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CADScor®System
Coronary Artery Disease (CAD) Diagnostic Aid

Unmet Need

Predictive Risk Stratification New onset stable chest pain is a common problem. Distinguishing between serious and benign chest pain is imperative, however the risk status in suspected significant coronary artery disease (CAD) is not well defined.[1]
There are many diagnostic testing options to evaluate the presence of significant coronary artery disease.[1] Many of these involve complex or invasive procedures (e.g. invasive coronary angiography), additional patient visits, the potential for increased or unnecessary healthcare system costs, and radiation exposure.[2] Nine out of ten patients assessed with stable chest pain in clinical studies do not have significant coronary artery disease.[3-5]
Using the CAD-score to risk stratify patients prior to further testing reduces unnecessary evaluation and risks. The CAD-score can thus aid the decision to initiate additional evaluations or not, or to observe the patient further prior to additional evaluations. The presence of other patient risk factors or conditions may influence this decision.[6]

Patient Access to Care Risk stratification can be especially challenging in care settings with limited cardiology resources or lack of access to diagnostic testing (i.e. rural settings, Medicaid and Medicare populations). Primary care risk stratification mitigates potential cardiology referrals access issues (i.e. lack of transportation, scheduling backlog), which may impact cardiac patient's follow up cardiac care compliance.

Technology

FDA Clearance The CADScor®System is an FDA De Novo cleared device (DEN190047) class II device, indicated for use as a diagnostic aid in symptomatic patients suspected of stable coronary artery disease (CAD) without a previous diagnosis of CAD.[7]

First-line Coronary Diagnostic Aid The CADScor®System can rapidly and accurately rule out significant coronary artery disease early in the diagnostic pathway, thus providing physicians, healthcare providers and healthcare systems with a non-invasive, first-line diagnostic aid for point-of-care risk stratification for patients who are experiencing stable chest pain to assess if additional invasive testing is indicated.[6]
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The CADScor®System Manufactured by Acarix, the CADScor®System is a point-of-care sensitive acoustics and advanced computational processing to analyze coronary blood flow to rule out significant coronary artery disease (CAD) in patients experiencing stable chest pain. The CADScor® System records heart sounds, murmurs, and vibration for calculation of a patient-specific score, indicating the risk of coronary stenosis, as an aid in cardiac analysis and diagnosis.[7]
The CAD-score is a patient specific heart murmur score indicative of Coronary Artery Disease (CAD)/Chronic Coronary Syndrome (CCS) for immediate risk stratification. The CAD-score can thus aid the decision to initiate additional evaluations, or to observe the patient further prior to additional evaluations.[6]

Mechanism of Action The CADScore®System uses highly sensitive acoustics and advanced AI to analyze coronary blood flow to rule out significant coronary artery disease (CAD) in patients experiencing stable chest pain.[6]

The CADScor®System is indicated as follows:
The intended use of the CADScor®System is to record heart sounds, murmurs and vibration for calculation of a patient specific score, indicating the risk of presence of coronary stenosis, as an aid in cardiac analysis and diagnosis.[7]

Published Clinical Data Several published clinical studies demonstrate the efficacy of the CADScor®System. Of note, are two peer reviewed published studies with independent patient populations (n=3977) demonstrating that a score of 20 or less indicates no significant CAD, with a negative predictive value (NPV) of 95.4%-97.2%.[8,9] The FDA labeling for the CADScor®System is an NPV of 96.2%.[6]

National Institute For Health and Care Excellence (NICE) NICE MIB defines CADScor®System as a as a stable coronary artery disease rule-out method after first clinical evaluation (clinical history, physical examination, 12-lead ECG) and before CT coronary angiography (CTCA). (www.nice.org.uk/advice/mib174/chapter/summary)

References

1. Gulati, Martha et al. "2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines." Circulation vol. 144,22 (2021): e368-e454. doi:10.1161/CIR.0000000000001029
2. Shaw LJ, Marwick TH, Zoghbi WA, Hundley WG, Kramer CM, Achenbach S, Dilsizian V, Kern MJ, Chandrashekhar Y, Narula J. Why all the focus on cardiac imaging? JACC Cardiovasc Imaging. 2010 Jul;3(7):789-94. doi: 10.1016/j.jcmg.2010.05.004. PMID: 20633864.
3. Therming C, et al. Eur Heart J Qual Care Clin Outcomes. 2018; 4:301-308
4. Winther S, et al. Heart 2018;104:928–935 (Dan-NICAD I)
5. Douglas et al, N Engl J Med 2015;372:1291-300 (Promise)
6. User manual US-FDA v.12.Y, prevalence 10,7%
7. https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN190047.pdf
8. Schmidt SE, Winther S, Larsen BS, et al. Coronary artery disease risk reclassification by a new acoustic-based score. Int J Cardiovasc Imaging. 2019;35(11):2019-2028. doi:10.1007/s10554-019-01662-1 https://pubmed.ncbi.nlm.nih.gov/31273633/
9. Rasmussen LD, Winther S, Karim SR, et al. Likelihood reclassification by an acoustic-based score in suspected coronary artery disease [published online ahead of print, 2023 Mar 16]. Heart. 2023;heartjnl-2023-322357. doi:10.1136/heartjnl-2023-322357 https://pubmed.ncbi.nlm.nih.gov/36878672/

CADScor®System Published Data

Study: Coronary artery disease risk reclassification by a new acoustic-based score;

Schmidt SE et al. The International Journal of Cardiovascular Imaging. 2019 Nov;35(11):2019-2028.
Retrospective Study n=2,245, 3 OUS Sites (PUBMED link)

OBJECTIVE: To determine the potential of CADScor System to reclassify patients with intermediate pre-test probability (PTP) and clinically suspected stable coronary artery disease (CAD) into a low probability group thereby ruling out significant CAD.

KEY FINDINGS: Reports results from three clinical studies (AdportCAD, Dan NICAD I, and BIO-CAC) combined, which was the dataset submitted for FDA clearance.

CAD-scores compared to gold standards (C & ICA).

CAD defined as ≥ 50% stenosis in vessel ≥ 2 mm

Performance:
- AUC=75% (CI: 71-79%)
- Sensitivity=89% (CI: 84-92%)
- Specificity=42% (CI: 40-44%)
- NPV=97% (CI: 96-98%)
- PPV=14% (CI: 12-16%)

Study: Diagnostic performance of an acoustic-based system for coronary artery disease risk stratification (Dan-NICAD I);

Winther S et al. Heart 2018 June;104:928–935.
Observational Study; n=1,675 2 OUS Sites (PUBMED link)

OBJECTIVE: The aim of this study was to test the diagnostic accuracy of a new portable acoustic device for detection of CAD.

KEY FINDINGS: In this large, first of its kind prospective trial, demonstrated that acoustic detection of CAD enables risk stratification in patients with suspected CAD.

CAD-scores compared to gold standards (CCTA & ICA).

Similar NPV when CAD assessed by QCA and FFR

CAD defined as ≥ 50% stenosis in vessel ≥ 2 mm

Performance:
- AUC=72% (CI: 68-77%)
- Sensitivity=80% (CI: 73-87%)
- Specificity=53% (CI: 50-56%)
- NPV=96% (CI: 94-97%)
- PPV=16% (CI: 14-19%)

Study: Likelihood reclassification by an acoustic-based score in suspected coronary artery disease (Dan-NICAD II);

Rasmussen L et al. Heart 2023 June;109(16), 1223–1230.
Observational Study; n=1,732 4 OUS Sites (PUBMED link)

OBJECTIVE: (1) To investigate the diagnostic performance of an acoustic-based CAD score and (2) study the reclassification potential of a dual likelihood strategy by the ESC-PTP and a CAD score.

KEY FINDINGS: Confirmed high NPV seen in Dan NICAD I in an independent patient population.

CAD-scores compared to gold standards (CCTA & ICA).

Similar NPV when CAD assessed by QCA and FFR

CAD defined as ≥ 50% stenosis in vessel ≥ 2 mm

Performance:
- AUC=70% (CI: 67-75%)
- Sensitivity=85% (CI: 80-90%)
- Specificity=40% (CI: 38-43%)
- NPV=95% (CI: 93-97%)
- PPV=16% (CI: 14-19%)

Study: Advanced heart sound analysis as a new prognostic marker in stable coronary artery disease;

Winther S, et al. European Heart Journal – Digital Health 2021 Mar;2(2): 279–289.
N=1,464 3 OUS Sites Clinical Trial #: NCT02264717 (PUBMED link)

OBJECTIVE: To investigate the prognostic value of heart sound analysis as two scores, the Acoustic-score, and the CAD-score, in patients with suspected CAD which is treated according to standard of care.

KEY FINDINGS: Significant decrease in combined primary endpoint (all-cause mortality and myocardial infarction) between patients with low and elevated CAD-score. No MI events in the low-risk CAD-score group.

