DIAGNOSTICS ASSESSMENT PROGRAMME

CaRi-Heart for predicting cardiac risk in suspected coronary artery disease

Early Value Consultation Document – Comments

THEME: RECOMMENDATIONS

Comment number	Name and organisation	Section number	Comment	NICE response
1	Caristo Diagnostics	1.1	Whilst CaRi-Heart® is not yet approved for widespread adoption in the NHS, it is clinically used in the private sector in the UK, Europe and Australia. Also, it is in use as part of clinical evaluations by selected NHS Trusts; CaRi-Heart® is currently the focus of a real-world evaluation study, funded by an NHS AI award, and is being used in clinical trials evaluating treatments that target inflammation in cardiovascular diseases. We request that the Committee changes the wording of this section accordingly, as follows: "CaRi-Heart is not recommended for use in the NHS pending generation of further evidence in the context of research to predict cardiac risk in people with suspected coronary artery disease (CAD)"	Thank you for your comment which NICE has considered. The wording in recommendation 1.1 has been amended to make it clear that the recommendation applies to the NHS.
2	Caristo Diagnostics	1.2	The Committee raised the question of a clinical trial to test the long-term effect of adopting CaRi-Heart® for stratification and risk prediction in a healthcare system. However, a prospective clinical trial powered to detect differences in major clinical endpoints or mortality would take 5 to 10 years to initiate, recruit, follow up and analyse. It is important to emphasise that diagnostic tests or technologies that provide information on patient stratification or identification in relation to eligibility for well-established routine therapies, do not	Thank you for your comment which NICE has considered. The difficulties of conducting a clinical trial for this technology are discussed in section 3.10 of the early value guidance. The recommendation in 4.1 has been reworded to make it clear that the

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			usually require testing in a clinical endpoint trial. This is principally because the impact of any diagnostic test on long-term clinical outcomes relies on the result of the test being actioned in accordance with established guideline-directed treatments. If the benefit of these guideline-directed treatments is well-established (such as the effect of statin treatment on cardiovascular events), then the clinical impact of the diagnostic test can be readily evaluated.	committee deemed a linked evidence approach to be acceptable if further studies demonstrating the link between treating coronary inflammation and reduction in cardiac events are published/conducted. Not all treatments suggested as part of the CaRi-Heart pathway were part of established UK guidelines (i.e. colchicine). Additionally, where guideline recommended treatments were suggested, the evidence these guidelines are based on did not include data utilising CaRi-Heart so the population and risks in these studies are different. The population identified by CaRi-Heart is different to that identified via standard of care because it provides further information such as coronary inflammation. It is therefore uncertain whether it is reasonable to assume that the same treatments will be similarly effective in two different

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				populations with different drivers of cardiovascular risk.
3	Caristo Diagnostics	4.1	We believe that the wording in relation to studies on targeting inflammation is not clear, or accurate, so we request that the wording is changed accordingly. Previous studies show an effect of treating patients with inflammation (e.g. the JUPITER, CANTOS, LODOCO, and COLCOT trials), but none of these studies addressed coronary inflammation, because until now there has been no method to detect or quantify coronary inflammation. We request that this sentence be changed to the following: “The Committee agreed that a linked evidence approach would be acceptable. The studies identified by the external assessment group (EAG) demonstrated the link between treating inflammation in patients with cardiovascular disease and reducing cardiac events or death but were not able to address coronary inflammation.”	Thank you for this comment which NICE has considered. The wording in section 4.1 has been updated to reflect that studies addressed inflammation but not coronary inflammation. In order to show that a test is clinically effective, it is crucial to be able to show that there is an effective treatment available to manage a condition/reduce risk in a specific population, as defined using that test. In some situations, this can be done by linking evidence, but where evidence to underpin the links is not available an outcome study may be needed. The recommendation in 4.1 has been reworded to make it clearer that a

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			With regard to the comment on future studies, we have addressed this issue in detail in our responses to paragraphs 1.2, 3.1 and 3.2. Apart from feasibility, we have pointed out that a long-term clinical outcomes trial is not ideal because it depends on the effectiveness of long-term treatment recommendations, which may change, and are not pre-specified by the trial of the diagnostic text being evaluated, or if they are, the trial becomes in part a trial of the effectiveness of the treatment, as well as the diagnostic test. We request that this sentence be changed to the following: “A clinical outcome study using CaRi-Heart to determine treatment strategy with people followed up for long enough to observe a reduction in cardiac events or death may be influenced by factors other than the performance of the diagnostic test”.	linked evidence approach would be acceptable if further studies can be identified better demonstrating the link between treating coronary inflammation and reducing cardiac events.

