NICE National Institute for Health and Care Excellence

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
The Society and College of Radiographers	1	19	2.2	'Computed tomography coronary angiography scans can be transferred directly to the company from the hospital picture archiving and communication system (PACS) using a gateway appliance installed in the healthcare provider's network and reports can be electronically transferred back to the originating PACS or sent by e-mail. 11'. Society of Radiographers' AI and Informatics Advisory Groups have previously expressed concerns with respect to limitations of anonymisation, psudo-anonymisation, or de-identification of individual patient images. What measures are taken to safeguard patient data during the transfer of person identifiable images from 1) the healthcare organisation's PACS, 2) upload to cloud services, and 3) on transfer back to originating PACS or email?	This is an implantation/regulatory issue and is outside the scope of this EVA.
The Society and College of Radiographers	2	20	2.2	'Images are acquired using a CTCA protocol on a 64-slice scanner or above.' Multiple vendors supply CT Scan equipment in the UK. This raises two questions, is the CaRi-Heart software capable of vendor agnostic function? Is the deep learning associated with one specific type of CT Scanner? Accordingly, there are possible limitations on the use / transferability of the deep learning algorithm and ability to implement across a range of settings. Also at this section, there are variable 'CTCA protocols' in operation across sites – more in-depth information is required with respect to the protocols that have been used. Consideration should be given to sites with varying protocols and ability to adapt protocols depending on individual patient circumstances - for example, adaptation to protocols for people needing reasonable adjustments to scan time etc, including people with dementia, learning disability, autism, parkinsons disease etc.	We did not identify any data to inform considerations of the possible effects of variations in CT equipment and/or protocols. The potential importance of obtaining such data may be an issue for discussion by the committee.

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The Society and College of Radiographers	3	20	2.2	'The company have stated that CaRi-Heart® Risk uses similar information to widely used clinical risk scores such as QRISK3 and that, therefore, minimal training (30-minute training session) is required to interpret the report because clinicians (who are the intended users of the report) are familiar with using risk calculators. 1' In the UK context, patients also receive access to clinical reports via NHS App. This may be immediate upon availability and prior to consultation with their clinician. In that case, patients are also in receipt of reports – what provision are the company making for clear explanation of reports, in lay terms, in those circumstances?	This is a question for the company.
The Society and College of Radiographers	4	23	Figure 2	On page 14 it was stated 'It should also be noted that colchicine is not currently recommended by NICE, or licensed in the UK, for this indication.' Figure 2 suggests the potential use of colchicine at the sections for non-obstructive and obstructive CAD. Given that NICE do not recommend, and it is not licensed in the UK, society of radiographers suggest that should be amended or with caveat until such time that it is licensed and recommended.	Section 5.3, page 54 of our report includes the statement: 'It should also be noted that colchicine is not currently recommended by NICE, or licensed in the UK, for this indication.' Figure 2 can be amended, prior to publication, if required.
The Society and College of Radiographers	5	78	7.6	The society of radiographers wish to commend the authors on this section, clearly reporting equality, diversity and inclusion factors. The society of radiographers would also like to raise a question – given the known differences between male and female sex & diagnosis of coronary artery disease, what provision is made by CaRi-Heart to mitigate for and record demographics in cases of people who are transgender, non-binary, and intersex/have variations in sex characteristics?	This is a question for the company.
The Society and College of Radiographers	6			Congratulations to the authors on a clear and thorough report that was a pleasure to read.	We thank the stakeholder for their comments.
Caristo Diagnostics	1	3	Abstract	We would draw attention to the fact that CaRi-Heart® is a CE-Marked medical device that went through a formal assessment of effectiveness and	The PROBAST assessment, reported in section 4.2 of the EAG report and referenced