Median follow up 3.1 years (Dan NICAD I cohort)

Study: Acoustic-based rule out of stable coronary artery disease: the FILTER-SCAD trial	
Bjerking LH et al. European Heart Journal, Published online September 1, 2024 Randomized trial, N=2,008, 6 OUS Sites Clinical Trial #: NCT04121949 (PUBMED link)	
OBJECTIVE: To investigate whether providing a CAD score and pre-test probability (PTP) to cardiologists was superior to PTP alone in limiting unnecessary testing	**KEY FINDINGS**: 23% reduction in unnecessary testing seen in low-risk patients (ESC PTP ≤ 5%) and fewer patients in the CAD-score group (2% vs. 29%) pursued additional testing suggesting a reassuring effect of the CAD-score strategy. Also 32% reduction in unnecessary testing at the Swedish site (high protocol compliance). CAD-scores were collected on 95% of patients. 40% of patients were deemed low risk by their CAD-score. MACE were low for all patients (2.5% at one year). Low protocol/guideline compliance noted by the investigators, clear signs of over testing in the population.
Health Economic Analysis: Economic Analysis of the CADScor System for Ruling Out Coronary Artery Disease in England;	
Javanbakht, M et al. PharmacoEconomics - open vol. 6,1 (2022): 123-135; (PUBMED link) .Data modeled from Dan-NICAD I Observational Study; n=1,675 2 OUS Sites (PUBMED link)	
OBJECTIVE: Our objective was to assess the cost utility of the CADScor System for the diagnosis of CAD at an early stage in the diagnostic testing pathway in England.	**KEY FINDINGS**: Findings indicated that the introduction of the CADScor System resulted in per-patient overall cost savings of £131 over a 1-year time horizon. This equates to over £92.6 million cost savings per each annual cohort of patients who have CAD symptoms and need further assessment in England.
Health Economic Analysis: COST-EFFECTIVENESS OF THE CADSCOR SYSTEM IN LOW RISK PATIENTS PRESENTING TO THE EMERGENCY DEPARTMENT WITH CHEST PAIN	
Baron, S et al. J Am Coll Cardiol. 2024 Apr, 83 (13_Supplement) 1300. Data modeled from Dan-NICAD I Observational Study; n=1,675 2 OUS Sites (PUBMED link)	
OBJECTIVE: To assess the cost utility of the CADScor System for the diagnosis of CAD in a low-risk emergency department patient population.	**KEY FINDINGS**: Results demonstrated that the CADScor System was economically dominant over other non-invasive cardiac tests without a substantial difference in adverse events. Economic results were consistent when CAD prevalence rates were varied from 2-30%. The overall cost savings was estimated to be $104.7 to 185.4 million USD per 100,000 patients.

*Note: Computed tomography is an ACC/AHA guideline class I recommendation for intermediate pre-test probability stable chest pain patients <65 years of age suspected of significant CAD (Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2021 Nov 30;144(22):e455]. Circulation. 2021;144(22):e368-e454. doi:10.1161/CIR.0000000000001029)

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ORIGINAL PAPER

Coronary artery disease risk reclassification by a new acoustic-based score

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Abstract
To determine the potential of a non-invasive acoustic device (CADScor®System) to reclassify patients with intermediate pre-test probability (PTP) and clinically suspected stable coronary artery disease (CAD) into a low probability group thereby ruling out significant CAD. Audio recordings and clinical data from three studies were collected in a single database. In all studies, patients with a coronary CT angiography indicating CAD were referred to coronary angiography. Audio recordings of heart sounds were processed to construct a CAD-score. PTP was calculated using the updated Diamond-Forrester score and patients were classified according to the current ESC guidelines for stable CAD: low < 15%, intermediate 15–85% and high > 85% PTP. Intermediate PTP patients were re-classified to low probability if the CAD-score was ≤ 20. Of 2245 patients, 212 (9.4%) had significant CAD confirmed by coronary angiography (≥ 50% diameter stenosis). The average CAD-score was higher in patients with significant CAD (38.4 ± 13.9) compared to the remaining patients (25.1 ± 13.8; p < 0.001). The reclassification increased the proportion of low PTP patients from 13.6% to 41.8%, reducing the proportion of intermediate PTP patients from 83.4% to 55.2%. Before reclassification 7 (3.1%) low PTP patients had CAD, whereas post-reclassification this number increased to 28 (4.0%) (p = 0.52). The net reclassification index was 0.209. Utilization of a low-cost acoustic device in patients with intermediate PTP could potentially reduce the number of patients referred for further testing, without a significant increase in the false negative rate, and thus improve the cost-effectiveness for patients with suspected stable CAD.

Keywords Stable coronary artery disease · Heart sounds · Non-invasive testing · Reclassification · Cost-effectiveness · Ultrasensitive phonocardiography

Introduction

For detection of stable coronary artery disease (CAD), patients undergo risk stratification, non-invasive and invasive testing [1]. However, recent studies have demonstrated that as low as 6–10% of patients referred to non-invasive testing suffer from significant CAD [2–4]. A safe and low-cost rule-out test reducing the number of patients with non-obstructive CAD referred to non-invasive testing could therefore reduce costs and potential risk of complications.

One approach for a simple and efficient tool for ruling out CAD is the automated analysis of heart sounds to identify abnormalities such as weak murmurs related to

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post stenotic turbulent flow in the coronary arteries [5] and abnormal myocardial vibration patterns [6, 7]. The first report of CAD-related heart sounds originates from the late sixties [8]. Since then a wide range of signal processing algorithms for detection of CAD have been proposed [7, 9–16]. Recently some of these methods have undergone clinical testing [2, 17–20]. One method is the automated stethoscope-like device (CADScor®System, Acarix A/S), which obtains heart sounds from the coronary circulation and myocardium during a 3 min recording period at the 4th left intercostal space. A CAD-score on a scale from 0 to 99 is estimated immediately after the recording using an integrated algorithm performing advanced analysis of the heart sounds in combination with age, gender and blood pressure information. A CAD-score ≤ 20 indicates low probability of CAD and a recent study demonstrated a negative predictive value of 96% in a low to intermediate probability population [2], positioning the device as a potential early rule-out modality before more extensive testing.

In the current study we assessed the potential of the CAD-score algorithm to reclassify patients suspected of stable CAD from intermediate to low likelihood of CAD, to illustrate the rule-out capacity of the CADScor®System.

Methods

Study population

Heart sound recordings and patient data from three clinical studies were combined in a database. In short, the Acoustic Data collection for Optimizing CAD-score Algorithm study (AdoptCAD, NCT01564628) included 255 subjects referred for either coronary CT angiography (CTA) or coronary angiography (CAG) [21]. Patients where CTA identified a stenosis were further referred to CAG. A total of 249 patients had a heart sound recording. In the Dan-Risk 5-year follow-up study (BIO-CAC; NCT02913144), a heart sound recording was obtained in 661 asymptomatic subjects undergoing coronary artery calcium scoring (CACS) [22, 23]. Subjects with a CACS above 400 were offered myocardial scintigraphy and subjects with a CAD-score (algorithm version 2) above 37 (n = 60) were offered CTA. Subjects with a positive CTA or myocardial scintigraphy test were offered CAG (n = 12). In the Dan-NICAD study (NCT02264717), heart sound recordings were successfully obtained in 1563 of 1675 patients with low to intermediate pre-test probability (PTP) referred for CTA with suspicion of CAD [2, 24]. Patients with at least one obstructive stenosis identified at CTA were referred for CAG. All studies were conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the studies. The local scientific ethics committees approved the research protocols.

The CAD-score

A CAD-score was estimated using an offline version of the CAD-score algorithm version 3.1 as embedded in the current CADScor®System. The CAD-score device obtains two recording: first 30 s of pre-test recording to validate the sound quality, next if the pre-test recording passes the algorithm quality control, 150 s are recorded. The heart sound signal is obtained by ultrasensitive phonocardiography using a microphone attached at the 4th intercostal space just to the left of the sternum. The algorithm automatically segments the heart sounds into systolic and diastolic periods [25]. Then the sounds are filtered before eight acoustic features that describe relevant properties of the heart sounds are extracted from the diastolic and systolic periods [2, 6, 26, 27]. These features are combined into an acoustic score using a linear discriminant function. Using logistic regression, the acoustic score is combined with gender, age, and hypertension (systolic blood pressure ≥ 140 mmHg or current treatment with antihypertensive medication) to generate the CAD-score. The CAD-score is scaled so that 90% of patients with CAD have a CAD-score > 20. Hence, a CAD-score value > 20 is categorized as abnormal, for further details see the online supplementary in Winther et al. [2].

The current algorithm version 3.1 was developed and calibrated in a subset including 1201 patients from the current database as described by Winther et al. [2]. Before final implementation of the algorithm in the device, model coefficients for both the linear discriminant analyses and logistic regression and the scaling were fine-tuned in the complete database reported here.

Reclassification

A simple reclassification scheme was applied to reclassify the probability of CAD in symptomatic patients with suspected CAD from the AdoptCAD and the Dan-NICAD study. PTP was calculated using the updated Diamond-Forrester score [28] according to the ESC guidelines [1]: low < 15%, intermediate 15–85% and high PTP > 85%. Patients in the intermediate PTP group (15–85%) were reclassified using the CAD-score. Patients with an intermediate PTP and a CAD-score ≤ 20 were reclassified to low probability, while patients from the intermediate PTP with a CAD-score > 20 were kept as intermediate probability. Patients with low (< 15%) or high (> 85%) PTP were not reclassified.

Diagnosis

The disease level was divided into three levels: non-CAD, mild-CAD and significant-CAD. Significant-CAD is defined as having a stenosis with at least 50% diameter reduction defined by CAG [29]. Non-CAD is defined as having a CACS at zero and no stenosis identified at CTA. Mild-CAD is having some degree of CAD either CACS higher than zero or having an insignificant stenosis ether by CTA or CAG. Since the diagnostic flow differs from study to study, specific supplementary rules are used in coding of the AdoptCAD and the BIO-CAC study (Supplementary Table 1).

Statistical analysis

Variables are expressed as mean (±standard deviation (SD) or total range). Categorical variables are reported as frequencies (percentages). The unpaired Student t test and ANOVA test were used for comparison between continuous variables. The chi square test was used for comparison between categorical variables. Pearsons correlation was used to analyse correlations between variables. The area under the receiver-operating characteristic (AUC) curve was calculated for continuous variables and in paired designs compared with the method described by DeLong et al. [30] and in unpaired cases with the method of Hanley et al. [31]. The CAD-score was divided as a binary variable with a cut point of 20 and the updated Diamond-Forrester score using a cut point of 15 to calculate sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratio (PLR and NLR). Performance values are presented with 95% confidence intervals. The post-test probability was calculated using pre-test odds and likelihood ratios by Bayesian statistics. Statistical analyses were performed using Matlab R2017b (MathWorks, US).

