ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

The CADScor System as a Rule-out Test for Symptomatic Patients Suspected to have Coronary Artery Disease

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ACE agency for care effectiveness

Summary of Key Points

- Coronary artery disease (CAD) is the second largest cause of death in Singapore, and accounted for 20.1% of all deaths in 2021.
- Initial diagnosis of CAD involves a multi-staged approach that includes clinical assessment, laboratory tests, imaging, and assessing likelihood of CAD using pre-test probability (PTP). Symptomatic patients with a PTP of 15% or less are considered to have a low probability of CAD, and can be deferred from further diagnostic tests such as computed tomography coronary angiography (CTCA). The updated Diamond-Forrester (DF) score is a common tool for determining PTP, but is rarely used in local practice.
- The CADScor system is a device that combines an acoustic-based method with patient parameters to detect CAD probability. CADScor values range from 0 to 99. A patient with a score of 20 or less is considered to have a low risk of CAD.
- The CADScor system has been found to be a safe and accurate device for assessing the likelihood of CAD in symptomatic patients suspected to have CAD.
    - No major adverse events were reported with the use of CADScor.
    - CADScor system was found to have similar area under curve (AUC) to the updated DF (66.1% to 75% vs 66.6% to 79.0%, respectively).
    - CADScor had a high negative predictive value (NPV; 90.5% to 97.2%), although it was slightly worse than the updated DF (98.1%).
    - CADScor system was able to reclassify patients considered low to intermediate risk based on their PTP scores to a lower risk group.
- The CADScor system also showed some prognostic value. Patients classified as low risk of CAD based on their CAD-score showed lower rates of mortality, myocardial infarction (MI) and revascularisation, compared to patients classified as intermediate to high risk of CAD.
- NICE reported that the CADScor system costs £4,460 (S$7,436) per unit, and has an estimated per patient cost of £49.12 (S$82).
- A company-sponsored cost utility analysis reported that CADScor system was cost saving in the diagnosis of CAD in England. A Markov model with one-year time horizon found CADScor had an overall per-patient cost savings of £131 over 1 year, translating into an annual cost saving of £92.6 million.
- The main limitation of the evidence is the lack of studies comparing the CADScor system with PTP scores other than updated DF and with other clinical risk assessment tools. Additionally, there is also the lack of studies on the impact of the CADScor system on patient outcomes.
- The main implementation considerations would be training of clinical staff and the establishment of protocols to ensure conformity of the device used according to Ministry of Health Artificial Intelligence in Healthcare Guidelines (AIHGle).

I. Background

Coronary artery disease (CAD) occurs due to a build-up of atherosclerotic plaque along the walls of the coronary arteries. This process, known as atherosclerosis, restricts the supply of oxygenated blood to cardiac muscles, and could potentially lead to a heart attack.[1] Angina (as a result of atherosclerosis) is the most common symptom of CAD.[1]

CAD is the foremost single cause of mortality and loss of disability adjusted life years (DALY) globally.[2] In 2021, 9.4 million deaths and 185 million DALYs globally were associated with CAD.[3] Locally, CAD was the second largest cause of death in 2021, accounting for 20.1% of all deaths in Singapore.[4]

Initial diagnosis of CAD involves a multi-staged approach that includes clinical assessment, laboratory tests, imaging, and assessing pre-test probability (PTP) to determine the likelihood of CAD.[5,6] The likelihood of obstructive CAD depends on the prevalence of the disease in the population studied and the clinical features of an individual patient, with PTP estimates of obstructive CAD based on age, sex, and the nature of symptoms.[5] Currently, one of the most commonly used PTP models reported in the literature is the updated Diamond-Forrester (DF) score. The original DF used a US-only population and was only able to predict the risk of CAD in patients between 30 to 70 years old.[7] The updated DF was created based on contemporary databases from both the US and Europe and is able to predict the risk of CAD from age 30 and above.[7] Although there are multiple PTP models to rule out obstructive CAD[8], studies continued to report high rates of redundant subsequent diagnostic tests in patients suspected of CAD[9] that are expensive and carry additional risks.[10] As a result, the updated DF is no longer recommended by NICE as a method for risk stratification before computed tomography coronary angiography (CTCA) due to the model's propensity to overestimate the probability of CAD.[11] As such, there is a need for a more accurate risk stratification tool to improve the rule out of CAD.