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				safety as part of the EU Medical Device Regulations (MDR) in 2021. A substantial portfolio of research and technical information was submitted and reviewed by the EU-designated Notified Body as part of the regulatory and approval process. Whilst some of the information considered in the context of the EU Medical Device Regulations incudes the research studies noted in the EVA, information on CaRi-Heart® also included a substantial portfolio of proprietary data and know-how which is not in the public domain, but which has nevertheless been reviewed formally and rigorously. In this regard we would respectfully point out that many of the technical points raised in the EVA will have been addressed. In addition, many of the major scientific publications that are referred to and cited in the EVA include extensive supplementary data and went through rigorous peer-review at journals such as *The Lancet*, as a part of which additional information was provided to reviewers. Specifically, the CRISP-CT study included a formally designed validation process that was described in detail in the paper and supplementary information and reviewed in great detail by *The Lancet* statistical review team. It is therefore incorrect to state that CaRi-Heart® has not been externally validated.	in the abstract, was specifically for the Oikonomou 2021 study, which reports the development and validation of the CaRi-Heart® Risk model. We apologise for any instances where the CaRi-Heart® may have been used instead of the CaRi-Heart® Risk model; these will be corrected ahead of publication. Our PROBAST assessment of the Oikonomou 2021 study is not a comment on the CRISP-CT study, reported in the Lancet (Oikonomou 2018), which did not meet the inclusion criteria for our review because it is a study of perivascular fat attenuation index (FAI), which does not evaluate the CaRi-Heart® Risk model and does not mention the CaRi-Heart® Device. The Oikonomou 2018 study is mentioned/discussed in the EAG report because the CRISP-CT study, which it reports, appears to have developed a multivariable model including FAI in combination with most of the same variables used in the CaRi-Heart® Risk model: It appears that the CaRi-Heart® Risk model, as reported in Oikonomou 2021 paper, included FAI score (FAI adjusted for 'anatomical factors related to fat distribution around the arteries', tube voltage, age, sex), clinical variables (hypertension, hypercholesterolaemia, diabetes mellitus, smoking), and modified Duke CAD index. Oikonomou 2018 assessed the prognostic value of FAI in a multivariable Cox regression analysis FAI adjusted for techical scanner

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					aspects such as tube voltage - based on analysis from both cohorts in 2018 paper), age, sex, hypertension, hypercholesterolaemia, diabetes mellitus, smoking, epicardial obesity (measured as total epicardial adipose tissue volume, modified Duke coronary artery disease index, and number of high-risk plaque features. We do not suggest that the model reported in the Lancet (Oikonomou 2018) paper lacked external validation. It is prior use of the two cohorts, in the Lancet (Oikonomou 2018) paper, which constitutes the problem with the 'external validation' of the CaRi-Heart® Risk model, reported in Oikonomou 2021. This is because the validation dataset, used in Oikonomou 2021, had previously been used, in the Lancet (Oikonomou 2018) paper, to develop a multivariable model using FAI and most of the same variables as implemented in the CaRi-Heart® Risk model (Oikonomou 2021). The multivariable models developed in Oikononmou 2018 and the CaRi-Heart® Risk model (Oikonomou 2021) include most of the same variables. As such, the European data used to develop the model version in Oikononmou 2018, is not appropriate to use as an "external validation" dataset for the multivariable model

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					version with most of the same variables developed in the CaRi-Heart® Risk model (Oikonomou 2021). These two models are likely to only differ based on prior knowledge gained during development of the model in the European data in Oikonomou 2018. This European patient data has then "been used in the development" as part of the CaRi-Heart® Risk model (Oikonomou 2021) development, and so is not a true "external validation" dataset. The prior use of the same European patient data (labelled as external validation data in Oikononmou 2021) to develop (development dataset in Oikonomou 2018) – a multivariable model using FAI and most of the same variables as implemented in the CaRi-Heart® Risk model (Oikonomou 2021) is clear from reported figures, tables and text. For example i. Kaplan Meier curves for the multivariable model are reported in Oikonomou 2018 as the development dataset for the multivariable model in figure 2A and 2B ii. Additional results using the European data as the development multivariable model, reporting model performance are shown in figure 3A and Table 3.

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					iii. In addition the European data was fully explored to establish the distribution of FAI events to the outcome events in this dataset, which means there was prior knowledge and fitting of the CaRi-Heart® Risk model to the European patient data during the development of the 2018 multivariable model using all the same variables as CaRi-Heart® Risk model, based on the development European dataset subsequently reported as the external validation dataset in 2021 paper. iv. For example Oikonomou 2018 reported "Adjusted fractional polynomial modelling showed a J-shaped relation between the perivascular FAI and the prospective risk of all-cause and cardiac mortality in both cohorts (appendix)." Both cohorts includes the European dataset. v. In addition the relationship between tube voltage which is incorporated into the FAI score in CaRi-Heart® Risk model (Oikonomou 2021) was explored based on both cohort datasets in Oikonomou 2018.