Since the current CAD-score algorithm version 3.1 is finetuned in the complete database, the current results could be a result of overfitting of the linear discriminant analysis and logistic regression. To test for overfitting, we did a 50 times repeated tenfold cross-validation test where both the linear discriminant analysis and the logistic regression were re-trained [32].

Results

In the pooled population, 2473 patients had at least one acoustic heart sound recording. A CAD-score with algorithm version 3.1 could be calculated in 2334 (94%) of the patients, the remaining 139 were excluded from the current analyses. Reasons for not obtaining a CAD-score were arrhythmia (n = 27), algorithm related errors (n = 60), too much noise/too weak heart sounds (n = 34) or missing clinical information such as symptoms or hypertension status (n = 18). Finally, 89 (3.6%) patients were excluded since they could not be assigned a disease level according the diagnostic scheme. The remaining 2245 patients were included in the current analyses.

The mean age of the population was 58.3 ± 8.4 years and included 1185 (52.8%) females and 1060 (47.2%) males (Table 1). The mean PTP for significant CAD according to the updated Diamond-Forrester score was 36.4%. A total of 370 (16.5%) patients had a PTP below 15%, 1824 (81.2%) a PTP between 15 and 85% and 51 (2.3%) had a PTP above 85%. CACS was conducted in 2239 patients (99.7%), 1614 patients (71.9%) underwent CTA and 455 (20.3%) underwent CAG. In total 212 (9.4%) patients had significant-CAD documented by CAG, 44.2% had mild-CAD and 46.4% had non-CAD (Supplementary Table 2).

The CAD-score

The average CAD-score in the pooled population was 26.4 ± 14.3. The average CAD-score was significantly higher in significant-CAD patients 38.4 ± 13.9 versus 25.1 ± 13.8 in the remaining patients ($p < 0.001$). The distribution of CAD-scores by disease level is shown in Fig. 1. There was a significant stepwise increase in the average CAD-score with increasing severity of disease level (Supplementary Table 3). In 300 patients, one additional recording was obtained after the first recording, the intra-patient correlation between the first and the second CAD-score was $r = 0.973$ ($p < 0.0001$).

Reclassification

Of 1673 patients referred for testing due to suspected CAD (patients from the AdoptCAD and the Dan-NICAD study), 227 (13.6%) patients were classified as having a low likelihood of CAD (< 15%) according to the PTP estimated by the updated Diamond-Forrester score. Post CAD-score-test this number increased to 699 (41.8%), thus reducing the number of patients classified with intermediate likelihood from 1395 (83.4%) to 923 (55.2%) (Fig. 2). Before testing 7 (3.1%) low PTP patients had significant-CAD, whereas post-reclassification this number increased to 28 (4.0%) ($p = 0.52$). The net reclassification index was 0.209.

Diagnostic performance

When separating significant-CAD patients from other patients (non-CAD and mild-CAD) the AUC of the CAD-score was 0.750 (0.710–0.789) (Fig. 3, Table 2). The sensitivity of a CAD-score > 20 was 88.7% (83.6–92.6%) and the specificity of a CAD-score ≤ 20 was 41.5% (39.4–43.7%). The NPV of a CAD-score ≤ 20 was 97.2% (95.9–98.2%) while the PPV of a CAD-score > 20 was 13.7% (11.9–15.6%). The NLR and

Table 1 Baseline characteristics of included studies

	All	AdoptCAD	Dan-NICAD	BIO-CAC
N	2245	199	1474	572
Sex (female)	1185 (52.8%)	93 (46.7%)	771 (52.3%)	321 (56.1%)
Age	58.3 ± 8.4 [20–86]	61.9 ± 11.0 [20–86]	57.1 ± 8.8 [40–80]	60.1 ± 5.0 [54–66]
BMI	26.9 ± 4.2	27.0 ± 4.3	26.6 ± 4.2	27.5 ± 4.4
Hypertension	1313 (58.5%)	137 (68.8%)	878 (59.6%)	298 (52.1%)
Dyslipidemia	1706 (76%)	159 (79.9%)	1100 (74.6%)	447 (78.1%)
Smoking				
Never	1068 (47.6%)	71 (35.7%)	712 (48.3%)	285 (49.8%)
Former	817 (36.4%)	86 (43.2%)	537 (36.4%)	194 (33.9%)
Active	360 (16.0%)	42 (21.1%)	225 (15.3%)	93 (16.3%)
Diabetes	118 (5.3%)	19 (9.6%)	75 (5.1%)	24 (4.2%)
Family history of CAD				
Yes	680 (30.3%)	0 (0%)	548 (37.2%)	132 (23.1%)
No	1346 (60.0%)	0 (0%)	926 (62.8%)	420 (73.4%)
Undefined	219 (9.8%)	199 (100%)	0 (0%)	20 (3.5%)
Symptoms				
Typical chest pain	490 (21.8%)	85 (42.7%)	399 (27.1%)	6 (1.1%)
Atypical chest pain	608 (27.1%)	81 (40.7%)	505 (34.3%)	22 (3.9%)
Non-specific symptoms	649 (28.9%)	33 (16.6%)	570 (38.7%)	46 (8.0%)
None	498 (22.2%)	0 (0%)	0 (0%)	498 (87.1%)
Updated Diamond-Forrester score	36.4% ± 21.2%	51.1% ± 24.2%	38.6% ± 21.5%	25.9% ± 13.3%
Pre-test probability groups				
< 15%	370 (16.5%)	14 (7.0%)	213 (14.5%)	143 (25.0%)
15–85%	1824 (81.2%)	165 (82.9%)	1230 (83.4%)	429 (75.0%)
> 85%	51 (2.3%)	20 (10.1%)	31 (2.1%)	0 (0%)

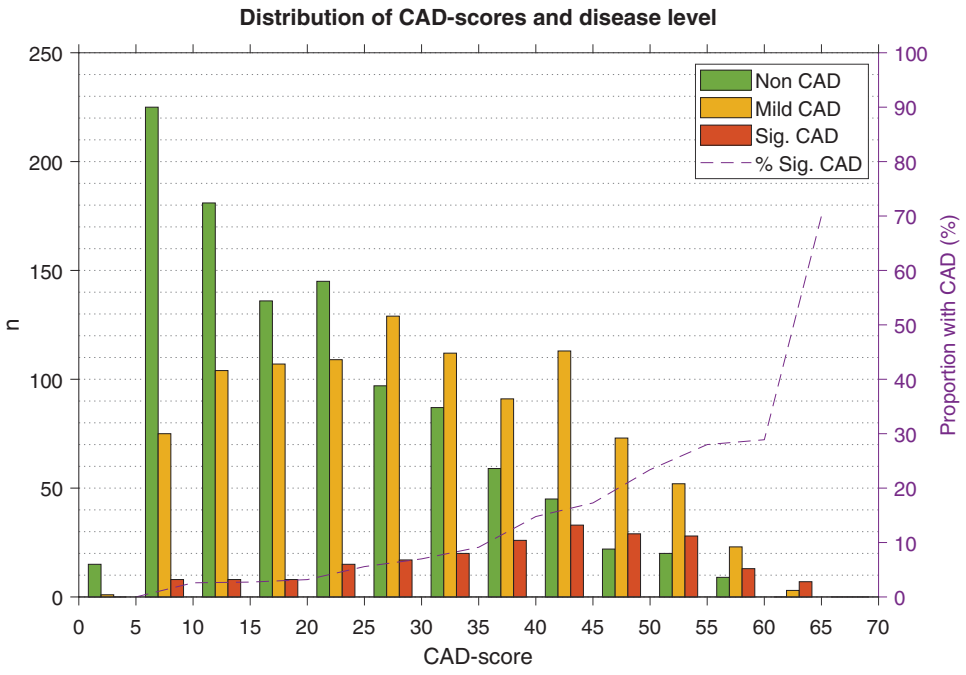

Fig. 1 Histogram showing the distribution of CAD-scores in Non-CAD, Mild-CAD and Significant-CAD patients. The dashed line shows the proportion of significant-CAD patients in each bin

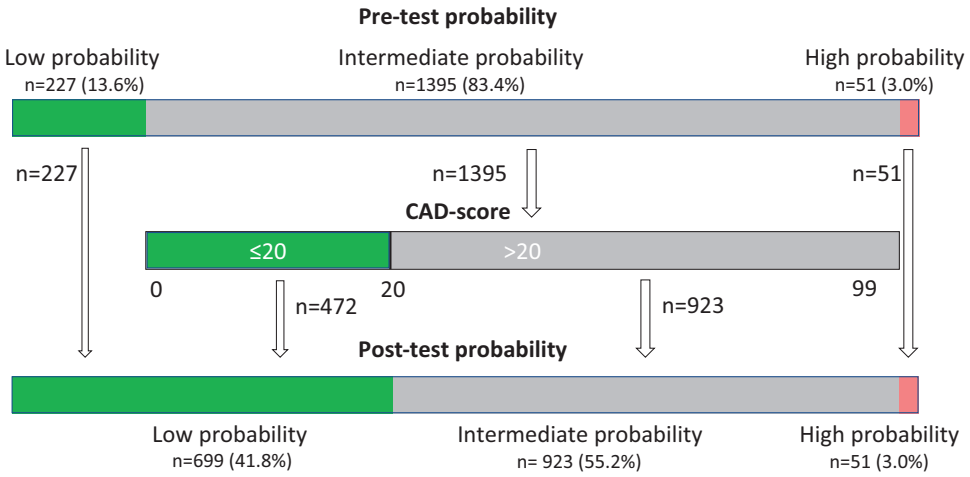

Fig. 2 Reclassification results using the propose reclassification scheme where patients with an intermediate PTP is reclassified to low probability in case of CAD-score ≤ 20

