NICE National Institute for Health and Care Excellence

NICE guidance

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

HealthTech guidance
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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces HTE4.

1 Recommendations

1.1 CaRi-Heart is not recommended for use in the NHS while further evidence is generated. It should only be used in research to predict cardiac risk in people with suspected coronary artery disease (CAD), while treatment strategies to reduce coronary inflammation and cardiac death are identified.

1.2 Further research is recommended (see the section on further research) on:

- how clinical outcomes might change for people with suspected CAD who have had CaRi-Heart testing and appropriate treatment
- how CaRi-Heart results affect clinical decision making compared with UK standard clinical practice
- the costs to the NHS of using CaRi-Heart
- how well CaRi-Heart predicts cardiac risk to validate it in a UK population; in particular, data should be generated in the following groups: women, people from different ethnic backgrounds, and people who do not have CAD identified on CT coronary angiography (CTCA).

Why the committee made these recommendations

CaRi-Heart assesses the extent of inflammation around the arteries, which a CTCA scan (part of the standard risk assessment) does not. So, it could better identify people (with or without CAD) who have coronary inflammation, and who may need further treatment to lower their cardiac risk. But it is unclear what treatments would be offered based on a CaRi-Heart result because they are not clearly defined. There is also no data on how clinical outcomes might change after a CaRi-Heart result. Without a clear treatment strategy, it is uncertain whether CaRi-Heart might improve outcomes for people with suspected coronary artery disease. So, its value is unclear.

Clinical evidence shows that CaRi-Heart improves cardiac risk prediction compared with using a model based on traditional clinical risk factors. But it is uncertain how CaRi-Heart would perform compared with UK standard clinical practice.

CaRi-Heart's cost to the NHS is unknown because the company has not yet specified the NHS price, and no data was identified on the costs or resource use associated with implementing CaRi-Heart. Based on the list price and the number of people who could be offered it, the costs to the NHS could be substantial if it were implemented while evidence is generated to demonstrate its value.

Because of the uncertainty around its benefits and costs, CaRi-Heart cannot be recommended for routine use in the NHS. But it might more accurately identify people at risk of heart attack or cardiac death than the standard risk assessment alone. So further research is recommended to see if CaRi-Heart testing can lead to effective treatment strategies to improve outcomes for people with cardiac risk.

2 The technology

The intervention

2.1 CaRi-Heart (Caristo Diagnostics) is a medical imaging analysis software that uses artificial intelligence (AI) to analyse images from CT coronary angiography (CTCA).

The comparator

2.2 The comparator was CTCA plus clinical assessment of risk factors for cardiovascular disease (CVD), such as hypertension, diabetes, dyslipidaemia, smoking, and a family history of CVD.

Clinical need

2.3 Coronary artery disease (CAD) affects the arteries that supply blood to the heart muscle. Fatty plaques can build up on the walls of these arteries, narrowing them. This reduces blood flow and can result in angina and heart attack. Heart attack risk is also linked to inflammation in the wall of the artery. This can cause plaque to form and rupture, which can block an artery, leading to acute coronary syndrome or sudden death.

2.4 In current standard practice people with recent-onset chest pain are referred to have a CTCA, which is non-invasive and visualises coronary arteries to identify abnormalities such as plaque build-up and narrowing. But CTCA scans do not identify inflammation in coronary arteries.

2.5 CaRi-Heart can identify inflammation, and its extent, by analysing images from CTCA scans. It aims to identify risk of cardiac mortality with greater discrimination than the currently used clinical risk-factor based models and improve outcomes by personalising prevention and treatment.

3 Committee discussion

The diagnostics advisory committee considered evidence on CaRi-Heart for predicting cardiac risk in suspected coronary artery disease (CAD) from several sources, including an early value assessment (EVA) report and an overview of the report. Full details are in the project documents for this guidance on the NICE website.

