in research only. The link between FAI and cardiac events is not yet well established and therefore could be explored during the assessment.

6.2 Absence of a recognised reference standard test

CaRi-Heart is said to be a prognostic test that predicts an 8-year risk of a fatal cardiac event based on an assessment of inflammation (fat attenuation index [FAI]) surrounding the coronary arteries combined with other medical information on an individual (see Section 2.2). Other risk prediction tools that incorporate medical information on an individual for predicting risk of having a heart attack or stroke (such as QRISK3) are available and are used in the NHS. However, none of these tools incorporate information on FAI and there is currently no recognised reference or gold standard test for measuring FAI that is in use in the NHS. Therefore, to assess the predictive accuracy of the

tool it is likely that data on future clinical outcomes (such as cardiac mortality) will be required.

6.3 Patient management following CaRi-Heart results

The company states that CaRi-Heart would be used to help inform and guide clinical decision making, in the same way that other risk-based tools already used in the NHS do (such as QRISK3). However, it is claimed that CaRi-Heart will be able to estimate risk more accurately and additional information provided by FAI score may change risk estimates for individuals compared with using CTCA alone or already established risk-based tools. The company has outlined how CaRi-Heart risk scores and FAI scores should be interpreted and has made suggestions as to how these may inform clinical decision making (see Figures 2 and 4). However, there are no established guidelines available on how patients should be managed based on CaRi-Heart results.

6.4 Ongoing studies

Evidence searches identified one ongoing trial, NCT05169333, the oxford risk factors and non-invasive imaging (ORFAN) study. This is a UK prospective, multi-centre, multi-ethnic cohort observational study collecting CT scans, biological material, and outcomes data. The study will combine imaging data with patient demographics and clinical information to aid 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 will recruit 15,500 participants who have been asked to undergo a CTCA by their clinical team or who have had a CTCA in the previous 6 months. The study will also retrospectively collect a dataset of 250,000 cardiac, abdomen, and pelvis CT scans. Prospectively recruited participants will be followed-up for 15 years and the study is anticipated to finish in February 2030.

The company have indicated that there is also an ongoing economic evaluation study currently being undertaken by the Department of Epidemiology and Public Health at the University of Oxford to evaluate the cost-effectiveness and impact of CaRi-Heart on healthcare pathways and outcomes (part of the company's NHS AI stage 3 award)The study will compare data from the implementation sites with data from a large registry study linking CaRi-Heart with the risk of fatal and non-fatal cardiac events, in patients who have had a clinically indicated CTCA. Data from 800 patients will be collected and the analysis is anticipated to finish by March 2023.

7 Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination, and fostering good relations between people with 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-today activities. Therefore, people with these conditions may be covered under the disability provision of the Equality Act (2010).

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.

8 Potential implementation issues

According to clinical experts and the company, adopting CaRi-Heart requires minimal training and can be used on nearly all CTCA images including those of lower quality. It was stated that the CaRi-Heart report is easy to read, and the test is less invasive than other methods used to assess cardiac risk such as invasive coronary angiography and stress echocardiogram.

Barriers to adoption identified included the cost of the technology and a lack of certainty on who would pay for it. It was reported that accessing CTCA, which is required to use CaRi-Heart, can be challenging due to limited availability of CT scanners. There were concerns around possible variability in results caused by differences in the skills and knowledge of those interpreting the scans, security concerns (when sending images to a remote site), capacity of existing IT systems and questions around whether the company could meet its commitment to report results within 24 to 48 hours if it were widely adopted.

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Appendix A Glossary of terms

Acute chest pain
Chest pain/discomfort which has occurred recently and may still be present, is of suspected cardiac origin and which may be due to acute myocardial infarction or unstable angina

Atherosclerosis
A build-up of plaque on the inside of blood vessels

Angiography
Angiography (also referred to as arteriography) is a medical imaging technique used to visualize the lumen of blood vessels and organs of the body, with particular interest in the arteries, veins, and the heart chambers. See also computed tomography coronary angiography and invasive coronary angiography

Computed tomography coronary angiography
A non-invasive test that uses X-rays to give detailed pictures of the heart and the blood vessels, including information about the degree of stenosis (obstruction) in the coronary arteries

Coronary artery disease
A disease (also referred to as coronary heart disease or ischemic heart disease) that involves a reduction of blood flow to the heart muscle, usually because of the build-up of plaque in the arteries of the heart. It is the most common of the cardiovascular diseases

Coronary artery stenosis (obstruction, narrowing)
A narrowing of the coronary artery leading to a reduction in blood flow, often because of the build-up of the plaque (fatty deposits) in the wall of the arteries

Biomarker
An objective measure of an indicator of a normal biologic process, a pathogenic process, or pharmacologic response to a therapeutic intervention.

Functional imaging
Functional imaging (or physiological imaging), is a medical imaging technique of detecting or measuring changes in physiological activities within a certain tissue or organ, for example, changes in blood flow

Electrocardiogram (ECG)
An ECG records the rhythm and electrical activity of the heart. A number of electrodes (small sticky patches) are placed on limbs and chest and are connected to a machine that records the electrical signals of each heartbeat.

Invasive coronary angiography
An invasive diagnostic test which provides anatomical information about the degree of stenosis (obstruction or narrowing) in a coronary artery. It involves manipulation of cardiac catheters from an artery in the arm or top of the leg. A contrast medium is injected into the coronary arteries, and the flow of contrast in the artery is monitored by taking a rapid series of X-rays. It is considered the ‘gold standard’ for providing anatomical information about coronary artery stenosis

Myocardial revascularisation
Restores a blood flow to the heart following a myocardial ischemia. It is usually done by percutaneous coronary intervention or coronary artery bypass grafting

Percutaneous coronary intervention (coronary angioplasty)
A non-surgical procedure used to treat stenosis (obstruction, narrowing) of the coronary arteries of the heart. It uses balloon catheter and a stent (a short wire-mesh tube) to dilate the artery and keep it open. The stent can be coated with a drug intended to reduce the risk of future blockages (drug-eluting stent) and an uncoated stent (bare-metal stent)

Stable angina
A type of chest pain that results from reduced blood flow. It is usually triggered by physical activity or emotional stress, and resolves with rest

Appendix B Abbreviations

CAD	Coronary artery disease
CTCA	Computed tomography coronary angiography
CHD	Coronary heart disease
ECG	Electrocardiogram
FFR	Fractional flow reserve
ICA	Invasive coronary angiography
MPS	Myocardial perfusion scintigraphy
SPECT	Single photon emission computed tomography
PACS	Picture archiving and communication systems