II. Technology

The CADScor system (Acarix A/S, Sweden) is a device that can perform acoustic-based detection of CAD. Its intended use is after first clinical evaluation and before CTCA, to rule out stable CAD in symptomatic patients aged 40 years and over.[11] In addition to patient factors such as gender and age, CADScor system detects and records coronary murmurs caused by turbulent blood flow in stenosed arteries, indicating obstructive CAD. The device is non-invasive and non-radioactive[12], avoiding the risk of radiation from CT scans in patients for whom CTCA is ruled-out by the CADScor system.[11]

The device consists of two units, the acoustic recording sensor, and a docking station to charge and ensure that the sensor is working properly. Single-use adhesive patches are required to secure the sensor on patient's chest.[11] An artificial intelligence (AI)-based algorithm calculates a CAD-score based on a combination of acoustic information recorded by the sensor and the patient's age, gender and blood pressure.[11,12]

Calculated CAD-scores will range between 0 to 99. A score of 20 or below suggests a low probability of CAD and further diagnostic testing is not recommended, as opposed to a CAD-

score above 20, which suggests a medium to high risk of CAD with further diagnostic testing required.[11] There are two versions of the CADScor algorithm – CADScor V2, which analyses four acoustic features to generate the CAD-score, and an updated version CADScor V3, which analyses eight acoustic features. Only CADScor V3 integrates the acoustic data with the patient's age, gender and blood pressure to generate a CAD-score.[13] The manufacturer claims that the CADScor system is able to generate the patient's CAD-score in 10 minutes.[12] The device is intended to be used by trained health professionals such as nurses, physicians and catheterisation laboratory technicians in both primary and secondary care settings.[11]

Figure 1. Image of the CADScor Device. Image adapted from https://www.acarix.com/

III. Regulatory and Subsidy Status

The CADScor system received its Conformite Europeenne (CE) mark in 2015, and its de novo clearance (DEN190047) from the US Food and Drug Administration (FDA) in 2020.

IV. Stage of Development in Singapore

☒ Yet to emerge	☐ Established
☐ Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☐ Established *but* modification in indication or technique
☐ Nearly established	☐ Established *but* should consider for reassessment (due to perceived no/low value)

V. Treatment Pathway

Both the 2019 European Cardiac Society (ESC)[5] and the 2021 American Heart Association (AHA) and American College of Cardiology (ACC)[6] guidelines on the management of stable symptomatic patients with angina recommend a clinical examination followed by initial tests such as blood tests, electrocardiogram (ECG), echocardiography and cardiac magnetic resonance. PTP scores are recommended by both guidelines (Appendix A, Figure A1), followed by CTCA if patients deemed to be above low risk of having CAD. According to both guidelines, a PTP score higher than 15% would show the most benefit from further non-invasive diagnostic testing.[5,6]

Locally, there are some variations in the role of PTP in the diagnostic pathway. Based on local clinician feedback, following a clinical assessment of the patient, some clinicians would recommend basic tests such as blood tests or ECG before any PTP score, while others would recommend they are conducted after (Personal communication: Senior Consultant from National Heart Centre Singapore, 1 April 2023). However, some local clinicians do not always assess the risk of CAD based on the formal use of a PTP score (Personal communication: Senior Consultant from National University Heart Centre Singapore, 3 April 2023). Locally used CAD risk assessment methods include the Framingham risk score (Personal communication: Senior Consultant from National University Heart Centre Singapore, 3 April 2023), the CAD consortium score and PRECISE (Predictive Risk scorE for CAD In Southeast Asians with chEst pain), which is a locally created diagnostic risk calculator (Personal communication: Senior Consultant from National Heart Centre Singapore, 1 April 2023). DF is rarely used in local practice.

The introduction of the CADScor system locally, if proven to demonstrate superior rule-out capability, could be an alternative, or supplement, to contemporary PTP rule-out testing for symptomatic patients with low or low-to-intermediate risk of CAD. Use of this system could help further reduce the unnecessary burden of redundant diagnostic tests on both the healthcare system and patients. The device's ability to provide a quantitative value on the likelihood of CAD and a cut-off CAD-score means it could also be used in primary care settings, where a clinician might not have specialised knowledge of PTP scoring or the clinical experience to determine the likelihood of CAD in a symptomatic patient.

VI. Summary of Evidence

This assessment was conducted using the Population, Intervention, Comparator and Outcome (PICO) criteria (Table 1). Literature searches were performed in Cochrane, PubMed, Embase and International Network of Agencies for Health Technology Assessment (INAHTA) databases. A search on FDA's Manufacturer and User Facility Device Experience (MAUDE) database was also conducted.

Table 1: PICO criteria

Population	Symptomatic patients suspected to have CAD
Intervention	CADScor System
Comparator	Clinical risk assessment methods for CAD (including PTP scores)
Outcome	Safety, Clinical and Cost Effectiveness

Abbreviations: CAD, Coronary artery disease; PTP, Pre-test probability.

