NICE advice

CADScor system for ruling out coronary artery disease in people with symptoms of stable coronary artery disease

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is CADScor. It can be used to rule out coronary artery disease in people aged 40 years or over with symptoms of stable coronary artery disease.
- The **innovative aspect** is that it is a new acoustic method of detecting coronary artery disease by recording coronary murmurs caused by turbulent flow and myocardial movement.
- The intended **place in therapy** would be as a stable coronary artery disease rule-out method after first clinical evaluation (clinical history, physical examination, 12-lead ECG) but before CT coronary angiography (CTCA).
- The **main points from the evidence** summarised in this briefing are from 2 prospective observational studies involving a total of 1,900 adults referred to coronary computed tomography or invasive coronary angiography because of symptoms suggestive of stable coronary artery disease. Based on the reported diagnostic accuracy of CAD-score for coronary artery disease, they show the CADScor system can allow risk stratification that is superior to clinical risk scores.
- **Key uncertainties** around the evidence are that it is limited in quantity, with no data from an NHS setting. Evidence supporting its diagnostic accuracy is in people of European family origin only.

- The cost of CADScor system is £4,460 per unit (exclusive of VAT). The technology may be resource releasing in the long term if it reduces the number of people being referred for CTCA or other alternative diagnostic investigations.

The technology

The CADScor system (Acarix A/S) is a medical device for acoustic detection of coronary artery disease (CAD). It is intended to be used before CT coronary angiography (CTCA) to rule out stable CAD in people aged 40 years and above who have symptoms suggestive of this condition. Heart sounds, murmurs and vibrations are recorded using the device and are converted into a CAD-score, in the range of 0 to 99. A CAD-score of 20 or below suggests a low probability of CAD and no further investigation is recommended. A CAD-score above 20 suggests a medium to high probability of CAD and further investigation is recommended, such as CTCA or invasive coronary angiography (ICA). The algorithm that is currently in use (version 3), combines acoustic measures with the patient's age, gender and blood pressure to generate a specific CAD-score.

The CADScor system consists of 2 units; the acoustic recording sensor and the docking station for charging and qualification of the sensor to make sure the sensor microphone is working properly. Single-use adhesive patches are also needed to connect the sensor to the patient's chest. The company claim the test can done in less than 10 minutes, including preparing the patient and readout of the CAD-score result.

Innovations

The CADScor system provides a new method of detecting CAD acoustically by recording coronary murmurs caused by turbulent blood flow. Normally, coronary blood flow is laminar, but when stenosis happens, blood flow can become turbulent and this usually manifests as coronary murmurs. Coronary murmurs can therefore suggest the presence of haemodynamically important CAD. The company claim that no other acoustic CAD rule-out technology is currently available in the UK that has comparable sensitivity and specificity to the CADScor system. They also claim that the device could allow further testing to be ruled out for 40 to 50% of people. The test is non-invasive and does not use radiation, avoiding radiation exposure from CT scans in people for whom CTCA is ruled out. Apart from patient data that are entered into the CADScor device before the test, no external inputs are needed.

Current care pathway

The current diagnosis of people presenting with suspected stable CAD is based on clinical assessment. NICE's guideline on the assessment and diagnosis of chest pain with recent onset

states this should include a detailed clinical history and physical examination. The following factors should be taken into account: age, whether the person is male, cardiovascular risk (history of smoking, diabetes, hypertension, dyslipidaemia, family history of premature CAD), other cardiovascular disease, and history of established CAD. CTCA is recommended as the first diagnostic test for people in whom stable angina cannot be excluded by clinical assessment alone. The guideline also recommends taking a resting 12-lead ECG as soon as possible in these patients. CTCA should be used if:

- clinical assessment suggests typical or atypical angina or
- clinical assessment suggests non-anginal chest pain but 12-lead resting ECG has been done and indicates ST-T changes or Q waves.

If CTCA has shown CAD of uncertain functional importance or if it is non-diagnostic, patients should be offered non-invasive functional imaging for myocardial ischaemia. ICA may be offered as a third-line when the results of non-invasive functional imaging are inconclusive.