Benefits of the technology

Risk prediction

3.1 The clinical experts explained that, although CT coronary angiogram (CTCA) can identify abnormalities in coronary arteries, such as plaque build-up and narrowing, it does not identify all people who are at risk of a cardiac event. They said that some people who are assessed as not having CAD go on to have a heart attack. Improved risk prediction could help to identify these people so that they can be offered treatment to lower their risk.

Telling people about their cardiac risk

3.2 A patient expert emphasised the importance of clearly communicating a CaRi-Heart result and explained that a 'high risk' result could make someone anxious. But they said that it may still help people to be better informed about their cardiac risk, provided they have clear information on possible treatments and how to lower their risk. The clinical experts added that clinicians have experience of communicating these types of results and that having an objective measure of risk could help with explaining how people can reduce their risk. And it may encourage people to take their medication and make lifestyle changes, which could improve outcomes.

Equity of access to treatment

3.3 The clinical experts said that particular groups, such as women, are often

underdiagnosed and may therefore have less access to treatment to reduce their cardiac risk. They explained that an objective measure of risk could improve equity of access if it accounts for factors such as sex, ethnicity and socioeconomic status, and improves risk prediction. The company noted that CaRi-Heart takes into account sex and that it is collecting data on how well it works in different groups as part of ongoing research.

Clinical effectiveness

Benefits of CaRi-Heart from the evidence

3.4 The external assessment group (EAG) found 1 study that assessed the prognostic performance of CaRi-Heart for predicting cardiac death in people with suspected stable coronary disease (Oikonomou et al. 2021). The study was a model development and validation study, which included 3,912 people having CTCA to assess stable coronary disease. The results of the study showed that it was better at predicting risk than a risk model based on traditional clinical risk factors (smoking, hypercholesterolaemia, hypertension, diabetes, Duke index, presence of high-risk plaque features, and epicardial adipose tissue volume). The EAG also found studies that supported a link between coronary inflammation and the risk of adverse cardiac events. The committee agreed that, based on the results of Oikonomou et al. (2021), CaRi-Heart was likely to improve risk prediction for cardiac death.

Comparator

3.5 The clinical experts said that the comparator used in the CaRi-Heart study did not reflect UK clinical practice, which limits the generalisability of the study. They said that standard UK practice involves assessing the CTCA image alongside clinical risk factors. Scores such as coronary artery calcium score may be used to guide risk assessment. The clinical experts also said that other risk scores such as QRISK3 may be used if someone has been assessed as not having CAD. One clinical expert said that QRISK3 has been validated in a primary care population, but not in people referred for CTCA for chest pain. But they added that people may

be referred back to primary care after a 'no CAD' result. The committee concluded that there was some uncertainty around the extent to which CaRi-Heart might improve risk prediction compared with current UK standard clinical practice. It said that the comparator for future studies should include assessing CTCA images alongside clinical risk factors, and that QRISK3 should be used in the 'no CAD' group.

External validation

3.6 The EAG suggested that the German dataset used in Oikonomou et al. (2021) to externally validate the CaRi-Heart prediction model had been used in a previous study that may have contributed to developing the algorithm used for CaRi-Heart. So, there was some uncertainty about whether its performance can be reproduced and is generalisable to a new and different population. The company explained that the dataset was only ever used in both studies to validate the algorithm. The EAG noted that the studies did not report enough information to be able to assess this. The clinical experts agreed that the reporting in the 2 studies was unclear, and that their results would have been more robust if they had used different datasets. They also questioned if there were likely to be differences between a German and a UK population. One clinical expert who had used CaRi-Heart said that the variables that are input are mostly objective ones. They thought that most would be similar for the 2 populations. But they thought the UK population might be slightly higher risk, and that levels of low socioeconomic status may be different between the 2 countries. The committee concluded that it was uncertain if the dataset used to validate CaRi-Heart was truly external, and that further external validation data would be useful, particularly in a UK setting. The company said that a validation study in the UK is ongoing.