The main evidence base consists of a medical technology innovation briefing by NICE[11], which consists of two studies assessing the diagnostic accuracy of CADScor. One of the included studies used the older CADScor V2 algorithm while the other looked at both the CADScor V2 and V3 algorithms. The rest of the evidence base included in this brief evaluated CADScor V3. Three additional studies on diagnostic accuracy[10,14,15], one cost-effectiveness analysis[16] and one feasibility study[17] were also included. An additional study on the prognostic value of CADScor was included as secondary evidence.[18] Although the study by Rasmussen et al (2023)[15] did not specify the version of the algorithm used, it is likely CADScor V3, due to publication recency. A major limitation of the evidence base is the lack of studies comparing the CADScor system to locally used PTP scores (Framingham risk score, CAD consortium score and PRECISE). Also of note is that most studies are supported or sponsored by the manufacturer Acarix. Additional details on the evidence base can be found in Appendix B.

Safety

Overall, there were no major safety concerns associated with the use of the CADScor system. NICE noted that the disposable chest pads may be a source of allergy for some patients.[11] The search on FDA's MAUDE identified no reports related to the CADScor system.

Effectiveness

Accuracy

There was a total of four studies[10,11,14,15] that assessed the accuracy of the CADScor system for the detection of CAD. Table 2 summarises diagnostic accuracy results from these studies. Table C1 in the Appendix C has more details on the diagnostic accuracy of CADScor and its comparators.

Table 2: Summary of diagnostic accuracy for detection of CAD

Scoring Method	AUC (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CADScor V3	66.1 to 75.0	80.4 to 97.6	14.5 to 53.0	13.7 to 41.7	90.5 to 97.2
Updated DF	66.6 to 79.0	96.7 to 100.0	0.0 to 17.9	10.9 to 39.4	98.1
CACS	86.0	NR	NR	NR	NR

Results were adapted from NICE (2019)[11], Schmidt et al (2019)[10], Renker et al (2021)[14], Rasmussen et al (2023)[15]
Abbreviations: AUC, Area-under-curve; CACS, Coronary artery calcium score; DF, Diamond-Forrester score; NPV, Negative predictive value; NR, Not reported; PPV, Positive predictive value.

Overall, when compared to the updated DF, similar AUC and sensitivity, and a higher specificity were reported for CADScor V3.[10,14] In addition, high NPV, although slightly worse than updated DF was reported for CADScor, indicating its potential to accurately rule out CAD. Based on the results from the accuracy studies, the CADScor system may be a valuable test to rule out CAD. Although most studies compared the CADScor system solely against updated DF, of note is that one study included in the NICE brief comparing CADScor V2 to the updated DF and coronary artery calcium score found CADScor to be similar in diagnostic accuracy with the updated DF ($p=0.12$) but not as accurate as coronary artery calcium scoring ($p<0.01$).[11]

Patient/Clinical outcome

No study assessing the impact of CADScor system on patient outcomes was identified.

The prognostic value of the CADScor system was assessed by Winther et al. (2021) in patients suspected to have CAD as a substudy of the Danish study of the Non-Invasive Testing in Coronary Artery Disease (Dan-NICAD) trial.[18] A total of 1464 patients with angina symptoms referred for CTCA were included in this study. The combined primary endpoint and secondary endpoints are summarised in Table 3. Endpoint events occurred in a higher proportion of patients with CAD score >20 compared to those with CAD-score ≤20. Figure C1 in the appendix shows the Kaplan-Meier plots for the primary and secondary endpoints.[18] An unadjusted Cox regression analysis of the combined primary endpoints found that in reference to a CAD-score of lower than 20, patients with a CAD-score above 20 had a hazard ratio of 5.4, with a 95% Confidence Interval of 1.9 to 15.7 (p <0.01).[18]

Table 3: Summarised table of events during follow-up according to CAD-score

Outcome	CAD-score ≤ 20	CAD-score > 20
Primary Endpoint: Composite Mortality and MI	0.6%	3.0%
Secondary Endpoints: Mortality (all cause), MI, Revascularisation (Early/Late*)	4.2%	16.2%
Adapted from Winther et al.[18] *The cut-off between early and late is 120 days. Abbreviations: MI, Myocardial Infarction.		

The CADScor system has reclassified patients to a lower risk group. Schmidt et al, (2019) reported that about one-third of patients initially classified as intermediate risk of CAD based on their PTP scores (15% to 85%) were reclassified as low risk with a CAD-score of 20 or less.[10] In the study by Rasmussen et al. (2023), 48% of patients initially classified as low risk of CAD based on their PTP scores (5% to 15%) were reclassified to very-low risk of CAD.[15] However, how the reclassification impacted on patient outcomes remains unknown.