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Caristo Diagnostics	2	3	Background	We agree with the non-clinical statistical Reviewer, that none of the risk scores used in clinical practice (QRISK3, ESC-SCORE) are supported by evidence from randomised clinical trials showing that change of treatments based on Risk, changes outcomes. This is why all risk scores have a Class I indication in clinical guidelines (i.e., should be used) but with Level of Evidence C (i.e., no RCTs). This is because Risk is treated in a standard way, and all current and novel therapeutics are reducing risk based on how they work, not based on how the risk was calculated. NICE has suggested during the NHS AI-Award that a reclassification exercise is what is needed, and this is where the company has focused in collecting evidence.	We are not clear to what text this comment refers.
Caristo Diagnostics	3	4	Results	We disagree with this statement. Please refer back to the Lancet 2018 and Cardiovasc Res 2021 papers to understand the improvement over and above the standard of care (in the true, geographically external validation cohort of CRISP-CT).	This comment is unclear; what is the statement with which the company disagrees?
Caristo Diagnostics	4	4	Conclusions	This is factually incorrect. The ORFAN study includes a cohort that will include 250k patients (currently includes 65k patients from the UK who had CTCA and were followed up for up to 15 years in ORFAN ARM 4). The 15,000 patients presumably refers to the arm of that study (ORFAN Arm 2) that evaluates circulating and genetic biomarkers and disease progression- that will mature in 2030. However, for building the evidence for the NHS health economic case, ORFAN Arm 4 is the one to be used (collection of the outcomes data has been completed).	We thank the company for this clarification and will correct our descriptions of the ORFAN study (at all points in our report) ahead of publication).
Caristo Diagnostics	5	11	Background, para 4	The CE Mark confirms the safety and effectiveness of the Medical Device, in accordance with the regulatory evaluation process, which included extensive proprietary information and data in addition to published material.	We acknowledge that the CaRi-Heart® device is CE Marked; this is an entry requirement for assessment by the NICE DAP and is not a substitute for full assessment of clinical and cost effectiveness.
Caristo Diagnostics	6	11	Objective 1	This is the label of the device. It is important that the Committee realises that CaRi-Heart® risk one of a number of different outputs produced by the CaRi-Heart® device.	We acknowledge that CaRi-Heart® Risk is one of a number of outputs of the CaRi-Heart® device. Our report includes data on other outputs (e.g. HR per unit increase in FAI score, Table 9).

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Caristo Diagnostics	7	11	Objective 2	Further data can be provided from CRISP-CT study.	Provision of these data may be useful for future evaluations.
Caristo Diagnostics	8	11	Objective 2	Evidence collected and will become available to the NICE Committee in due course (early 2023).	Provision of these data may be useful for future evaluations.
Caristo Diagnostics	9	12	Objective 3a	Evidence will be collected as part of the NHS AI-Award.	Provision of these data may be useful for future evaluations.
Caristo Diagnostics	10	12	Objective 3b	As with any clinically used risk score with Class I indication for use, the effects of changes based on the patient Risk can only be modelled.	The EAG does not agree with this statement; see research recommendations in section 8.2 of our report.
Caristo Diagnostics	11	12	Objective 4	A health economic study is happening as part of the NHS AI-Award	The results of this study may be useful for future evaluations.
Caristo Diagnostics	12	12	Objective 5	The interchangeable use of the term 'CaRi-Heart®' (the Medical Device that generates all outputs) vs. 'CaRi-Heart® Risk' (a risk score quantifying the absolute 8-year risk of CV death) is incorrect. CaRi-Heart® risk is just one of the outputs of CaRi-Heart®, which also reports other clinically actionable readouts such as inflammation scores (FAI Score) for each coronary artery.	We apologise for any errors in the terms used (throughout our report). We will review the use of the terms CaRi-Heart® and CaRi-Heart® Risk, throughout, and amend (as necessary) ahead of publication.
Caristo Diagnostics	13	12	Methods	Our understanding is that these are statistical non-clinical reviewers, who are unable to evaluate 9 out of the 10 outputs of the device, and the focus is only (incorrectly) on the CaRi-Heart® Risk readout.	The review process was undertaken, as is usual, by members of the EAG with relevant methodological expertise and the outcomes evaluated are those specified in the protocol for the assessment.
Caristo Diagnostics	14	13	Results, para 1	This is factually incorrect, as the literature was not read in the appropriate depth. There is confusion between the development of the Medical Device and the published literature. The published literature describes the scientific research that led to the development of the Device, but not the Device itself, which is a proprietary device that has been subjected to regulatory review and has a CE Mark. This is a summary of the process followed for the development of the Device: 1. The discovery that FAI is a measure of inflammation (Antonopoulos et al Science Transl Med 2017) led to the development of the CaRi-Heart®	Please see response to comment 1