Population, setting and intended user

The CADScor system is proposed by the company to be used early on in the current care pathway as a CAD rule-out test before CTCA. It will be used in people over the age of 40 who present with symptoms suggestive of stable CAD, and in accordance with the manufacturer's instructions for use. It is intended to be used by trained health professionals, which may include nurses, physicians and catheterisation laboratory technicians. It could be used in both primary and secondary care settings. Product-specific training on how to use the device will be needed for healthcare professionals. Training sessions of up to 3 hours are provided by the company for all new primary users of the device. Training includes an instruction presentation followed by a CADScor practical test session.

Costs

Technology costs

The cost of the CADScor system is £4,460 per unit (excluding VAT). Assuming the technology has a lifespan of 2 years and is used to test 3 patients per day, 4 days a week for 41 weeks of the year, the company estimate a per-test cost of £49.12.

Costs of standard care

Per-patient costs for standard care tests are based on 2018/19 hospital resource group (HRG) tariffs, and are as follows:

- CTCA: £196 (HRG code RD28Z, Complex CT Scan [including the cost of reporting]).
- Calcium scoring: £71 (HRG code RD20A, CT scan, 1 area, no contrast [including the cost of reporting]).
- ICA: £834 to £8,016 (HRG codes EY43A-F, standard cardiac catheterisation).

Resource consequences

Use of the technology has the potential to be resource releasing if it can reduce the number of people referred for CTCA or other alternative diagnostic investigations.

Regulatory information

The CADScor system was CE marked as a class IIa medical device in 2015. It is not currently in clinical use in the UK.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Coronary artery disease (CAD) is more common in men and in people over the age of 50, with the risk of developing CAD increasing with age. Cardiovascular disease is more common in people of South Asian and African or Caribbean family origin. The technology is only validated for use in people aged 40 years and over. Sex, age and race are all protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Two prospective studies involving a total of 1,900 people with symptoms of coronary artery disease (CAD) who were referred to CT coronary angiography (CTCA) or invasive coronary angiography (ICA), are summarised in this briefing.

Table 1 summarises the clinical evidence as well as its strengths and limitations.

Overall assessment of the evidence

A study by Winther et al. (2016) of 225 people with symptoms suggestive of stable angina, compared the diagnostic accuracy of the technology with that of the Diamond-Forrester score, coronary artery calcium score (CACS), and their combinations (using quantitative ICA as the reference standard). This study showed that CAD-score version 2 (V2; the acoustic component only) had a diagnostic accuracy of 72%. This was similar to the Diamond-Forrester score (79%) but lower than the CACS (86%). Combining the CAD-score V2 and the Diamond-Forrester score increased accuracy to 82%. Nearly a third of patients (31%) were re-classified as having very low risk using the Diamond-Forrester score and CAD-score combined, suggesting a potential for this technology in risk stratification.

The Dan-NICAD study (Winther et al. 2018) involved 1,675 patients with symptoms, who had a low to intermediate risk of CAD. This study looked at 2 CAD-score algorithms: the previously used version, CAD-score V2; and the newer algorithm, CAD-score V3, which combined the acoustic algorithm with clinical risk factors. At a cut-off CAD-score of more than 20 the newer algorithm had a sensitivity, specificity, positive predictive value and negative predictive value of 81%, 53%, 16% and 96%, respectively, for detecting haemodynamically important CAD (using invasive fractional flow reserve as a reference standard).

The evidence base for the CADScor system is limited in quantity, with only 1 of the studies evaluating the latest algorithm, which includes both the acoustic and clinical parameters. All of the available data come from centres in Denmark and may not be generalisable to NHS practice

because of differences in the initial management and stratification of patients before further diagnostic investigations (CTCA and ICA). Also, most of the comparative data for the technology is against the Diamond-Forrester clinical risk score, which is no longer recommended by NICE as a method for risk stratification before CTCA. This is because the model is known to overestimate the probability of CAD relative to its true prevalence. In the largest multicentre study (Winther et al. 2018), most people (99%) were of European family origin. Further studies in a more heterogeneous population might clarify whether diagnostic accuracy is linked to family origin.