Schnaubelt et al. (2022) assessed the feasibility of CADScor in 101 patients with angina in a high-volume tertiary emergency department.[17] It found that a CAD-score was successfully calculated in 80% of patients, with 74% obtained on the first attempt. Both patients and investigators found the device to be highly feasible in an emergency department setting, giving a 9.0 and 8.9 (out of 10) on the Likert scale, respectively.[17] Workflow was not interrupted as the CADScor system was used when the patient was waiting.[17]

Cost Effectiveness

Javanbakht et al. (2021) assessed the cost utility of the CADScor system for CAD diagnosis in the diagnostic testing pathway in England.[16] A two-part economic model was developed, comprising a decision tree representing short-term costs and diagnostic outcomes associated with introduction of CADScor, and a Markov model exploring the longer-term health and economic implications at 1-year after CAD diagnosis (Figure C2 and Figure C3 in Appendix respectively).

The decision tree model revealed that, compared to the standard diagnostic pathway, the introduction of the CADScor system before CTCA resulted in a saving of £123 per patient.[16] This represented a 16% reduction in overall costs of diagnostic testing. The Markov model

showed that use of the CADScor system resulted in an overall savings of £131 per-patient over one year, and a marginal improvement of 0.00001 QALY gained per patient.[16] This translated to £92.6 million cost savings annually in England. Probabilistic analysis results found a 100% probability of CADScor being cost saving and a >99% probability of being cost effective at £20,000 willingness-to-pay threshold.[16] Sensitivity analyses indicated that the results were most sensitive to the accuracy and cost of the CADScor System, and the prevalence of CAD. However, caution should apply in interpreting the study results as it was funded by Acarix.

Ongoing Trials

A search on ScanMedicine (NIHR Observatory) yield one ongoing randomised controlled trial looking at the cost effectiveness of using both the DF Score and a CAD-Score as a rule-out strategy for symptomatic patients suspected to have CAD, compared with DF Score alone (Table 4).

Table 4: Ongoing trials for the CADScor system

Study name (Trial ID)	Estimated Enrolment	Aim of Trial	Estimated Study Completion Date
FILTER-SCAD (NCT04121949)	2000	A Prospective, Randomized, Controlled, Parallel-group, Multicentre Trial to Examine the Cost-effectiveness and Safety of Adding the CADScor System as a Rule-out Test in Patients Referred With Symptoms Suggestive of Stable Coronary Artery Disease.	September 2023

Summary

In summary, the CADScor system appears to perform similarly to the updated DF score as a rule-out test for patients suspected to have stable CAD, reflected by its high NPVs (90.5% to 97.2%). The CADScor system was shown to reclassify patients considered low to intermediate risk based on their PTP scores to a lower risk group. The feasibility of the CADScor system was high in a high-volume emergency department. The CADScor also demonstrated some prognostic value, with better prognosis in patients classified to have low risk of CAD (CAD-score ≤ 20) when compared to those at intermediate to high risk of CAD (5% vs 19.2%, respectively). In a company-sponsored study, CADScor was shown to be cost-effective in the diagnostic pathway in England, with a 16% reduction in per-patient diagnostic cost and overall savings to the NHS of roughly £92.6 million annually.

There are certain limitations to the evidence base. The major limitation is that the CADScor system was mainly compared against the updated DF score in current evidence, and no comparison was made with locally used PTP scores. Secondly, there is a lack of studies on the impact of the CADScor system on patient outcomes. Thirdly, most of the studies are partially or fully funded by the manufacturer or have authors with conflicts of interest.

VII. Estimated Costs

According to NICE, the CADScor system costs £4,460 (S$7,436)[a] per unit. The manufacturer estimated that the technology had a per-test cost of £49.12 (S$82)[a], based on the assumption that the device has a lifespan of two years and is used to test three patients per day, four days per week and 41 weeks per year.[11]

For comparison, Table 5 shows per-patient costs for other standard care tests reported by NICE that may be avoided with improved patient risk classification with the CADScor system.

Table 5: Per-patient cost of various standard care diagnostic tests

Standard Care Tests	Cost (Per-Patient)[a]
CTCA (CT scan, includes cost of reporting)	£196 (S$327)
Calcium Scoring (CT scan (1 area, no contrast), includes cost of reporting)	£71 (S$118)
ICA (Standard cardiac catheterisation)	£834 to £8,016 (S$1391 to S$13,366)
Adapted from NICE's MIB for the CADScor System.[11] Abbreviations: CT, Computed tomography; CTCA, Computed tomography coronary angiography; ICA, Invasive coronary angiography; NICE, National Institute for Health and Care Excellence; MIB, Medtech innovation briefing.	