Important groups

3.7 The committee discussed inequity of access to treatments for some groups of people, in particular women. The company said that the Oikonomou study presents some data that suggests the prognostic performance of CaRi-Heart is consistent by groups including age, sex, CAD status (obstructive and non-obstructive) and ethnicity. The

committee concluded that it would be important to collect this data in any ongoing validation of CaRi-Heart to address equality issues identified during the assessment. It also said that data should be collected to demonstrate prognostic performance in people who do not have CAD identified on CTCA (the 'no CAD' group). The company noted that it is collecting data on geographical distribution, demographics and ethnic background as part of ongoing research. The study also includes people who do not have significant CAD.

Impact on risk assessment

3.8 The EAG found no evidence on how CaRi-Heart analysis changes risk assessment or clinical decision making for people with suspected CAD who have a CTCA. The Oikonomou study presented data on how risk groups (low, medium, and high risk) changed when a CaRi-Heart score was used, compared with a clinical risk score. However, the clinical experts said that the clinical risk score used in the study was not used in UK clinical practice. Therefore it was still uncertain how using CaRi-Heart would affect the outcome of a risk assessment compared with CTCA (see section 3.5). The company said that a study was ongoing in the UK and that clinicians in the study were changing their risk assessments after seeing CaRi-Heart reports. It said that other outputs of CaRi-Heart, such as fat attenuation index-score (FAI-score), are being used alongside the risk score to give a better overall picture of cardiac risk. The company noted that FAI-score for each major coronary artery is provided by the device and that this alone provides an age and sex-specific comparison of cardiovascular risk with the general population. The committee concluded that how CaRi-Heart influences risk assessment was currently uncertain but that the ongoing study would likely address this.

Treatment strategies

3.9 The committee discussed the treatments available for people identified with no CAD (low risk), non-obstructive CAD (medium risk) and obstructive CAD (high risk) after a CTCA and how these might change with the introduction of CaRi-Heart. It noted the company's suggestions included starting statins for the low-risk group, increasing the intensity of

statins for the medium-risk group, and introducing other anti-inflammatory medicines such as colchicine for the high-risk group. The clinical experts said that colchicine was not licensed or recommended in the UK for this indication. The company pointed out that the latest European Society of Cardiology guidelines suggest low-dose colchicine can be considered for selected people who have a high-risk. The clinical experts discussed other treatments that may be used more widely in the future, such as PCSK9 inhibitors and inclisiran. But they said that higher quality evidence is needed to show that these treatments could reduce cardiac events and mortality in this population because they were expensive. The clinical experts said that there is good evidence on the effectiveness of starting and intensifying statins, so treatment strategies for people with no CAD or non-obstructive CAD may be clearer. The company said that its ongoing study in the UK, which is part of an NHS artificial intelligence (AI) award, is collecting data on changes in management after a CaRi-Heart result, which may give more insight into how CaRi-Heart affects treatment choices. It noted that initial results indicate that the largest impact is on people who would otherwise be stratified as low risk. The committee concluded that further evidence is needed on how CaRi-Heart changes management, and that this may be partially addressed by the ongoing study.

Clinical outcomes

3.10 No evidence was found on how CaRi-Heart affects patient outcomes such as cardiac mortality and morbidity. The EAG found no studies on targeting treatments using any measure of coronary inflammation. It identified evidence that supported the effect of colchicine on reducing cardiac events and some inflammatory markers, but stressed that this did not provide an indication of the efficacy of targeting this treatment using CaRi-Heart or any other measure of coronary inflammation. The committee noted that there was already a lot of evidence showing the effectiveness of statins in reducing cardiac risk. Therefore, people identified as having no CAD on CTCA may have the most potential to benefit from the introduction of CaRi-Heart if they were then offered statins. However, they also said some people having CTCA for chest pain have comorbidities and so may already be on treatments such as statins even if they have no CAD identified on CTCA. For these people it is not

clear what further treatments could be offered, and how this would affect their cardiac risk. The committee noted that there is evidence that shows statins may have benefit for all, regardless of CAD status. Therefore, if guidance changes in the future to recommend statins more widely then this could affect the extent to which CaRi-Heart can influence treatment options. At the time of publishing this guidance (March 2023), the recommendations on statins in NICE's guideline on risk assessment and reduction of cardiovascular disease are being updated.