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				algorithm that calculated FAI as a metric of inflammation. The CaRi-Heart® device was first developed to only measure FAI and coronary inflammation. 2. The ability of FAI in each coronary artery to predict future fatal cardiac events was then evaluated in two parallel and independent cohorts (1 European and 1 US cohort with up to 10y follow up) in the CRISP-CT study (Lancet 2018). The prognostic value of FAI in the context of Cox-regression models was evaluated in parallel as a continuous variable in the two cohorts, and the value of adding FAI on top of the baseline models that represent standard of care (age, gender, risk factors, degree of coronary stenosis, high-risk plaque features, measures of adiposity) was demonstrated. For graphical reasons, in order to generate figures for the better visualization of the data (Kaplan-Meyer curves), a cut-off of FAI (-70.1HU) was calculated in the European cohort and then applied in the US cohort to confirm consistency across both cohorts. 3. Following the publication of the CRISP-CT study, and unpublished results from the VIP study and other internal technical validation studies done within Caristo Diagnostics, the CaRi-Heart® device was updated to generate the FAI-Score for each artery projected in nomograms of the CRISP-CT population, and the CaRi-Heart® Risk was generated. Please note that the CaRi-Heart® Risk (8-year risk for fatal cardiac events) was trained in the US cohort of CRISP-CT and then externally tested in the European cohort. The European cohort was a true external validation cohort, as it did not participate in any way in training any parameter that was included in the training dataset. This is the approach recommended by the FDA as well as by the European regulators, who recognised the European cohort as true external validation cohort for the CaRi-Heart® Risk model. 4. When the device was ready and regulatory cleared, we published part of the validation results in Cardiovasc Res 2021.	
Caristo Diagnostics	15	13	Results, para 1	The CaRi-Heart® Risk is the absolute risk for fatal cardiac events. However, the device does not only provide CaRi-Heart® Risk. CaRi-Heart® also provides FAI-Score and FAI, which was demonstrated to predict also non-fatal cardiac events in CRISP-CT while peri coronary attenuation (a	We acknowledge that CaRi-Heart® Risk is one of a number of outputs of the CaRi-Heart® device. Our report includes data on other outputs (e.g. HR per unit increase in FAI score, Table 9).

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				simplified version of FAI) was also shown to predict non-fatal 5-year events in SCOTHEART trial. Please note that there is now a very extensive literature, from several different groups, demonstrating that FAI detects the vulnerable atherosclerotic plaques which lead to adverse cardiac events. Clinicians are taking FAI-Score and FAI into account in deciding where to deploy statins and/or colchicine. [redacted]	We have also included a pragmatic review of the published literature on FAI as a predictor of cardiovascular risk (section 5.2 of the EAG report).
Caristo Diagnostics	16	13	Results, para 3	This is being evaluated in the ongoing ORFAN study.	No response required
Caristo Diagnostics	17	13	Results, para 4	More information on the disposition of patients in to low, medium or high-risk categories will be available from the ongoing ORFAN study and NHS AI Award.	No response required
Caristo Diagnostics	18	13	Results, para 4	Health economic study underway via NHS AI-Award to evaluate the costs, from a UK NHS and PSS perspective, of using CaRi-Heart®.	No response required
	19	14	Para 1	We accept that the evidence identified does not provide any indication of the efficacy of targeting statins or colchicine treatment using CaRi-Heart®. Equally, there is no equivalent RCT evidence for altered clinical outcomes following the use of QRISK3 or any other widely used risk prediction score (e.g. ESC SCORE), hence why the prognostic models have Class IC indication. Accurate risk prediction is designed to trigger optimal and appropriately targeted risk-reduction strategies. Colchicine is already included as an anti-inflammatory treatment to reduce the risk of MACE in high-risk individuals (ESC Clinical Guidelines for prevention, EHJ 2021). ColCot and LoDoCo2 have shown ~30% reduction of events in the high-risk populations. Statins have been the mainstay of risk reductions strategies in	The EAG notes the company's point regarding the lack of evidence for altered clinical outcomes following the use of clinical risk scores, such as QRISK3 and ESC score. However, the EAG respectfully notes that these scores are not being assessed as new interventions, which may be adopted by the UK NHS, with associated costs.