VIII. Implementation Considerations

A 3-hour training session provided by the manufacturer would be required for healthcare staff to familiarise with the technology.[11] Guidelines to incorporate CADScor into the local diagnostic pathway for patients suspected to have CAD would also be necessary to standardise the practice.

As the CADScor system involves AI algorithms to generate the CAD-score, there is a need for the vendor to adhere to the Ministry of Health Artificial Intelligence in Healthcare Guidelines (AIHGle).[19] This would require a proper documentation process including updates to current diagnostic workflows, conducting risk assessment related to the use and potential failures of the CADScor system, and ensuring the accuracy and performance of the AI within the system. There will be a need to obtain proper consent from patients, as the system requires their information to generate the CAD-score.

IX. Concurrent Developments

The CADence device is another FDA approved non-invasive acoustic and ECG device used to detect CAD.[20]

Although not employing an acoustic-based methodology to detect for CAD, the Cardiac Phase Space Tomography Analysis (cPSTA) System is another non-invasive tomographic imaging method that also uses AI technology to assess the presence of CAD.[21] The device assesses the patient at rest in a supine position and does not require contrast media, exercise or

[a] Based on the Monetary Authority of Singapore exchange rate as of 12 May 2023: £1=S$1.6673. Figures were rounded to the nearest dollar.

pharmacological stress. However, this technology has not been approved by FDA yet (Table 6).

Table 6: Concurrent developments similar to CADScor

Device	FDA Approval
CADence (AUM Cardiovascular Inc)	Approved
Cardiac Phase Space Tomography Analysis (cPSTA) (A4L, Analytics For Life)	Not Approved

X. Additional Information

The CADScor system has been tested to detect for MI. In a study by Lehmacher et al. involving 167 patients and a cut-off CADScor V3 <20, the device demonstrated sensitivity of 87.5%, specificity of 13.4%, positive predictive value of 10.8% and negative predictive value of 90.0% for the diagnosis of MI.[13] This suggests potential use for the CADScor system to rule out MI in an outpatient setting, given the high sensitivity and high negative predictive values.

Local clinician feedback cited potential concerns on the accuracy of the CADScor system in detecting stenosis below 70% or between 99% to 100% stenosis. There were also concerns on CADScor's additional value, given its additional cost, since it was found to be similar in performance to the updated DF score (Personal communication: Senior Consultant from National University Heart Centre Singapore, 1 June 2023).