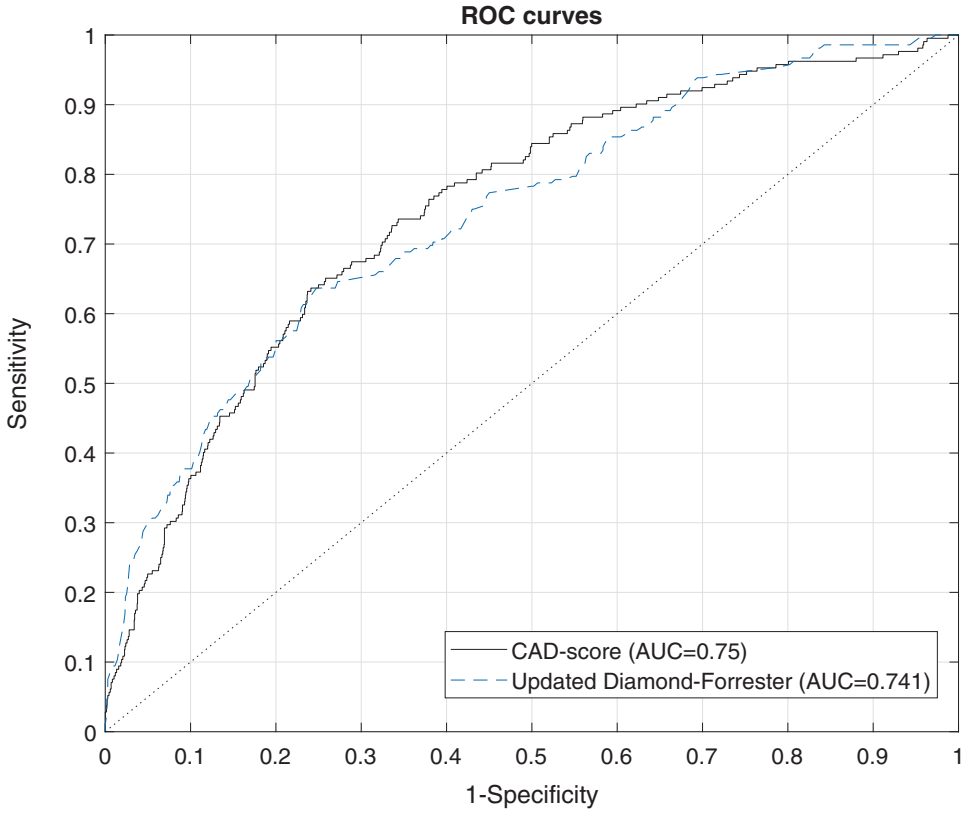

Fig. 3 Receiving operating characteristics curve of the CAD-score and the updated Diamond-Forrester score

PLR were 0.27 and 1.52, respectively (Table 2). An increasing CAD-score was associated with a higher risk of having CAD (Fig. 1).

The AUC of the cross-validation, testing for overfitting, was 0.741, which is 0.009 lower than the AUC of the concluding CAD-score.

Comparison to the updated Diamond-Forrester score

The AUC of the CAD-score was marginally superior to the updated Diamond-Forrester score; 0.750 versus 0.741 (p = 0.64) when separating significant-CAD patients from

Table 2 Diagnostic performance of the CAD-score and the updated Diamond-Forrester score (significant-CAD vs. other)

	All	AdoptCAD	Dan-NICAD	BIO-CAC
CAD-score				
N: Other (Non-CAD and Mild-CAD)	2033	141	1321	571
N: Significant-CAD	212	58	153	1
Prevalence of CAD	9.4%	29.1%	10.4%	0.2%
True negative	844	44	565	235
False negative	24	1	23	0
False positive	1189	97	756	336
True positive	188	57	130	1
AUC	0.750 (0.710–0.789)	0.768 (0.690–0.846)	0.720 (0.673–0.768)	–
Negative predictive value (p = 0.008)	97.2% (95.9–98.2%)	97.8% (88.2–99.9%)	96.1% (94.2–97.5%)	–
Positive predictive value (p < 0.001)	13.7% (11.9–15.6%)	37% (29.4–45.2%)	14.7% (12.4–17.2%)	–
Sensitivity (p = 0.02)	88.7% (83.6–92.6%)	98.3% (90.8–100%)	85% (78.3–90.2%)	–
Specificity (p = 0.03)	41.5% (39.4–43.7%)	31.2% (23.7–39.5%)	42.8% (40.1–45.5%)	41.2% (37.1–45.3%)
Likelihood ratio positive	1.52	1.43	1.49	–
Likelihood ratio negative	0.27	0.06	0.35	–
Updated Diamond-Forrester score				
N: Other (Non-CAD and Mild-CAD)	2033	141	1321	571
N: Significant-CAD	212	58	153	1
Prevalence of CAD	9.4%	29.1%	10.4%	0.2%
True negative	363	14	206	143
False negative	7	0	7	0
False positive	1670	127	1115	428
True positive	205	58	146	1
AUC	0.741 (0.702–0.781)		0.661 (0.612–0.71)	–
Negative predictive value (p = 0.072)	98.1% (96.1–99.2%)	100% (76.8–100%)	96.7% (93.3–98.7%)	–
Positive predictive value (p < 0.001)	10.9% (9.56–12.4%)	31.4% (24.7–38.6%)	11.6% (9.86–13.5%)	–
Sensitivity (p = 0.25)	96.7% (93.3–98.7%)	100% (93.8–100%)	95.4% (90.8–98.1%)	–
Specificity (p < 0.001)	17.9% (16.2–19.6%)	9.93% (5.54–16.1%)	15.6% (13.7–17.7%)	25% (21.5–28.8%)
Likelihood ratio positive	1.18	1.11	1.13	–
Likelihood ratio negative	0.18	0	0.29	–

Negative predictive values, specificity, True Negative, False Negative and Likelihood ratio negative are calculated for CAD-scores ≤ 20 and updated Diamond-Forrester scores < 15%. Positive predictive values, sensitivity, True Positive, False Positive and Likelihood ratio positive are calculated for CAD-scores > 20 and updated Diamond-Forrester scores ≥ 15%

other patients (Table 2). In patients referred for testing due to suspected CAD (patients from the AdoptCAD and the Dan-NICAD study) the AUC of the CAD-score was 0.749 which was higher (p = 0.01) than the AUC of the updated Diamond-Forrester score 0.703 (p = 0.01). Similar in the Dan-NICAD study the CAD-score performed superior to the updated Diamond-Forrester score with AUCs of 0.720 versus 0.661 (p = 0.01) respectively. In the AdoptCAD study alone the updated Diamond-Forrester score performed comparable to the CAD-score with AUCs of 0.776 versus 0.768 (p = 0.79), respectively. The 15% PTP limit for the updated Diamond-Forrester score resulted in a sensitivity of 96.7% (93.3–98.7%) and a specificity of 17.9% (16.2–19.6%) (Table 2). Combining the CAD-score and the updated Diamond-Forrester score using a linear discriminant function increased the AUC significantly to 0.774 (p = 0.013 versus the CAD-score and p = 0.0002 versus the updated Diamond Forrester score) in the complete database.

Correlation to disease level and diagnostic performance in sub-groups

In patients undergoing CAG a weak correlation (r = 0.23, p < 0.0001) was found between the maximal stenosis degree and the CAD-score and a trend was seen towards an increase in CAD-score with increasing number of diseased vessels (r = 0.22, p < 0.0001) (Fig. 4). The CAD-score correlated with the logarithm of the CACS (r = 0.41, p < 0.0001). The negative predictive value was comparable between males and females, while the sensitivity of the CAD-score was

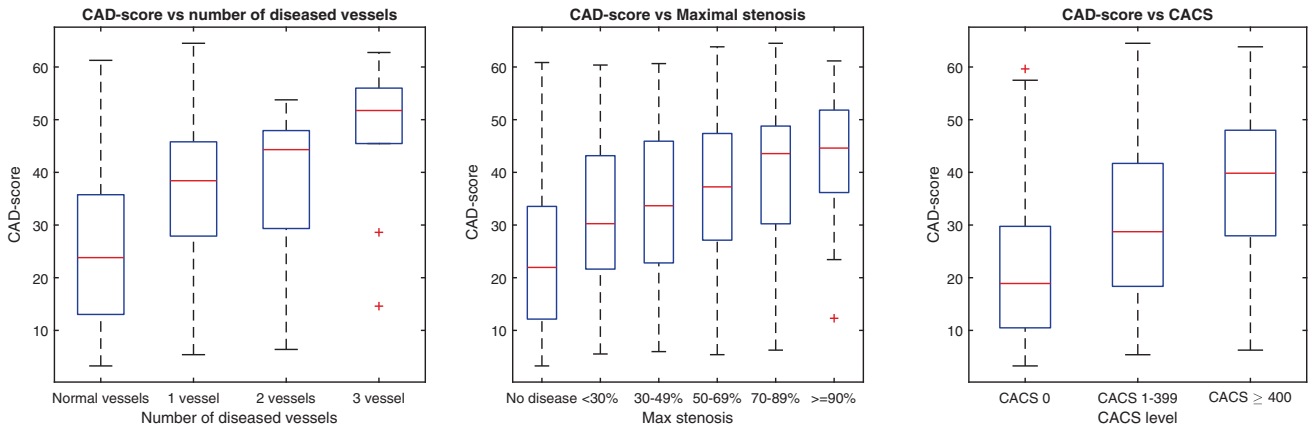

Fig. 4 Box plots of CAD-scores dependent on the number of diseased vessels, the maximal stenosis degree according to QCA and the CACS