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				all clinical guidelines for over 30 years. The purpose of a risk score is to identify high-risk individuals, with treatments guided by risk.	
Caristo Diagnostics	20	14	Conclusions, para 1	The last sentence is factually incorrect statement. See Cardiovasc Res 2021- external validation of the device and incremental value over standard of care clinical risk-factors based model.	The EAG does not consider that this statement is factually incorrect. Full details of our reasoning are provided in the body of the report (please see sections 7.2 and 7.3 of the EAG report). Word limits preclude the inclusion of more detail in the scientific summary.
Caristo Diagnostics	21	14	Conclusions, para 2	Safety and effectiveness were assessed in the CE Mark regulatory process. More information on the wider application and patient disbursement related to CaRi-Heart® analysis will be forthcoming from ongoing studies including the ORFAN study.	Please see response to comment 5
Caristo Diagnostics	22	30	4.1, para 1	The review missed the main scientific discovery publication that describes the development of FAI (Science Transl Med 2017) and the rest of the literature on FAI (e.g. JAMA Cardiol 2019, etc). The review did not evaluate the CaRi-Heart® Medical Device as a whole, but only one of the readouts of the Device, which is the absolute risk prediction (CaRi-Heart® Risk).	The scope of the assessment (defined by NICE) did not include FAI as an intervention/alternative technology. Please also see response to comment 15.
Caristo Diagnostics	23	30	4.1, para 2	The literature uses FAI, while many other names (like PCAT) correspond to uncorrected measurement of perivascular attenuation and should be considered.	Please see response to comments 15 and 22, above.
Caristo Diagnostics	24	31	Para 1, Q3	This is not applicable in devices that measure risk.	The EAG does not agree with this statement; if a risk assessment does not inform changes that can affect clinical outcomes, it would be difficult to see the justification for making such an assessment.
Caristo Diagnostics	25	31	Para 1, Q4	This is being evaluated in an ongoing study.	No response required
Caristo Diagnostics	26	36	Development and validation	This is factually incorrect. Reference 10 did not use the European cohort for developing a model. It was only used to define cut-off values of the FAI biomarker, for analysis/presentation purposes. The CaRi-Heart® Device	See response to comment 1. The multivariable models developed in Oikononmou 2018 and the CaRi-Heart® Risk

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				does not use any such cut-off but treats FAI as a continuous variable. Therefore, no model was trained in the European cohort.	model (Oikonomou 2021) include most of the same variables. As such, the European data used to develop the model version in Oikononmou 2018, is not appropriate to use as an "external validation" dataset for the almost identical multivariable model version with most of the same variables developed in the CaRi-Heart® Risk model (Oikonomou 2021). These two models are likely to only differ based on prior knowledge gained during development of the model in the European data in Oikonomou 2018. This European patient data has then "been used in the development" as part of the CaRi-Heart® Risk model (Oikonomou 2021) development, and so is not a true "external validation" dataset. The question as to whether FAI score is included in the model as a continuous variable or using cut-off is not relevant. See response to comment 1 for at least 5 reported results in Oikonomou 2018, where data/results were presented for the developement dataset (the same European dataset) that was then used as an external validation dataset for CaRi-Heart® Risk model version (Oikonomou 2021), a multivariable model based on most of the same variables as in the multivariable model in Oikonomou 2018.