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Appendix

Appendix A: Relevant information

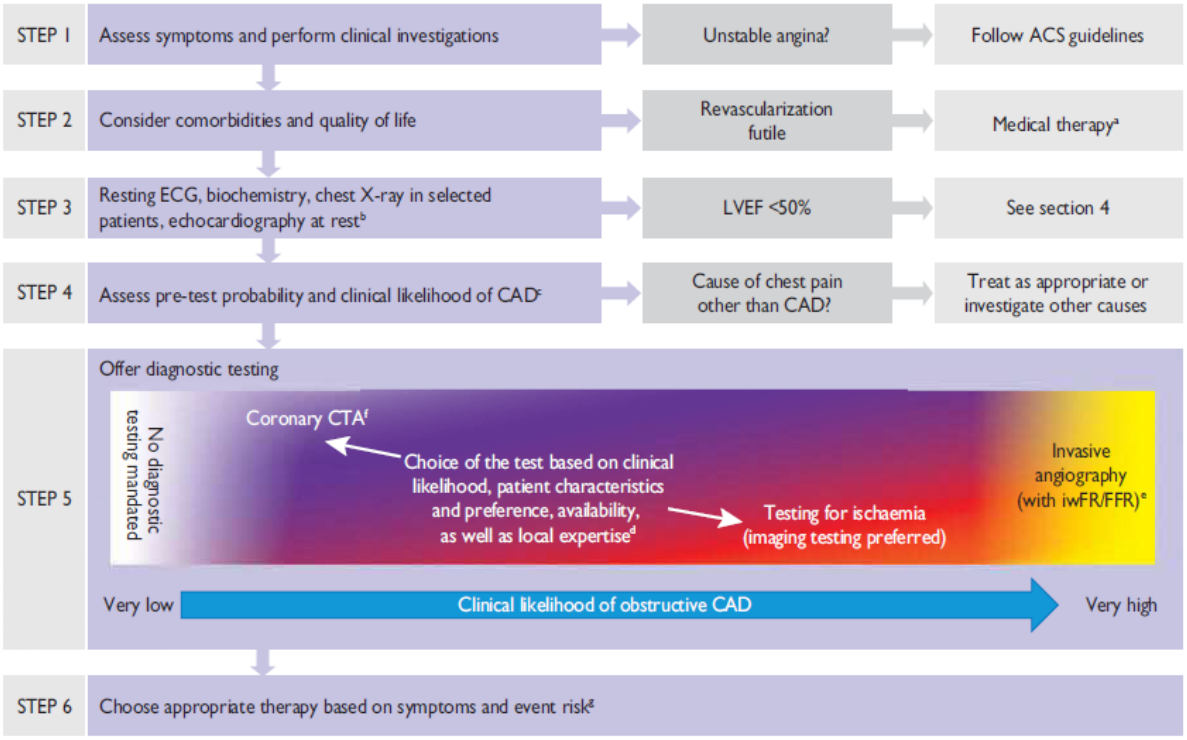

Figure A1: Diagnostic Pathway for CAD Diagnosis. Adapted from the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.[5] Abbreviations: ACS, Acute coronary syndrome; CAD, Coronary artery disease; CTA, Computed tomography angiography; ECG, Electrocardiogram; FFR, Fractional flow reserve; iwFR, Instantaneous wave-free ratio; LVEF, Left ventricular ejection fraction.

Appendix B: Studies identified and study design

Table B1: List of included studies

Type of study	Number of Studies
Key evidence base	
Medtech innovation brief	1
Comparative studies	2
Single-arm studies	2
Economic analysis	1
Supplementary evidence base	
Single-arm studies	1

Note:

1. Inclusion criteria
    a. Studies that fulfil the PICO criteria listed in Table 1.
2. Exclusion criteria
    a. Studies only in abstract form

Table B2: Design and characteristics of included studies

Study	Study design	Number of studies/patients	Patient Type
Key evidence base			
NICE (2019)[11]	Medtech innovation briefing	2 studies 1930 patients Intervention: CADScor V2, CADScor V3 Comparators: CACS, DF Reference Standard: CTCA/ICA	Symptomatic patients suspected to have CAD referred for CTCA or ICA, Symptomatic patients with low-to-intermediate likelihood of CAD referred for CTCA
Schmidt et al. (2019)[10]	Retrospective, comparative analysis of pooled data (3 trials)	2245 patients Intervention: CADScor V3 Comparators: UDF Reference Standard: ICA	Patients with low-to-intermediate likelihood of CAD
Renker et al. (2021)[14]	Comparative study	213 patients Intervention: CADScor V3 Comparators: UDF Reference Standard: ICA	Patients suspected to have CAD referred to ICA
Schnaubelt et al. (2022)[17]	Single-arm study	101 patients Intervention: CADScor V3 Comparators: None Reference Standard: NA	Hemodynamically stable symptomatic patients in an ED
Rasmussen et al. (2023)[15]	Single-arm study	1683 patients Intervention: CADScor (Version not specified) Comparators: None Reference standard: ICA	Symptomatic patients referred for CTCA
Javanbakht et al. (2021)[16]	Economic analysis	Intervention: CADScor V3 Comparators: None Reference Standard: NA	NA
Supplementary evidence Base			
Winther et al. (2021)[18]	Single-arm study	1464 patients Intervention: CADScor V2, CADScor V3	Symptomatic patients referred for CTCA

		Comparators: None Reference Standard: NA	
Abbreviations: CAD, Coronary artery disease; CTCA, Computed tomography coronary angiography; ED, Emergency department; ICA, Invasive coronary angiography; NA, Not applicable NICE, National Institute for Health and Care Excellence.			

Appendix C: Supplementary tables and figures

Table C1: Diagnostic accuracy of CAD from evidence base

Study	Number of patients (Reference Standard)	Interventions and Comparators	AUC (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NICE (2019)[11]	255 (ICA)	CADScor V2	72.0	NR	NR	NR	NR
		UDF	79.0 (p=0.12)[a]	NR	NR	NR	NR
		CADScor V2 + UDF	82.0 (p<0.01)[a]	NR	NR	NR	NR
		CACS	86.0 (p<0.01)[a]	NR	NR	NR	NR
	1675 (ICA)	CADScor V3	72.4	80.4	53.0	16.4	95.9
Schmidt (2019)[10]	2334 (ICA)	CADScor V3	75.0	88.7	41.5	13.7	97.2
		UDF	74.1 (p=0.64)[b]	96.7	17.9	10.9	98.1
Renker (2021)[14]	213 (ICA)	CADScor V3	66.1	97.6	14.5	41.7	90.5
		UDF	66.6 (p=0.69)[b]	100.0	0.0	39.4	N.A.
Rasmussen (2023)[15]	1683 (ICA)	CADScor V3	NR	85.4	40.4	16.1	95.4

[a]AUC of CADScor V2 was used as reference.