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THEME: COMPARATOR

Comment number	Name and organisation	Section number	Comment	NICE response
4	Caristo Diagnostics	3.5	The comparator is an interesting question, as highlighted by the clinical experts. To address these concerns, the HERC at the University of Oxford (see previous response to paragraph 1.2) is building two health economic models: a) Using as comparator real life UK standard of care that takes into account the images, QRISK3, and any other information the UK clinicians are using like ESC score, calcium score etc. This comes from the real-world evaluation in the NHS via the NHS AI award and it will be available before full NICE submission. b) Using as comparator state of the art implementation of NICE guidelines, with accurate measurements of lipid levels in a core laboratory, assuming no deviation from what is the NICE guidance. This comes from the prospective arm of the ORFAN study, in which patients from a range of NHS Trusts were recruited at the time of their CCTA and blood samples were obtained to perform state of the art risk assessment. This will be available before full NICE submission.	Thank you for your comment which NICE has considered. The committee agreed 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. This is detailed in section 3.5 of the early value guidance. The committee was encouraged by the health economic work being conducted.

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THEME: BENEFITS

Comment number	Name and organisation	Section number	Comment	NICE response
5	Caristo Diagnostics	3.1	We agree with the clinical experts that some people who are not identified as having coronary artery disease on a CT coronary angiogram nevertheless go on to have a heart attack. Indeed, we would emphasise that in the majority of patients who have a heart attack the specific cause of the heart attack is not a plaque within a coronary artery that causes significant stenosis. The simple clinical evidence of this is that most patients presenting as an emergency with a heart attack have not had preceding angina chest pain. In addition, multiple scientific studies have concluded that the plaques causing acute heart attacks are typically those that do not cause significant stenosis of the artery, and may cause no visible stenosis, for example the recent understanding that erosion of the surface of an inflamed artery can cause occlusion of the artery, a mechanism that is more common in women.	Thank you for your comment which NICE has considered. The population being considered for this assessment is “Adults with stable chest pain who undergo a CTCA” as detailed in the final scope. Therefore, people presenting as an emergency with a heart attack who have not had preceding angina chest pain are outside the scope of this assessment.
6	Caristo Diagnostics	3.4	We are grateful to the Committee for emphasising that the predictive value of CaRi-Heart® is independent of, and in addition to, the predictive value of known clinical risk factors (smoking, hypercholesterolaemia, hypertension, diabetes) as well as the presence of other CTCA scan-derived factors such Duke index, high-risk plaque features, and epicardial adipose tissue volume.	Thank you for your comment which NICE has considered. Further detail has been added to section 3.8 of the early value guidance to clarify that FAI-score for each major coronary artery is provided and that this is said to provide an age and sex-specific

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			The major additional predictive value of CaRi-Heart® is driven by the new biomarker of coronary artery inflammation, Fat Attenuation Index (FAI). The CaRi-Heart® analysis provides the FAI-Score for each major coronary artery, and the FAI-Score alone provides an independent predictor of CV Risk, as an age- and sex-specific hazard ratio. The inclusion of other clinical risk factors in the CaRi-Heart® Risk calculator enables calculation of an absolute % cardiovascular risk for that individual patient, but the clinical risk factors are not required for the overall predictive power of FAI Score, expressed as an age- and sex-related hazard ratio.	comparison of cardiovascular risk with the general population. The EAG report includes a full critique of the results presented in Oikonomou 2021.
7	Caristo Diagnostics	3.9	The implications of the draft updated guidance from NICE published very recently (12 January 2023) are very important. The updated guidance recommends that the risk threshold at which statins should be offered to prevent cardiovascular events such as heart disease and strokes remains unchanged (i.e. a 10% or higher risk of an event over 10 years), but they can also now be considered for people who are deemed to be at higher cardiovascular risk but with a threshold that is lower than 10% over 10 years. We strongly support the new guidance as it means that more people can benefit from treatment to reduce their risk.	Thank you for your comment which NICE has considered. It is important to note that the efficacy of statins in relation to risk groups identified by CaRi-Heart or based on another measure of coronary inflammation has not been established. There may be a role for subclassifying lower risk groups to help clinical decision making as described but at this point in