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Caristo Diagnostics	27	38	2.2	Predictor assessments were made without knowledge of outcome data.	We thank the company for this additional information, which was not explicit in the published report.
Caristo Diagnostics	28	38	Rationale of Applicability rating	The CaRi-Heart® Device includes proprietary algorithms that generate risk prediction, from analysis of the CTCA data.	No further detail has been provided regarding what CTCA parameters are included in the 'proprietary algorithms'; therefore, the concern identified by the EAG remains.
Caristo Diagnostics	29	38	Rationale of Applicability rating	Epicardial adipose tissue volume (EAT) calculated from the CTCA, is included in the algorithm and captures metabolically unhealthy obesity with greater precision and power than BMI.	We thank the company for this additional information, however, we are not clear whether the inclusion of this variable refers to the model reported in Oikomonou 2018 (Lancet), or the CaRi-Heart® Risk model reported in Oikomonou 2021, or both. The EAG considers that provision of a full list of parameters included in the algorithm/CaRi-Heart® Risk model could be helpful to the committee's discussions.
Caristo Diagnostics	30	38	Rationale of Applicability rating	Family history of premature CAD is frequently not available in clinical practice, and/or is expressed in variable or non-objective ways (age at onset, genetic degree of relative etc.,) that are not statistically rigorous, so is not included.	This is an issue for discussion by the committee.
Caristo Diagnostics	31	39	3.4	Outcome was determined without knowledge of predictor information.	We thank the company for this additional information, which was not explicit in the published report.
Caristo Diagnostics	32	39	3.6	Outcomes data was collected independently on a periodic basis from the two cohorts as a separate exercise by the Investigators managing the cohorts. These Investigators were not involved in image analysis.	We thank the company for this additional information, which was not explicit in the published report. The EAG notes that, whilst Oikonomou 2018 reported that investigators who determined outcomes were independent of the team conducting analyses, no information was provided about whether investigators who conducted outcome adjudication were

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					independent from those who extracted predictor data from medical records.
Caristo Diagnostics	33	39	Applicability	8-year outcomes data was used in the device as statistically significant prognostic value was achievable for this duration, driven by the number of events that accrued within the 10 year follow up period.	We thank the company for this clarification.
Caristo Diagnostics	34	40	Risk of bias, para 3	The statement here is incorrect. The method was developed and published in Antonopoulos et al Sci Transl Med 2017. The German cohort was a true external validation cohort. In the 2018 paper the two cohorts were evaluated in parallel. There is some confusion about the study - as before. Please note that FAI Score was not developed in 2018.	See response to comment 1. The FAI metric "Briefly, the FAI is the average attenuation (reduction in signal) of adipose tissue within a volume of interest as measured from reconstructed CT." was developed in Antonopoulos et al Sci Transl Med 2017. However in Oikonomou 2018, FAI is now a score, which includes adjustment for technical scanner aspects such as tube voltage and based on analysis from both cohorts (including the European patient data) in 2018 paper. In addition, a multivariable model using most of the same variables as used in the CaRi-Heart® Risk model version (Oikonomou 2021), is developed using the same European dataset used as "external validation" of the CaRi-Heart® Risk model version (Oikonomou 2021). Thus the European dataset has already been analysed during the development of a multivariable model using most of the same variables on all the same patients, in the Oikonomou 2018 paper.

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Caristo Diagnostics	35	41	Describe any Participants who were Excluded from the analysis	The 2021 paper cites the 2018 paper that included the full study description of CRISP-CT. This comment is incorrect.	The comment is not incorrect; it references the list of excluded participants (with details), as reported in Oikonomou 2018 and reproduced in the text under Domain 1 (pg 37 of the EAG report).
Caristo Diagnostics	36	41	4.2	This is not correct. On what basis is it no?	Thank you. We should have put unclear, as insufficient information was reported to understand if all predictor variables were handled appropriately. We had put “no” based on our understanding that the FAI score was included based on a threshold established in the European data development dataset in Oikonomou 2018, which was the same dataset claimed as “external validation” in Oikonomou 2021. Thank you for clarification that the FAI score was a continuous measure in Oikonomou 2021.
Caristo Diagnostics	37	41	4.3	This was fully justified in the study description Lancet 2018	The EAG agrees that the list of excluded participants (with details), as reported in Oikonomou 2018, but does not consider that full justification was provided.
Caristo Diagnostics	38	41	4.5	The selection of variables is presented in Lancet 2018	The EAG notes that this risk of bias assessment was for the model reported in Oikonomou 2021. The company have stated (comment 42, below) that ‘no prediction model was developed in the Lancet 2018 study’; it is not clear how any results reported in this study may have been used to select some or all of the variable included in the model reported in Oikonomou 2021.