Table 1 Summary of selected studies

Winther et al. (2016)	
Study size, design and location	Prospective observational study involving 255 people referred to either CTCA or ICA because of symptoms suggestive of CAD.
Intervention and comparator(s)	Intervention: CADScor. Comparator: CACS and DF score.
Key outcomes	Diagnostic accuracy (ROC AUC) was 72% for the CAD-score and 79% for DF score (p=0.12), and 86% for CACS (p<0.01). Combining the CAD-score and DF score increased diagnostic accuracy to 82%, which was statistically significantly higher than the standalone CAD-score (p<0.01) and DF score (p<0.05), and comparable to CACS alone (p=0.28). There was a limited benefit in combining CAD-score or DF score with CACS or combining all 3 together. The optimal CAD-score threshold was 24.2. At this value the sensitivity, specificity, PPV and NPV were 76%, 59%, 42% and 87%, respectively. When using CAD-score combined with DF, 31% of people were re-classified as having very low risk of CAD compared with 13% of people with DF score alone. Results from this study suggest that combining clinical risk factors with the use of the CADScor system may optimise patient selection for diagnostic investigation.
Strengths and limitations	Patients were recruited consecutively. Single-centre study that was part-funded by the company. Patients with diastolic murmurs were not included in the study. Data from the study population were used in the development and validation of the CAD-score, implying a risk of overfitting the algorithm to this population.
Winther et al. (2018)	

Study size, design and location	Prospective observational study involving 1,675 people with low to intermediate likelihood of CAD who had been referred for CTCA because of symptoms suggestive of obstructive CAD.
Intervention and comparator(s)	Intervention: CADScor system QCA and FFR were used as reference standards.
Key outcomes	In this study, an updated CAD-score algorithm that included both acoustic features and clinical risk factors was developed and validated. Low risk was indicated by a CAD-score value of equal to or more than 20. CAD-Score correlated moderately with coronary artery calcium score (CACS; r=0.38, p<0.001), with a statistically significant decrease in CAD-score between the CACS groups. 50% of people in the study had an updated CAD-score value ≤20. At this cut-off, sensitivity was 81%, specificity 53%, PPV 16% and NPV 96% for diagnosing haemodynamically important CAD (using QCA as a reference standard). The diagnostic accuracy of CAD-score in detecting anatomically obstructive stenosis (using FFR as a reference standard) was comparable at the same cut-off. Compared with DF, CAD-score had a significantly better diagnostic accuracy in detecting anatomically obstructive CAD (ROC AUC: 66% compared with 72%, p<0.01). CAD-Score was not related to the location of the stenosis.
Strengths and limitations	Involved a large number of consecutively enrolled patients. The cohort was almost entirely Caucasian (99%) with low to intermediate prevalence of CAD, generalisation of results to other populations and healthcare environments may not be possible. Current research is part-funded by the company.
Abbreviations: AUC, area under the curve; CACS, coronary artery calcium score; CTCA, CT coronary angiography; DF, Diamond-Forrester score; FFR, fractional flow reserve; ICA, invasive coronary angiography; NPV, negative predictive value; PPV, positive predictive value; QCA, quantitative coronary analysis; ROC, receiver operating characteristic.	

Recent and ongoing studies

Two ongoing studies were identified:

- Danish study of non-invasive diagnostic testing in coronary artery disease 2 (Dan-NICAD 2). ClinicalTrials.gov identifier: NCT03481712. Status: recruiting. Indications: angina pectoris, atherosclerosis, CAD, myocardial ischaemia. Interventions: multiple diagnostic tests; CADScor

- system will be compared with the Diamond-Forrester score with CTCA and invasive coronary angiography (ICA)-quantitative coronary angiography as reference standard.
- Prospective, consecutive, blinded, clinical investigation validating the performance of the CADScor System against invasive coronary angiography in subjects with symptoms of stable CAD referred for invasive coronary angiography (VALIDATE). German clinical trials register identifier (DRKS-ID): DRKS00010492. Status: recruiting complete, follow-up complete. Indication(s): atherosclerotic cardiovascular disease. Interventions: CADScor system, ICA.

Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field. The comments received are individual opinions and do not represent NICE's view.

None of the specialist commentators were familiar with the technology or had used the CADScor system before.

Level of innovation

All experts agreed that the technology is novel in its concept and design, and none of the commentators were aware of any comparable technologies currently in clinical use within the NHS. One commentator noted that although acoustic detection of flow-limiting coronary artery disease (CAD) is a novel concept, other acoustic devices for non-invasive detection of CAD exist.