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Comment number	Name and organisation	Section number	Comment	NICE response
			However, to achieve this benefit for more people requires a strategy to identify the people with higher risk but who do not meet the '10% in 10 years' criterion. When these people have been identified, they need clear and objective advice in order to justify treatment, and to maintain compliance in the long term. The updated NICE guidance on the use of statins significantly strengthens the use case for clinical application of CaRi-Heart®. First, the largest group of patients for whom CaRi-Heart® has clinically-actionable results are those who do not meet the '10% in 10 years' criterion. Thus, clinical use of CaRi-Heart® will be an important route to realise the full benefit of the updated NICE guidance, by identifying patients who are deemed to be lower risk based on traditional clinical risk estimates but are in reality are at high risk and will benefit significantly from initiation of statin treatment. Indeed, pilot data from the NHS AI award project indicates that CaRi-Heart® identifies a substantial proportion of patients to be at significantly increased risk for their age and sex, despite having a less than 10% 10-year risk estimated on clinical risk	time this has not yet been established or proven. If guidance changes to recommend consideration of statins for people with a lower cardiovascular risk as described in the draft clinical guideline consultation documents this could also mean CaRi-Heart will change the treatment strategy for fewer people. It has now been noted in the early value guidance that the clinical guideline for risk assessment and reduction of cardiovascular disease is being updated in section 3.10.

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Comment number	Name and organisation	Section number	Comment	NICE response
			scores, with no coronary artery stenoses, no diabetes or elevation of cholesterol. Second, identifying high risk patients by CaRi-Heart® has important implications for the received advice and/or initial treatment to reduce cardiovascular risk. The NICE guidance recommends the lower dose of atorvastatin 20 mg for the primary prevention of CVD for people with a 10-year risk of less than 10% but where there is concern that the person's risk of a cardiovascular event may be underestimated. In this group, clear identification of higher risk would justify treatment with the usual atorvastatin dose of 40 mg daily.	

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Early Value Consultation Document – Comments

THEME: PATIENT CONSIDERATIONS

Comment number	Name and organisation	Section number	Comment	NICE response
8	Caristo Diagnostics	3.2	We agree with the patient expert that informing patients about their cardiovascular risk, and the results of diagnostic tests that help to assess their risk, requires sensitivity and clinical skills to ensure effective communication. Moreover, disclosing new information to a patient that has the potential to significantly change their recommended management may be unexpected, so we agree that the high level of diagnostic re-classification following CaRi-Heart® analysis would need to be communicated as part of an effective clinical relationship with the patient. We would also point out that these important issues are no more or less highlighted by CaRi-Heart® than any other diagnostic test, or clinical advice, that points out clinical risks to a patient. Clinicians routinely point out high risk factors to patients, which is the basis for clear advice about lifestyle factors and/or treatments to reduce this risk. Everyday examples include robust advice on the risks of smoking, high blood pressure, high cholesterol, or diabetes etc., all of which clinical staff discuss with patients on a day-to-day basis, as part of an appropriate clinician-patient relationship.	Thank you for your comments which NICE has considered. Benefits to patients of having more information about their cardiac risk are described in section 3.2 of the early value guidance. Clarification has been added to this section that clinicians have experience of communicating these types of results.

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			Indeed, the decision to undertake a CT coronary angiogram, to evaluate possible coronary artery disease, and the prognostic implications of the findings, should have already been discussed with the patient by the referring clinician. CaRi-Heart® provides more detailed and effective information for the clinician to advise the patient, from a test that was already carried out on the basis of clinical factors suggesting high cardiovascular risk.	

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Early Value Consultation Document – Comments

THEME: ONGOING EVIDENCE GENERATION

Comment number	Name and organisation	Section number	Comment	NICE response
9	Caristo Diagnostics	3.3	We agree that gender is important in risk prediction. Indeed, FAI-Score generated by CaRi-Heart® is derived using gender-specific nomograms. In the ORFAN study, we will present sensitivity analyses for different subgroups represented in the UK population of patients undergoing CTCA.	Thank you for your comment which NICE has considered. Further detail has been added to section 3.3 that CaRi-Heart takes into account sex (clarified via email with the company that the comment is referring to sex rather than gender) and that data is being collected on its performance in different subgroups as part of ongoing research.
10	Caristo Diagnostics	3.6	The ORFAN study will provide validation of the predictive power of CaRi-Heart®. Furthermore, the ORFAN cohort includes information on geographical distribution, demographics and ethnic background, which will allow all of these points to be addressed. We respectfully point out that in the CRISP-CT study, two separate cohorts were used, with approximately 2000 patients each from Erlangen in Germany and from the Cleveland Clinic in the USA, the same data set was not used for discovery and for validation. However, to address the Committee's concerns, we are conducting a new study within the ORFAN cohort, that will evaluate the prognostic value of CaRi-Heart in a UK population.	Thank you for your comment which NICE has considered. Further details of the data being collected has been added to section 3.7 of the early value guidance. The committee concluded that whether the same data set was used for discovery and validation was uncertain because not enough detail was included in the publication by the study authors. This is discussed in section 3.6 of the early value guidance.