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Caristo Diagnostics	39	41	4.6	These papers underwent extensive, independent clinical and statistical review by experts from the two journals (Lancet and Cardiovascular Research).	The EAG, respectfully, notes that no peer review process is infallible, and that peer reviewed publication should not preclude further questioning.
Caristo Diagnostics	40	41	4.7	These papers underwent extensive, independent clinical and statistical review by experts from the two journals (Lancet and Cardiovascular Research).	The EAG, respectfully, notes that no peer review process is infallible, and that peer reviewed publication should not preclude further questioning.
Caristo Diagnostics	41	41	Validation	You incorrectly say there is no external validation. This is incorrect as the European cohort was an independent cohort that was used for external validation and accepted by both the Lancet and EU Notified Body for this purpose	We are evaluating the description of “external validation” dataset in the Oikonomou 2021, not in the Lancet paper Oikonomou 2018. We note that in the Lancet paper Oikonomou 2018, that the European cohort was used as the “development” dataset, and so is not used for external validation in Oikonomou 2018. We are not responsible for decisions made by the EU notified body.
Caristo Diagnostics	42	41	Rationale of Bias rating	This is incorrect. No prediction model was developed in the Lancet 2018 study, which validated the prognostic value of FAI in two parallel cohorts. For analytical and graphical reasons, a cut-off was measured in European cohort and then applied in the US cohort, but that cut-off is not used in the CaRi-Heart® Device, as it treats FAI as a continuous variable, and was evaluated and designated as a CE-Marked Medical Device on this basis, not on the basis of a FAI cut-off. There was no training of a model in the European cohort that could affect the Device's model. This is a key misunderstanding from the two papers that needs to be clarified for the Committee.	The Lancet paper Oikonomou 2018 developed a multivariable model based on most of the same variables as used in the CaRi-Heart® Risk model version (Oikonomou 2021). The prior use of the same European patient data was in the development (development dataset in Oikonomou 2018) of a multivariable model using FAI and most of the same variables as implemented in the CaRi-Heart® Risk model (Oikonomou 2021). The prior use of the same European data for essentially a slightly different version of the

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					same model, is clear from reported figures, tables and text (development dataset in Oikonomou 2018) where the multivariable model is used in conjunction to the same survival events. This is essentially using the multivariable model to predict survival and in addition model performance. For example i. Kaplan Meier survival curves for the multivariable model are reported in Oikonomou 2018 (European development dataset for the multivariable model) in figure 2A and 2B ii. Additional results using the European data as the development multivariable model, reporting model performance are shown in figure 3A and Table 3.
Caristo Diagnostics	43	42	Rationale of Bias rating, model methods	The models were extensively reviewed by the independent statistical reviewers at The Lancet, who agreed that clinically relevant variables were included into the model. Indeed, everything was done according to the Lancet statistical reviewers.	The EAG, respectfully, notes that no peer review process is infallible, and that peer reviewed publication should not preclude further questioning. The EAG further notes that whether or not all clinically relevant variables were included in the model is a matter for consideration/judgement by the committee.
Caristo Diagnostics	44	42	Rationale of Bias rating, model methods	The reclassification reported in Oikonomou 2021 is according to the ESC guidelines using SCORE.	We thank the company for this additional information.

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Caristo Diagnostics	45	42	Summary of Sources of Potential bias	We reiterate once again that external validation has been undertaken.	See previous responses to previous comment
Caristo Diagnostics	46	42	Summary of Sources of Potential bias	Information on the effectiveness and safety of CaRi-Heart®, including the data used to make the claims, have been validated as part of the CE Mark process, and much of the information is not in the public domain. This information is not included in the clinical papers.	The EAG, respectfully, notes that we cannot assess based on information that has not been provided. The EAG further notes that CE marking is an entry requirement for assessment by the NICE DAP and cannot be considered a substitute for the assessment process.
Caristo Diagnostics	47	43	Overall judgement about risk Of bias	Information from clinical observations from the CTCA scan are taken into account. In clinical guidelines, the only information from the CTCA scan that is recorded is whether there is a significant stenosis or not. The degree of stenosis (Duke score) is already included in the CaRi-Heart® model. The device performs equally well in those without significant stenosis as well as those with significant stenosis.	It remains unclear precisely what information from the CTCA is included in the CaRi-Heart® Risk model. The company's comment appears to indicate that this is limited to: 'The degree of stenosis (Duke score) is already included in the CaRi-Heart® model.' Whether or not it is the case that 'the only information from the CTCA scan that is recorded is whether there is a significant stenosis or not' is true/representative of current standard care is a matter for clinical expert opinion/discussion by committee.
Caristo Diagnostics	48	43	Summary of Applicability concern, point 4	Extensive detail on the set up and running of the models are included in the supplement of the Lancet paper. In addition, information on adjustments for tube voltages have been evaluated extensively, are a key part of the CaRi-Heart® device but are proprietary to the company and not in the public domain.	The EAG notes that this risk of bias assessment was for the model reported in Oikonomou 2021. The statement, in this comment, that 'extensive detail on the set up and running of the models are included in the supplement of the Lancet paper,' appears to conflict with the company's earlier statement (comment 42, below) that 'no prediction model was developed in the Lancet 2018 study'.