Table 3 Diagnostic performance of the CAD-scores in sub-groups

	n	Prevalence	AUC	Sensitivity	Specificity	NPV	PPV
Gender		p < 0.0001	p = 0.36	p < 0.0001	p < 0.0001	p = 0.69	p < 0.0001
Males	1060	13.9%	0.720 (0.671–0.769)	94.6% (89.6–97.6%)	27.3% (24.4–30.3%)	96.9% (94.0–98.6%)	17.3% (14.8–20.1%)
Females	1185	5.5%	0.688 (0.615–0.761)	75.4% (63.1–85.2%)	53.1% (50.2–56.1%)	97.4% (95.8–98.5%)	8.54% (6.4–11.1%)
Diabetes		p = 0.0001	p = 0.15	p = 0.26	p < 0.0001	p = 0.61	p = 0.0061
Yes	118	19.5%	0.666 (0.535–0.797)	95.7% (78.1–99.9%)	22.1% (14.2–31.8%)	95.5% (77.2–99.9%)	22.9% (15.0–32.6%)
No	2127	8.9%	0.753 (0.712–0.794)	87.8% (82.3–92.1%)	42.5% (40.3–44.7%)	97.3% (95.9–98.3%)	13% (11.2–14.9%)
Symptoms		p < 0.0001	p = 0.0066	p = 0.012	p = 0.66	p = 0.076	p < 0.0001
Typical chest pain	490	19.6%	0.795 (0.739–0.851)	92.7% (85.6–97.0%)	43.7% (38.7–48.7%)	96.1% (92.1–98.4%)	28.6% (23.7–34.0%)
Atypical chest pain	608	9.9%	0.691 (0.614–0.768)	78.3% (65.8–87.9%)	41.2% (37.1–45.5%)	94.6% (90.9–97.1%)	12.7% (9.5–16.6%)
Non-specific symptoms	649	8.5%	0.746 (0.669–0.823)	92.7% (82.4–98.0%)	40.9% (36.9–45.0%)	98.4% (95.9–99.6%)	12.7% (9.6–16.3%)
BMI		p = 0.53	p = 0.013	p = 0.73	p < 0.0001	p = 0.66	p = 0.027
< 20	70	10.0%	0.823 (0.628–1.00)	100% (59.0–100%)	58.7% (45.6–71.0%)	100% (90.5–100%)	21.2% (9.0–38.9%)
20 and < 25	724	10.6%	0.791 (0.729–0.852)	89.6% (80.6–95.4%)	49.5% (45.5–53.4%)	97.6% (95.3–98.9%)	17.4% (13.8–21.5%)
25 and < 30	962	8.5%	0.706 (0.641–0.771)	86.6% (77.3–93.1%)	39.7% (36.4–43.0%)	96.9% (94.6–98.5%)	11.8% (9.3–14.6%)
30	483	9.3%	0.750 (0.666–0.835)	88.9% (75.9–96.3%)	31.5% (27.2–36.1%)	96.5% (92.0–98.9%)	11.8% (8.5–15.7%)
Heart valve disease*		p = 0.81	p = 0.53	p = 0.37	p = 0.006	p = 0.56	p = 0.90
Yes	58	10.3%	0.686 (0.440–0.930)	100% (54.1–100%)	23.1% (12.5–36.8%)	100% (73.5–100%)	13.0% (4.9–26.3%)
No	2187	9.4%	0.750 (0.710–0.790)	88.3% (83.2–92.4%)	42.0% (39.8–44.2%)	97.2% (95.9–98.2%)	13.7% (11.9–15.6%)

Negative predictive values (NPV) and specificity are calculated for CAD-scores ≤ 20. Positive predictive values (PPV) and sensitivity are calculated for CAD-scores > 20

*Only the Dan-NICAD included subjects with heart valve disease

higher in males compared to females.(Table 3). The CAD-score had similar sensitivity in all BMI groups, but there was a trend toward lower specificity with increasing BMI (Table 3). The sensitivity was highest in patients with typical chest pain and non-specific symptoms compared to atypical chest pain. Diabetes reduced the specificity of the CAD-score (Table 3). Only the Dan-NICAD dataset included patients with pathological heart valve disease. In these patients, the sensitivity was increased to 100%, while the specificity was decreased to 23.1% (Table 3).

Discussion

Recent findings of low diagnostic yield at non-invasive testing calls for a more rational approach to avoid unnecessary testing, providing both clinical and economic advantages. In this study we analysed the rule-out potential of a new CAD-score utilized before non-invasive testing of patients with suspected stable CAD. We found that the CAD-score enabled a significant and safe reclassification of patients, which could reduce the need for more expensive testing in patients presenting with chest pain.

The CADScor®System as a rule-out device

According to the current ESC guideline patients with intermediate PTP (15–85%) should undergo non-invasive testing [1]. In patients referred for testing due a suspicion of CAD we reclassified patients from the intermediate PTP group into the low probability group for negative CAD-scores. Thereby 699 (41.8%) patients could potentially avoid further costly testing, which is more than three times as many as if only the Diamond-Forrester score was used for rule-out (227 patients, 13.6%). Of notice, the 2016 NICE guidelines mention the CAD-score as a potential clinically relevant prediction model [33]. The proposed procedure was associated with a minor and insignificant increase in the proportion of significant-CAD patients in the low probability group from 3.1% to 4.0%.

A positive CAD-score (>20) resulted in a sensitivity of 88.7% which in the present low prevalence population (9.4% CAD) leads to a NPV at 97.2%. Thereby the probability of having significant-CAD was 2.8% for patients with a negative CAD-score (≤ 20). This probability is much lower than the 15% PTP threshold defined by the ESC guidelines for stable CAD that states that it is safe to assume that patients with a PTP below 15% have no significant CAD and no further testing is recommended. This suggests that the CAD-score safely rules-out CAD in the low and intermediate PTP population. The proposed use of the CADScor®System is as a first-line test before other non-invasive testing. This is reflected in the Dan-NICAD population which had an average PTP at 38.6%, where the CAD-score had a significantly higher AUC than the Diamond-Forrester score.

The CAD-score in sub-groups

Investigating the effect of risk factors potentially interfering with the CAD-score result, such as high BMI, diabetes or heart valve disease resulted in similar or increased sensitivity of the CAD-score in sub-group analyses, and in lower specificity, see Table 3. This indicates that the rule-out efficacy is lower in these sub-groups, but the rule-out safety is the same as in the remaining population. As in other risk models including gender, the sensitivity was lower in females compared to males. Despite this, the CAD-score had comparable rule-out safety in males and females, with similar negative predictive values.

Study limitations

The current study is a retrospective analysis of pooled data from existing cohorts and might therefore not capture all aspects of the clinical workflow. The database included a group of asymptomatic subjects from a screening study and it included a group of patients referred for CAG. Neither of these subjects are typical representatives for patients referred for non-invasive testing. However, the baseline characteristics such as age, gender and PTP of the pooled data corresponded well to the characteristics of the Dan-NICAD study which included only patients referred for non-invasive testing. The conclusion of the current study is limited to low to intermedia risk patients since the number of high-risk patients (updated Diamond Forrester score $>85\%$) was very low in the current study. The CAD-score algorithm described in the current paper is finetuned in the complete database before implementation in the CAD-score device. This induces the risk of overfitting the algorithm to the data, however the cross-validation of the algorithm showed only a small decrease in AUC of 0.009 thereby the degree of overfitting can be considered unimportant for the overall results. As recommended in the current ESC guidelines, the updates Diamond-Forrester score was used for PTP estimation. Other risk assessment models like the CAD-consortium scores [34] or PROMISE Minimal-Risk Tool [35] estimate lower risk levels which might alter interaction between PTP and the CAD-score. To further understand the interaction between long term in risk and CAD-scores future studies should include long term follow up data.

Conclusion

In the current study, we simulated use of the CAD-score to rule-out CAD in patients with intermediate PTP and suggest that the method potentially can reduce the number of

patients who should be referred for non-invasive testing, without a significant increase in the false negative rate. If these finding can be replicated in prospective studies, the use of the CAD-score could significantly alter the current practise of early rule-out of stable CAD providing important clinical and economic advantages.

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Compliance with ethical standards

Conflict of interest SES holds significant shares in Acarix, works significantly as Expert Witness for Acarix and received institutional research grants from Acarix. MB works as Expert Witness in Acarix and received institutional research grants from Acarix to conduct clinical studies. BSL is an industrial PhD student at Acarix. MSN is full-time employee at Acarix.