[b]AUC of CADScor V3 was used as reference.

Abbreviation: AUC, Area under curve; CAD, Coronary artery disease; ICA, Invasive coronary angiography; NICE, National institute for health and care excellence; NPV, Negative predictive value; N.A., Not applicable; NR, Not reported; PPV, Positive predictive value; UDF, Updated Diamond-Forrester score.

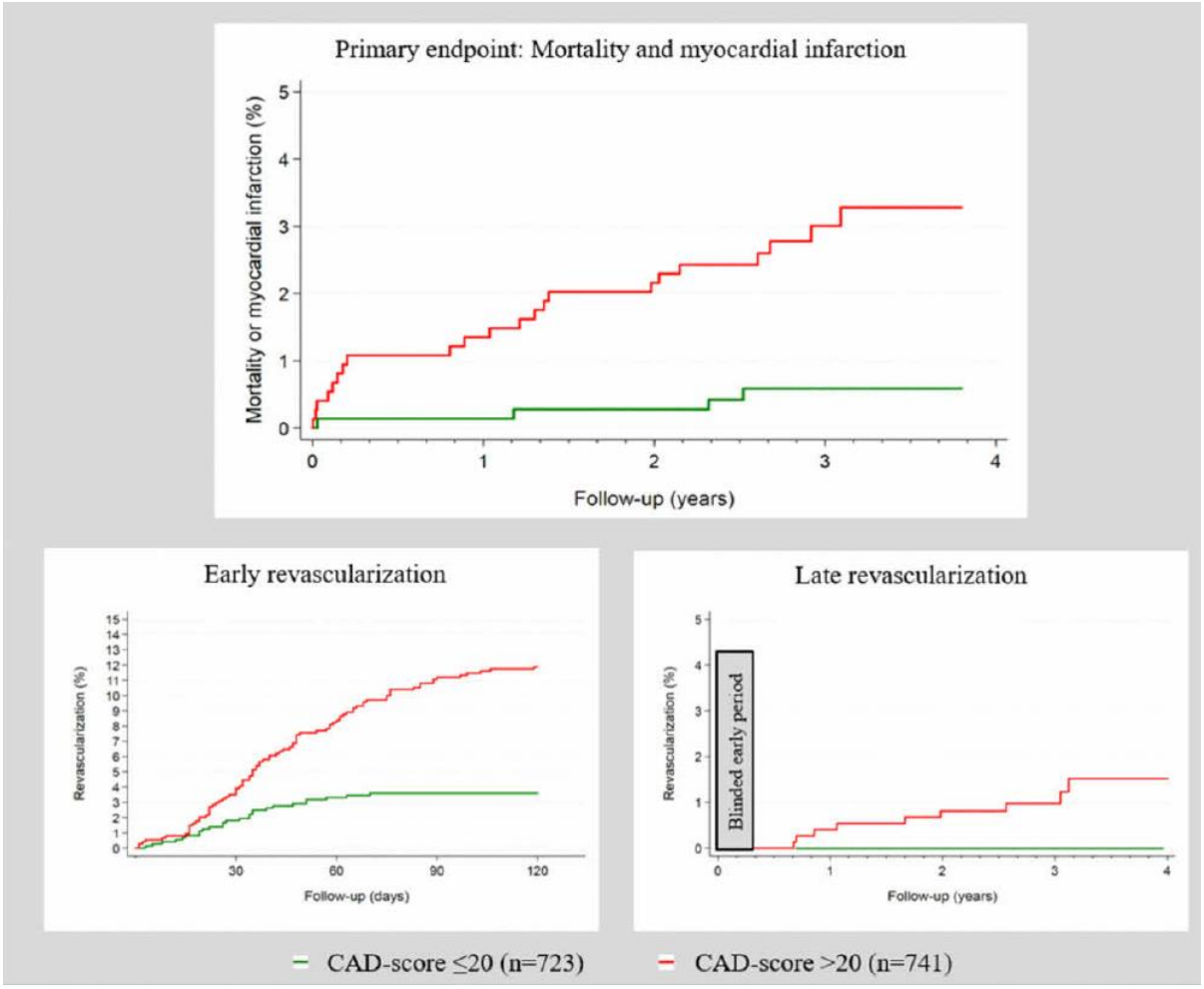

Figure C1: Primary and secondary endpoints according to the CAD-score. Adapted from Winther et al.[18] Abbreviation: CAD, Coronary artery disease.