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THEME: ONGOING EVIDENCE GENERATION

Comment number	Name and organisation	Section number	Comment	NICE response
				The committee is supportive of the ongoing research. The following is already noted in section 3.6 of the early value guidance – “"The company said that a validation study in the UK is ongoing. " Therefore, no further changes have been made to the early value guidance.
11	Caristo Diagnostics	1.2	We agree that further research is important, and there are intense current efforts in a number of research studies that will address the points raised by the Committee. The predictive value of CaRi-Heart® in a UK population, including a very large number of subjects representing a wide range of geographical distribution, demographics and ethnic background is being studied in the ORFAN study, sponsored by the University of Oxford. This study of patients undergoing CT coronary angiogram in the UK, will yield validating data on the predictive value of CaRi-Heart®. Initial results are anticipated by Q2 2023. Since the majority of patients undergoing CT coronary angiograms do not have significant coronary artery	Thank you for your comment which NICE has considered. Further details have been added to section 3.7 of the early value guidance about the ongoing studies. The ongoing health economic research is noted in section 3.12 of the early value guidance. The committee is supportive of the ongoing evidence generation. The EAG noted that as explored in sections 5 and 8.2 of the EAG report, taking a linked evidence approach currently is problematic, because (as emphasised by the company, see comment 6) the population

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			stenosis, this study will also enable the predictive value of CaRi-Heart® to be validated specifically in this sub-group. The costs, and costs benefit, of using CaRi-Heart® in the NHS, will be revealed in a health economic study currently being undertaken by colleagues in the Health Economic Research Centre (HERC) at the University of Oxford (see also response to paragraph 3.5). These results will be published when available. The anticipated health economic benefits of CaRi-Heart® are expected to relate to the identification of patients who are currently missed by routine risk prediction pathways. Identifying these people will enable them to be treated effectively, for example with statins, for which there is a very well-evidenced health economic benefit resulting from a reduction in future cardiovascular events. The health economic benefits include a reduction in the major healthcare costs related to acute hospital admissions, reduced need for additional long-term treatment and follow up, and maintaining the benefits to the workforce and economy.	identified by CaRi-Heart is different from that identified by other risk scores that do not include information about inflammation/FAI, i.e. the 'target condition' is, in effect, different. It is therefore questionable whether it is reasonable to assume that the same treatments will be similarly effective in two populations with different drivers of vascular risk (broadly, stenotic vs. inflammatory), on the basis that these two populations may have similar overall numerical estimates for risk of cardiac death. As discussed in section 3.10 and recommendation 4.1 the committee agreed that a linked evidence approach would be acceptable but that further studies would be required to demonstrate the link between treating coronary inflammation and reducing cardiac events.

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Comment number	Name and organisation	Section number	Comment	NICE response
			The Committee raised the question of a clinical trial to test the long-term effect of adopting CaRi-Heart® for stratification and risk prediction in a healthcare system. On this point, we agree with the Committee that a trial of CaRi-Heart® to test clinical effectiveness will be very important to guide clinical implementation. We are currently testing how CaRi-Heart® changes the clinical decision-making and recommendations for statin treatment in an NHS setting in 4 NHS Hospital Trusts in England (selected for geographic and demographic diversity). Initial results indicate that the largest impact of CaRi-Heart® is on patients who would otherwise be stratified as low risk and would not be identified as justifying statin treatment. A substantial proportion of patients undergoing routine CCTA scans are identified by CaRi-Heart® analysis as requiring initiation or escalation of statin treatment, that was not identified by the routine CCTA scan reporting. This project, supported by an NHS AI award, is due to complete and report initial findings very soon, by end of Q1 2023.	

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THEME: COMMENTS IN SUPPORT OF GUIDANCE

Comment number	Name and organisation	Section number	Comment	NICE response
12	Caristo Diagnostics	4.2	We agree with the conclusions and have no further comment.	Thank you for your comment
13	Caristo Diagnostics	4.3	We agree with the conclusions and have no further comment.	Thank you for your comment
14	Caristo Diagnostics	4.4	We agree with the conclusions and have no further comment.	Thank you for your comment
15	British Cardiovascular Society	N/A	British Cardiovascular Society understands the proposed recommendation and looks forward to more research in the area which may inform future use of CaRiHeart in the NHS.	Thank you for your comment