References

1. Montalescot G et al (2013) 2013 ESC guidelines on the management of stable coronary artery disease. Eur Heart J 34:2949–3003
2. Winther S et al (2018) Diagnostic performance of an acoustic-based system for coronary artery disease risk stratification. Heart 104:928–935
3. Therming C et al (2018) Low diagnostic yield of non-invasive testing in patients with suspected coronary artery disease: results from a large unselected hospital-based sample. Eur Heart J - Qual Care Clin Outcomes 4:301–308
4. Douglas PS et al (2015) Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 372:1291–1300
5. Dragomir A et al (2016) Acoustic detection of coronary occlusions before and after stent placement using an electronic stethoscope. Entropy 18:281
6. Cohn PF, Vokonas PS, Williams RA, Herman MV, Gorlin R (1971) Diastolic heart sounds and filling waves in coronary artery disease. Circulation 44:196–202
7. Schmidt SE et al (2011) Coronary artery disease and low frequency heart sound signatures. Comput Cardiol 38:481–484
8. Dock W, Zoneraich S (1967) A diastolic murmur arising in a stenosed coronary artery. Am J Med 42:617–619
9. Semmlow J, Rahalkar K (2007) Acoustic detection of coronary artery disease. Annu Rev Biomed Eng 9:449–469
10. Akay M, Semmlow JL, Welkowitz W, Bauer MD, Kostis JB (1990) Noninvasive detection of coronary stenoses before and after angioplasty using eigenvector methods. IEEE Trans Biomed Eng 37:1095–1104
11. Akay M, Akay YM, Welkowitz W, Lewkowicz S (1994) Investigating the effects of vasodilator drugs on the turbulent sound caused by femoral artery stenosis using short-term Fourier and wavelet transform methods. IEEE Trans Biomed Eng 41:921–928
12. Akay M et al (2009) Dynamics of diastolic sounds caused by partially occluded coronary arteries. IEEE Trans Biomed Eng 56:513–517
13. Gauthier D (2007) Spectral analysis of heart sounds associated with coronary occlusions. In: 6th international special topic conference on information technology applications in biomedicine, pp 49–52
14. Schmidt SE, Holst-Hansen C, Graff C, Toft E, Straijk JJ (2007) Detection of coronary artery disease with an electronic stethoscope. Comput Cardiol 34:757–760
15. Akay M (1994) Automated noninvasive detection of coronary artery disease using wavelet-based neural networks. Artif Neural Netw. Eng Proc 4:517–522
16. Semmlow J, Welkowitz W, Kostis J, Mackenzie JW (1983) Coronary artery disease–correlates between diastolic auditory characteristics and coronary artery stenoses. IEEE Trans Biomed Eng 30:136–139
17. Thomas JL, Winther S, Wilson RF, Bøttcher M (2017) A novel approach to diagnosing coronary artery disease: acoustic detection of coronary turbulence. Int J Cardiovasc Imaging 33:129–136
18. Thomas JL et al (2018) The clinical evaluation of the CADence device in the acoustic detection of coronary artery disease. Int J Cardiovasc Imaging 34:1841–1848
19. Makaryus AN et al (2013) Utility of an advanced digital electronic stethoscope in the diagnosis of coronary artery disease compared with coronary computed tomographic angiography. Am J Cardiol 111:786–792
20. Azimpour F, Caldwell E, Tawfik P, Duval S, Wilson RF (2016) Audible coronary artery stenosis. Am J Med 129(5):515–521. https://doi.org/10.1016/j.amjmed.2016.01.015
21. Winther S et al (2016) Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. Int J Cardiovasc Imaging 32:235–245
22. Grønhøj MH et al (2018) External validity of a cardiovascular screening including a coronary artery calcium examination in middle-aged individuals from the general population. Eur J Prev Cardiol 25:1156–1166
23. Diederichsen SZ et al (2017) CT-detected growth of coronary artery calcification in asymptomatic middle-aged subjects and association with 15 biomarkers. JACC Cardiovasc Imaging 10:858–866
24. Bøttcher M et al (2016) Danish study of non-invasive testing in coronary artery disease (Dan-NICAD): study protocol for a randomised controlled trial. Trials 17:262
25. Schmidt SE, Holst-Hansen C, Graff C, Toft E, Struijk JJ (2010) Segmentation of heart sound recordings by a duration-dependent hidden Markov model. Physiol Meas 31:513–529
26. Schmidt SE, Holst-Hansen C, Hansen J, Toft E, Struijk JJ (2015) Acoustic features for the identification of coronary artery disease. IEEE Trans Biomed Eng 62:2611–2619
27. Lewkowicz S, Welkowitz W, Akay M, Palti Y, Akay YM (2006) Dynamics of the sounds caused by partially occluded femoral arteries in dogs. Ann Biomed Eng 22:493–500
28. Knuuti J et al (2011) A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. Eur Heart J 32:1316–1330
29. Harris PJ et al (1980) The prognostic significance of 50% coronary stenosis in medically treated patients with coronary artery disease. Circulation 62:240–248
30. DeLong ER, DeLong DM, Clarke-Pearson DL (2006) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 44:837

31. Hanley JA, McNeil BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143:29–36
32. Taylor JMG, Ankerst DP, Andridge RR (2008) Validation of biomarker-based risk prediction models. Clin Cancer Res 14:5977–5983
33. National Institute for Health and Care Excellence (2016) Chest pain of recent onset: assessment and diagnosis | Guidance and guidelines | NICE. Clin Guid 95
34. Genders TSS et al (2012) Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ 344:e3485. https://doi.org/10.1136/bmj.e3485
35. Fordyce CB et al (2017) Identification of patients with stable chest pain deriving minimal value from noninvasive testing: the PROMISE minimal-risk tool, a secondary analysis of a randomized clinical trial. JAMA Cardiol. 2(4):400–408. https://doi.org/10.1001/jamacardio.2016.5501

Original research

Likelihood reclassification by an acoustic-based score in suspected coronary artery disease

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ABSTRACT

Objective Validation studies of the 2019 European Society of Cardiology pretest probability model (ESC-PTP) for coronary artery disease (CAD) report that 35%–40% of patients have low pretest probability (ESC-PTP 5% to <15%). Acoustic detection of coronary stenoses could potentially improve clinical likelihood stratification. Aims were to (1) investigate the diagnostic performance of an acoustic-based CAD score and (2) study the reclassification potential of a dual likelihood strategy by the ESC-PTP and a CAD score.

Methods Consecutive patients (n=1683) with stable angina symptoms referred for coronary CT angiography (CTA) underwent heart sound analyses by an acoustic CAD-score device. All patients with ≥50% luminal stenosis in any coronary segment at coronary CTA were referred to investigation with invasive coronary angiography (ICA) with fractional flow reserve (FFR). A predefined CAD-score cut-off ≤20 was used to rule out obstructive CAD.

Results In total, 439 patients (26%) had ≥50% luminal stenosis on coronary CTA. The subsequent ICA with FFR showed obstructive CAD in 199 patients (11.8%). Using the ≤20 CAD-score cut-off for obstructive CAD rule-out, sensitivity was 85.4% (95% CI 79.7 to 90.0), specificity 40.4% (95% CI 37.9 to 42.9), positive predictive value 16.1% (95% CI 13.9 to 18.5) and negative predictive value 95.4% (95% CI 93.4 to 96.9) in all patients. Applying the cut-off in ESC-PTP 5% to <15% patients, 316 patients (48%) were down-classified to very-low likelihood. The obstructive CAD prevalence was 3.5% in this group.

Conclusion In a large contemporary cohort of patients with low CAD likelihood, the additional use of an acoustic rule-out device showed a clear potential to downgrade likelihood and could supplement current strategies for likelihood assessment to avoid unnecessary testing.

Trial registration number NCT03481712.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In patients with suspected obstructive coronary artery disease (CAD), 35%–40% of patients have low pretest likelihood (5% to <15%).

⇒ Acoustic detection of coronary stenoses could potentially improve likelihood stratification.

WHAT THIS STUDY ADDS

⇒ In patients with low pretest likelihood, nearly half of patients are down-classified to very-low likelihood by additional acoustic information with preserved low prevalence of obstructive CAD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Acoustic pretest likelihood modification could reduce the proportion of patients undergoing inappropriate downstream testing based on clinical likelihood stratification alone.

INTRODUCTION

Despite a continuing effort to improve clinical pretest likelihood scoring algorithms for obstructive coronary artery disease (CAD) identification, the incidence of normal downstream diagnostic tests remains high.[1] The 2019 European Society of Cardiology-endorsed pretest probability model (ESC-PTP) reclassifies approximately 50% of patients to lower likelihood categories compared with previous models.[2 3] In validation studies, however, 35%–40% of patients are 'grey zone patients' with an ESC-PTP 5% to <15%.[3 4] In general, guidelines are ambiguous on the need for downstream testing in 'grey zone patients',[5 6] and decisions relies on traditional risk factors and a 'clinical likelihood (CL) concept' without provision of likelihood tables to depict the patient-specific CL of obstructive CAD which is recognised as a 'gap in evidence'.[5]

The contemporary CL of obstructive CAD was recently reported to have decreased substantially,[2] and the risk of false positives increases in lower likelihood categories. Stratification tools with the ability to rule out obstructive CAD (ie, with high negative predictive value (NPV)) are needed to improve early patient triage after the initial likelihood estimation and before diagnostic testing.

Acoustic detections of coronary stenosis from automatically recorded and analysed heart sounds is a technology potentially useful for likelihood modification before coronary CT angiography (CTA).[7] One of these devices outlines a CAD score

which extracts acoustic features related to turbulent blood flow emerging from stenosed coronary arteries.[8] The intended use of the CAD-score device is to record heart sounds, that is, murmurs and vibration for calculation of a patient-specific score, the CAD score, indicating the likelihood of coronary stenosis as an aid in CAD stratification. Recent studies demonstrated that a CAD score is superior to conventional likelihood scores.[9] Additionally, adding an acoustic-based strategy as the initial test for chest pain, >40% of patients can be down-classified to very-low likelihood without significantly increasing CAD prevalence, thus indicating an acoustic-based reclassification potential.[10] However, the reclassification potential of a recently updated CAD-score algorithm (V.3.1) has not been validated.

In the Danish Study of Non-Invasive Diagnostic Testing in Coronary Artery Disease 2 (Dan-NICAD 2),[11] the aims of this study were to (1) investigate the diagnostic performance of the CAD-score V.3.1 compared with the 2019 ESC-PTP using invasive coronary angiography (ICA) with fractional flow reserve (FFR) as reference for obstructive CAD, and (2) validate the reclassification potential of the CAD score V.3.1 in grey zone patients with ESC-PTP 5% to <15%.