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					Please, also see response to comment 42.
Caristo Diagnostics	49	55	Para 3	It would be broadly accepted that a clinical trial with an anti-inflammatory drug, aiming to reduce cardiac events because of its anti-inflammatory action (proven to be a key regulator of acute coronary syndromes biologically), would reduce events by reducing inflammation, although absolute statistical and mechanistic proof that this is indeed the mechanism is not usually proven. In this regard, colchicine is widely acknowledged to reduce events by reducing inflammation. With statins, there is strong evidence for direct anti-inflammatory effects on human arteries (pleiotropic effects), and this is believed to be the reason why LDL reduction with other means like ezetimibe is less effective in reducing events, for similar LDL lowering effect size. One could argue that even for statins there is no unequivocal evidence that they reduce MACE by reducing LDL, simply because they reduce LDL and reduce MACE at the same time. However, overwhelming clinical mechanistic biological findings supporting the role of LDL lowering in reducing MACE.	Opinion only, no response required.
Caristo Diagnostics	50	56	5.4	We would emphasise that when FAI Score identifies people at higher risk who would not otherwise be treated with a statin, or when the statin dose is increased, treating more people with a statin will reduce events in keeping with the very strongly evidenced and quantified secondary prevention effects of treatment.	Opinion only, no response required.
Caristo Diagnostics	51	80	Point 1-5	We agree that these are potential priorities for future work, but most of these points are not required elements of the CE Marked Medical Device that is the subject of the EVA, and/or relate to work that is already in progress, so will be available in future. The CaRi-Heart® device is based on the risk of fatal events, as these are the most statistically powerful end point, and are more rigorously ascertained in large cohort studies. Whilst we will analyse non-fatal events in the ORFAN study, the addition of non-fatal events to the CaRi-Heart® Device would, from a regulatory perspective, constitute a new product/upgrade which would require separate evaluation and approval. It is not therefore the topic for the	Please see response to comment 5. The EAG acknowledges the company's point, regarding regulatory requirements and the inclusion of not-fatal MACE, but notes that these outcomes were included in our assessment in-line with the NICE scope. We

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				current EVA. More data will accumulate over time and as more scans are analysed and followed up. CaRi-Heart® is an approved Device for prediction of risk of fatal events – and this already provides very robust, clinically-actionable information. We also point out that CaRi-Heart® includes several complementary biomarkers that provide clinically actionable information for physicians – not only CaRi-Heart® risk. For example, the vessel-specific FAI Score enables inflammation in each coronary artery to be evaluated and can be compared if sequential CTCA scans have been done, or in response to treatments or other interventions.	further acknowledge that data collection is ongoing, as noted in our report (Appendix 3) The remaining text in this paragraph is opinion only, no response required.
				[redacted]	The EAG considers that the relevance, or otherwise, of this statement is a matter for consideration by the committee.
				We strongly agree that the health economic analysis will be very informative. As you are aware, this work is currently ongoing.	No response required.
				With regard to the helpful comments and suggestions for future long-term clinical trials, we agree that these will be interesting and important. The RCT or cluster RCT is the ideal approach, but as acknowledged a prospective RCT with clinical endpoints of CV events or mortality would take many years to complete. However, we are already undertaking the clinical trials to quantify the immediate effects of CaRi-Heart® on clinical decision-making and treatment recommendations, for example through the NHS AI-Award.	No response required.
				[redacted]	

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				[redacted]	We thank the company for provision of this additional information. The EAG considers that the comment that [redacted] is speculation, and further notes that the unreferenced approximate effect size reported would have been derived from studies which selected patients for statin treatment based on some criteria other than CaRi-Heart® Risk. It would be expected that the use of CaRi-Heart® Risk would select a different group of patients (if it did not there would be no reason to use the CaRi-Heart® device). The EAG therefore questions whether it is reasonable to assume a constant treatment effect.