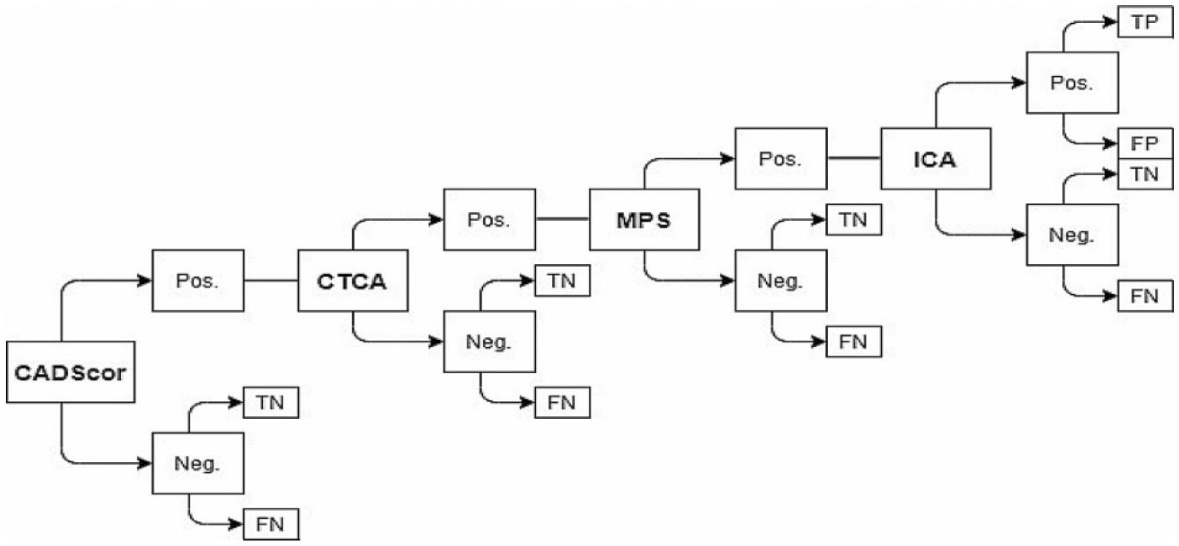

Figure C2: Decision tree economic model. Adapted from Javanbakht et al.[16] Abbreviations: CTCA, Computed tomography coronary angiography; FN, False negative; FP, False positive; ICA, Invasive coronary angiography; MPS, Myocardial perfusion scan; Neg., Negative; Pos., Positive; TN, True negative; TP, True positive.

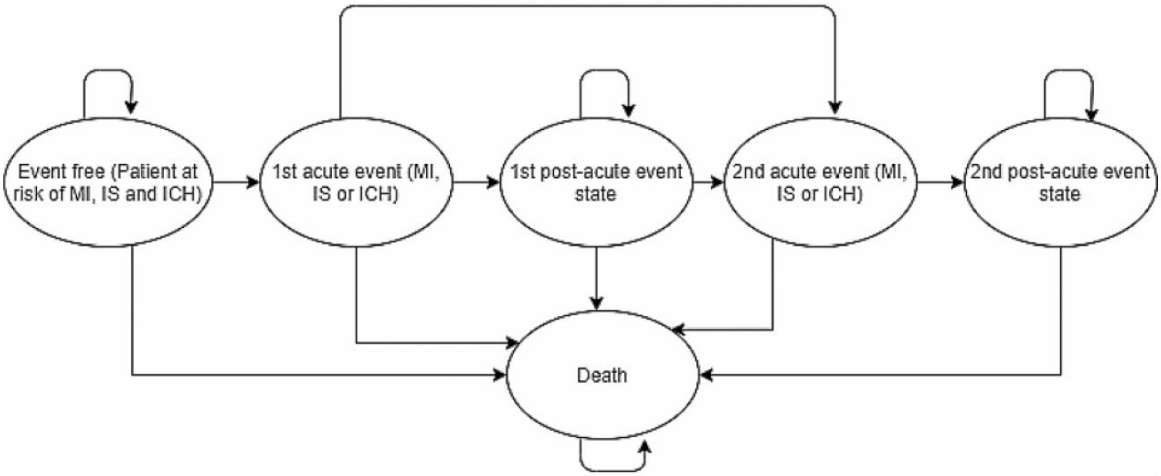

Figure C3: Markov economic model. Adapted from Javanbakht et al.[16] Abbreviations: ICH, Intracranial haemorrhage; IS, Ischaemic stroke; MI, Myocardial infarction.