METHODS

Study population and design

This was a prespecified substudy of the Dan-NICAD 2 study which had a sample size of 1600–2000 patients to ensure sufficient power for the main Dan-NICAD 2 objective of comparing diagnostic performances of stress perfusion positron emission tomography (PET) and cardiac magnetic resonance (CMR) against obstructive CAD by ICA with FFR in patients with suspected stenosis on coronary CTA.[11] In total, 460 patients were expected to have suspected stenosis on coronary CTA of whom 80% were expected to complete both PET, CMR and ICA with FFR. Inclusion of 2000 patients would enable prediction of diagnostic performance parameters with a minimum of 6% absolute precision for the expected sensitivity (80%) and specificity (80%) at a disease prevalence of 50% at both imaging tests.

The Dan-NICAD 2 study protocol,[11] including eligibility criteria, and main findings[12] have been reported. In summary, 1732 consecutively enrolled patients without known CAD but with symptoms suggestive hereof underwent coronary CTA as first-line diagnostic test from January 2018 to December 2020. Referral decisions were made during an outpatient visit by a cardiologist.[5] Prior to coronary CTA, a systematic interview assessing coronary risk factors and symptoms and a review of medical records were conducted. Following this, sound recordings were performed using the CADScorSystem (Acarix, Denmark). Based on the interview, the ESC-PTP[5] likelihood was determined. Readings of coronary CTA classified stenoses as (1) diameter stenosis 0% and coronary artery calcium score=0; (2) diameter stenosis 0%–29%; (3) diameter stenosis 30%–49%; diameter stenosis 50%–100%. Patients with per-patient maximal diameter stenosis 50%–100% (equivalent to >70% area (luminal) stenosis) were suspected of having obstructive CAD and referred for invasive FFR.

The study was registered at ClinicalTrials.gov (Identifier: NCT03481712).

The CAD score

Heart sound recordings were obtained transcutaneously using the CAD-score device. As per protocol, the patient lied down for 3 min during the recording and was asked to hold his/her breath four times, each time for 8 s, in an undisturbed room. Using a fully automated and device-embedded software, the CAD score was estimated immediately after the recording using the V.3.1 algorithm which is based on eight acoustic properties and takes into account clinical risk factors (gender, age and hypertension defined as systolic blood pressure ≥140 mm Hg and/or receiving antihypertension medication).[13] In cases of insufficient recording quality, the recording device requested a new recording, and a second attempt was made to calculate the CAD score. In total, four attempts were possible per patient. Using a prespecified binary cut-off, a CAD score >20 was categorised as abnormal.[13] The CAD-score results were not available for the assessors of the reference standards (coronary CTA and ICA), and conversely.

Invasive coronary angiography and absolute coronary flow

The ICA examination was performed according to clinical guidelines. Intracoronary nitroglycerine was administered before angiographic acquisition. Invasive FFR was measured in lesions with visually estimated 30%–90% diameter stenosis located in vessels with a reference diameter >2.0 mm using a clinical FFR system (PressureWire X, Abbott Laboratories, USA).

At ICA, haemodynamically obstructive CAD was identified in a blinded core lab as one or more of the following: (1) FFR value ≤0.80, (2) luminal diameter stenosis reduction >90% or (3) three-dimensional quantitative coronary angiography luminal diameter stenosis reduction ≥50% if FFR was indicated but not performed for technical, anatomical or other reasons. If none of the thresholds for abnormality were reached, non-obstructive CAD was concluded.

For comparison with previous studies on the CAD-score device, two-dimensional QCA (2D QCA) analyses indicating anatomically obstructive CAD were retrospectively performed by an independent corelab (CORRIB Corelab, Galway, Ireland) blinded to results of the original ICA using CAAS V.8.2.4 (PIE Medical Imaging, Maastricht, The Netherlands). Anatomically obstructive CAD was defined as lesions at 2D QCA with luminal diameter stenosis reduction ≥50%.

Statistical analyses

Continuous variables are reported as mean (±SD or total range) or median (range), categorical variables as frequencies (percentages). The unpaired Student's t-test and analysis of variance test were used for comparison between Gaussian-distributed variables, while the Wilcoxon rank-sum test and the χ^2 test were used for comparison between non-Gaussian distributed and categorical variables, respectively. Pearson's test and Spearman's test were used to analyse correlations of variables of Gaussian and non-Gaussian distributions, respectively.

The area under the receiver operating characteristic curves (ROC AUC) were calculated and compared for continuous variables in accordance with DeLong *et al*[14] using a theory of generalised U-statistics to generate an estimated covariance matrix and testing the equality of ROC areas for the CAD score and ESC-PTP against haemodynamically obstructive CAD.

Using the binary ≤20 CAD-score cut-off for CAD rule-out, sensitivity, specificity, positive predictive value (PPV) and NPV were calculated.

The 2019 ESC-PTP was determined and divided according to the recommended cut-offs of very-low (≤5%), low (5% to ≤15%) and moderate/high (>15%) likelihood of obstructive CAD.[5] For binary analyses of diagnostic performance, a 2019 ESC-PTP >5% was considered abnormal. Since the CAD score was originally validated against the 2013 ESC-PTP, this model

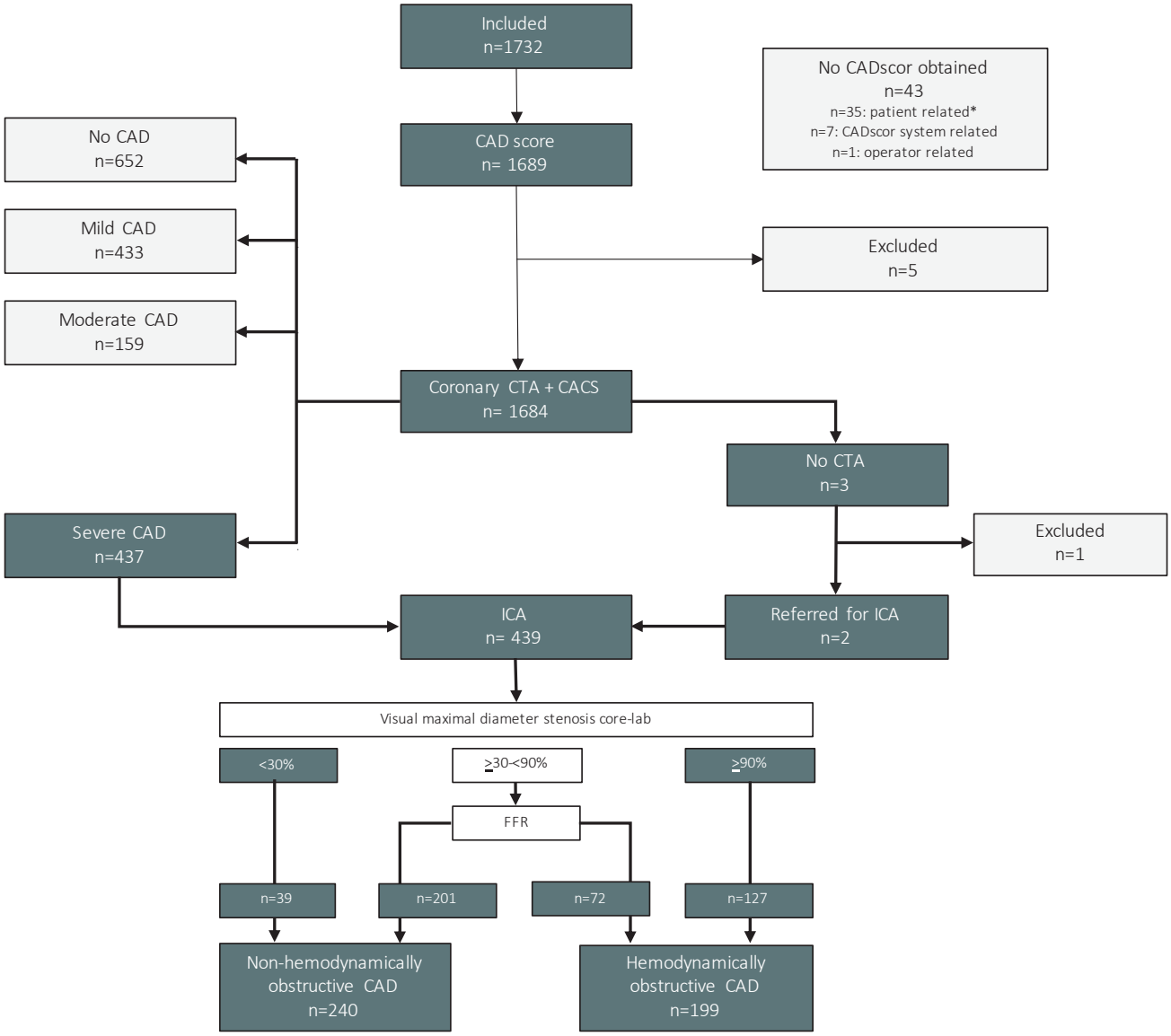

Figure 1 Patient flow chart. *A CAD score was not obtained due to tachycardia (n=7), patient declination (n=4), lack of patient corporation (n=3), delayed CT programme (n=10), bradycardia (n=1) and high ambient noise (n=10). CACS, coronary artery calcium score; CAD, coronary artery disease; CTA, CT angiography; FFR, fractional flow reserve; ICA, invasive coronary angiography.

was applied in secondary analyses where 2013 ESC-PTP ≥15% was considered abnormal.

RESULTS

In total, 1732 patients were included, of whom 49 (2.8%) were excluded (figure 1). Two patients did not undergo coronary CTA but were instead referred directly for invasive assessment. Data for statistical analyses were available in 1683 patients.