The committee discussed how it is likely that a very large study would be needed, with a long follow up, to capture the most important clinical outcome of cardiac death. The clinical experts highlighted that treatments could change during this time, which could mean results were out of date by the time the study reports. The feasibility of a linked evidence approach using the studies identified by the EAG was considered by the committee. It agreed that this approach would be acceptable, but that the studies identified by the EAG were not enough to demonstrate the link between treatments targeted using a measure of coronary inflammation and improved cardiac outcomes. The committee concluded that evidence of a reduction in cardiac events or death from a study assessing treatment for people with high and low coronary inflammation was needed.

Cost and resource use

Price and population

3.11 No evidence was identified on the costs or cost effectiveness of CaRi-Heart. The company explained that it has not yet specified the price of CaRi-Heart to the NHS but that the price in private practice is £495 per scan. This covers the costs of doing the CaRi-Heart analysis and reporting it, and training clinicians to interpret the report. The clinical experts said that the population eligible for CaRi-Heart if it was implemented with data collection is large, so the cost of using it while data is generated could be substantial.

Costs and resource use

3.12 The committee heard that there was no evidence on how CaRi-Heart might affect resource use because of changes in treatments or the potential reduction in cardiac events. The EAG said that the University of Oxford was developing an economic model that may address some uncertainties. But it added that there will still be substantial uncertainty because of the lack of evidence around how CaRi-Heart might change treatments and therefore clinical outcomes (see section 3.10). The clinical experts said that treatments such as statins are low cost but if more expensive treatments were offered this could have a much bigger impact on the costs of implementing CaRi-Heart. They said that it would be important to understand the impact of CaRi-Heart on resource use, including primary care follow-up appointments and cardiologist time for interpreting and communicating the results of the CaRi-Heart analysis. The clinical experts said that the Oxford model contains implementation costs, but that these were currently unknown. The committee considered the differences between a conceptual model developed by the EAG and the University of Oxford model. The clinical experts said that they preferred a lifetime time horizon for the model because the end point was cardiac death. They also preferred people in the model to be stratified by CAD status (no CAD, non-obstructive CAD or obstructive CAD) as well as CaRi-Heart risk as per the EAG conceptual model.

4 Recommendations for further research

4.1 Further research is recommended to address the uncertainty around clinical outcomes for people with suspected coronary artery disease (CAD) undergoing CT coronary angiography (CTCA) for chest pain who have had CaRi-Heart testing. The committee said that a clinical outcome study using CaRi-Heart to determine a treatment strategy with people followed up for long enough to observe a reduction in cardiac events or death would be ideal. But because this may be difficult it agreed that a linked evidence approach would be acceptable (see section 3.10). The studies identified by the external assessment group (EAG) demonstrated the link between treating inflammation more generally in people with cardiovascular disease and reducing cardiac events or death, but were not able to address coronary inflammation. The committee agreed that further studies were needed (see section 3.10). Data on groups defined by CTCA (no CAD, non-obstructive CAD and obstructive CAD) would also be useful.

4.2 Further data on how CaRi-Heart affects clinical decision making and clinical management compared with UK standard clinical practice (CTCA alongside clinical risk assessment) should be collected (see section 3.8 and section 3.9). QRISK3 should be included as a comparator for people who have no CAD identified on CTCA (see section 3.5).

4.3 External validation of CaRi-Heart in a UK setting would be useful (see section 3.6). Research should also include groups by sex, age, ethnicity, socioeconomic status, and CAD status if possible (see section 3.7).

4.4 Data should be collected on the costs associated with using CaRi-Heart, including implementation costs, training costs, and impact on costs and resource use later in the treatment pathway (see section 3.12).

5 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

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