Potential patient impact

The non-invasive, rapid rule out of CAD, leading to a reduced need for more complex investigations in patients with a low likelihood of CAD, was the main benefit identified by specialists. This was said to reduce the exposure of individuals to ionising radiation and to the risks of invasive procedures. One commentator added that the technology may provide greater confidence of rule out in low-risk patients who present with atypical or non-specific symptoms. One commentator thought the benefits to patients were limited, noting that obstructive coronary artery disease would not be definitively ruled out and people with continuing symptoms may need to have further investigations, regardless of a low CAD-score. Most commentators said the technology was unlikely to lead to substantial changes to current practice or clinical outcomes, but may shorten the pathway for some patients by reducing the need for CT coronary angiography (CTCA) and invasive coronary angiography (ICA). Most of the commentators agreed that the technology would be of most benefit for patients presenting with suspected symptoms with a very low or low to intermediate risk of CAD.

Potential system impact

The potential to release resources and provide cost-savings by reducing the need for more complex investigations, such as CTCA and ICA, was identified as a key benefit to the healthcare system. The potential to reduce the use of ionising radiation was also identified as a benefit by 1 commentator. Apart from the initial upfront cost associated with the purchase of the system, most commentators agreed that use of the CADScor system may provide savings to the NHS provided it led to fewer complex and costly tests being done. The resource impact of adopting the technology included the purchase of hardware and disposables as well as the additional staff time to do the test, but should reduce the burden on CT services and other investigational pathways for chest pain. Commentators noted the technology could be used as an outpatient hospital procedure, in accident and emergency departments or in the community setting to avoid unnecessary trips to hospital, but is unlikely to shift care from secondary to primary setting. Most commentators agreed that the technology would be an addition to standard care but may replace additional investigations (CTCA or invasive coronary angiography [ICA]) in a proportion of patients. None of the commentators were aware of any major changes to facilities or infrastructure needed to adopt the technology. Staff training on how to use the device and interpret results was identified as a need by 4 of the specialists.

General comments

All commentators noted that the CADScor system is not used in the NHS. None of the commentators were aware of any safety concerns surrounding the technology, although 1 noted that an allergy to the disposable chest pads may happen in some patients. Most commentators were not aware of any issues with the usability of the technology, but 1 said that it is unclear if obesity or lung disease (which could obscure or confuse the acoustic signal) affect the sensitivity and specificity of the test. The main barrier to adoption identified by most commentators was the lack of randomised controlled data from an NHS setting; 2 commentators stated that at present the available evidence is not enough to support the use of the technology in routine clinical practice. Commentators highlighted that existing data only relates to Danish experience in a low-risk cohort of patients, adding that validation in a large and diverse UK population (that is, different family origins, high BMI, older or younger patients, varying levels of disease severity and stenosis) is needed before adoption. Longer-term data surrounding the clinical and cost implications of adopting the technology into standard NHS practice, including the effects on resource utilisation and the time to diagnosis, would also be useful. Specialists highlighted that the CADScor system may be unable to identify premature atheroma, limiting its role as a surrogate for future cardiovascular risk reduction. One commentator thought the test may theoretically miss cases of atherosclerosis that are only flow-limiting in a dynamic state, because of the test being done under

resting conditions. According to 1 commentator, NHS trusts do not currently use CAD risk scoring algorithms, adding that some CAD risk scoring algorithms have historically over predicted CAD and are becoming obsolete, with a preference towards using clinical symptom evaluation and an ECG alone (as recommended in NICE's guideline on chest pain of recent onset: assessment and diagnosis).

Specialist commentators

The following clinicians contributed to this briefing:

- Peter Ludman, professor of cardiology and consultant, University Hospital Birmingham, did not declare any interests.
- Dr Adelle Dawson, consultant cardiologist, Aberdeen Royal Infirmary, Member of SIGN Guideline Development Group for Guideline 151: Management of Stable Angina, from 2014 to April 2018; an investigator for the SCOT-HEART study looking at the role of CT coronary angiography in patients with suspected angina, from 2014 to August 2018.
- Dr Ronak Rajani, consultant cardiologist, Guy's and St Thomas' NHS Foundation Trust, did not declare any interests.
- Dr Tom Johnson, consultant cardiologist, University Hospitals Bristol NHS Foundation Trust, did not declare any interests.
- Dr Ian Purcell, consultant interventional cardiologist, Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, did not declare any interests.
- Dr Robert Henderson, consultant cardiologist, Nottingham University Hospitals NHS Trust, a paid medical advisory board member for Creavo Medical Technologies, which are developing a magnetocardiography device for use in the assessment of patients with suspected acute coronary syndrome, financial interest arose in 2014 and is ongoing.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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