Baseline, coronary CTA and ICA characteristics are outlined in table 1. Coronary CTA found suspected obstructive CAD in 437 patients of whom 199 (45.5%) met the prespecified criteria for haemodynamically obstructive CAD by ICA with FFR. The prevalence of obstructive CAD in the entire cohort was 11.8%. A total of 628 (37%) patients had a CAD score ≤20, indicating very-low likelihood.

Of the 1683 patients in which CAD scores were obtained, no adverse events related to the use of the CAD-score device were recorded. One patient was excluded from the analysis due to missing CAD score due to itching at the site of patch placement.

Diagnostic performance of CAD score

The mean CAD score was higher for patients with haemodynamically obstructive CAD than for patients without (36.0±13.4 vs 25.5±13.9, p<0.001). The AUC for diagnosing haemodynamically obstructive CAD was 0.70 (95% CI 0.67 to 0.75) which was lower than for the 2019 ESC-PTP (AUC 0.74 (95% CI 0.70 to 0.78, p=0.04)) (figure 2).

The diagnostic performance of the CAD score with the ≤20 CAD-score cut-off for diagnosing haemodynamically obstructive CAD is presented in table 3 and online supplemental table 1. In the total cohort, the sensitivity was 85.4% (95% CI 79.7% to 90.0%), specificity 40.4% (95% CI 37.9% to 42.9%), the PPV 16.1% (95% CI 13.9% to 18.5%) and the NPV 95.4% (95% CI 93.4% to 96.9%).

Table 1 Patient demographics and imaging study characteristics

Characteristics (n=1683)	
Race, Caucasian	1666 (99.0%)
Sex, male	963 (57.2%)
Age, years	59.5±9.5
Family history of premature CVD	562 (33.4%)
Body mass index (kg/m^2)	27.2±4.3
Abdominal circumference (cm)	98±12.8
Blood pressure	
Systolic	135±18.1
Diastolic	84±10.0
Heart rate	59±8.1
Smoking	
Never	737 (43.8%)
Former	710 (42.2%)
Active	236 (14.0%)
Diabetes	103 (6.1%)
Hypertension	678 (40.3%)
Dyslipidaemia	427 (25.4%)
Medication (n=1683)	
Aspirin/P2Y12	268 (15.9%)
Vitamin K antagonist/NOAC	101 (6.0%)
Statins	427 (25.4%)
Beta-blockers	199 (11.8%)
ACE/AT2 receptor blockers	235 (14.0%)
Calcium channel antagonists	293 (17.4%)
Isosorbide nitrate	285 (16.9%)
Diuretic treatment	32 (1.9%)
Biochemistry (n=1683)	
Total cholesterol (mmol/L)	5.2 (4.4–5.9)
LDL-cholesterol (mmol/L)	3.0 (2.30–3.70)
HBA1c (mmol/mol)	34 (34–35)
Symptoms (n=1683)	
Typicality	
Typical chest pain	345 (20.5%)
Atypical chest pain	653 (38.8%)
Non-specific	393 (23.4%)
Other (dyspnoea/arrythmia)	292 (17.3%)
2019 ESC-PTP	
Very-low likelihood (ESC-PTP ≤5%)	213 (12.7%)
Low likelihood (ESC-PTP 5% to ≤15%)	659 (39.2%)
Moderate/High likelihood (ESC-PTP >15%)	811 (48.2%)
Echocardiography (n=1672)	
Left ventricular ejection fraction	59±4.2
Cardiac valve disease, any	143 (8.5%)
Aorta insufficiency (mild to moderate)	93 (5.5%)
Other systolic valve disease (mild to moderate)	50 (3.0%)
Coronary artery calcium score (n=1683)	
Median	8 (0–119)
Coronary artery calcium score groups	
None (=0)	724 (43.0%)
Low/Moderate (1–399)	750 (44.6%)
High (≥400)	209 (12.4%)
Coronary CT angiography (n=1683)	
CAD severity	
Diameter stenosis 0% and coronary artery calcium score=0	652 (38.7%)
Diameter stenosis 0%–29%	433 (25.7%)
Diameter stenosis 30%–49%	159 (9.7%)
Diameter stenosis 50%–100%	437 (26.0%)
Invasive coronary angiography (FFR, functional disease) (n=439)	
CAD severity	
Non-significant disease	240 (14.4%)
Functional disease	199 (11.7%)
Coronary vessel disease	
One-vessel	131 (7.8%)
Two-vessel	36 (2.1%)
Three-vessel or left main	32 (1.9%)

Baseline characteristics. Values are n (%), mean±SD or median (IQR). Please find the definition of obstructive CAD in the 'Methods' section.
CAD, coronary artery disease; CVD, cardiovascular disease; ESC, European Society of Cardiology; FFR, fractional flow reserve; HBA1c, haemoglobin A1c; NOAC, novel oral anticoagulant; PTP, pretest probability.

The diagnostic performance of the CAD score for diagnosing anatomically obstructive CAD is outlined in online supplemental table 1 and figure 1. The prevalence of anatomically obstructive CAD was 12.9% (217/1683). For comparison, the diagnostic performance of the ESC-PTP models is outlined in online supplemental table 2.

Reclassification potential of the CAD score

Table 2 and the figure 3 present the reclassification potential of the CAD score in low likelihood (ESC-PTP 5% to ≤15%) patients. In total, 316 patients (48.0%) could be down-classified to an obstructive CAD prevalence of 3.5% using the ≤20 CAD-score cut-off. In this subgroup, sensitivity was 65.6% (95% CI 46.8% to 81.4%), specificity 48.6% (95% CI 44.7% to 52.6%), PPV 6.1% (95% CI 3.8% to 8.2%) and NPV 96.5% (95% CI 93.9% to 98.2%) (table 3). Of the down-classified patients, 108 (34.2%) had non-obstructive CAD determined by coronary CTA (table 2), whereas 0 patients had left main and/or three-vessel disease determined by ICA with FFR.

In all patients with ESC-PTP >5% and CAD score ≤20, the prevalence of obstructive CAD was 5.4% (table 3). In this subcohort, 3/1470 (0.2%) patients had left main and/or three-vessel disease, all patients with ESC-PTP >15%.

DISCUSSION

In this prespecified, prospective substudy of Dan-NICAD 2,[11] we studied a cohort of symptomatic patients with predominantly very-low/low likelihood of CAD referred to coronary CTA as a first-line diagnostic modality for obstructive CAD rule-out. The overall rule-out properties of the acoustic-based CAD score were excellent with an NPV of 95.4% but sensitivity only moderate. In our cohort, the primary hypothesis was not met as the CAD score did not improve risk stratification compared with the guideline-endorsed ESC-PTP against obstructive CAD by invasive FFR. However, the CAD score improved reclassification beyond the ESC-PTP model as it was able to down-classify nearly half of all grey zone patients (ESC-PTP 5% to ≤15%) without increasing obstructive CAD prevalence.

Pretest likelihood stratification in CAD

The guideline-endorsed ESC-PTP stratifies patients according to likelihood of obstructive CAD.[5] Comparing models predicting CAD likelihood, adding risk factors to a basic 'age-gender-symptoms' model improves obstructive CAD identification.[15–17] In accordance with this, a previous study found that the CAD score V.3.0 system combined with risk factors performed better

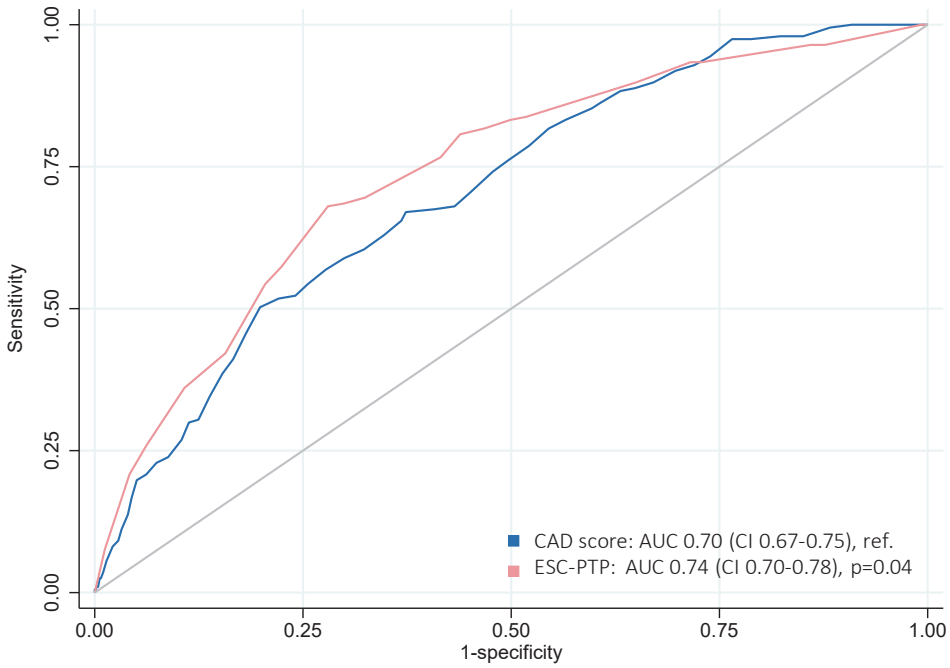

Figure 2 Receiver operating characteristic curves of the CAD score and 2019 ESC-PTP. AUC, area under the curve; CAD, coronary artery disease; ESC, European Society of Cardiology; PTP, pretest probability.

compared with a model based solely on acoustic information.[9] Adding risk factors different from the ones applied in the ESC-PTP, one could argue that the discriminative performance of the CAD score is partially risk factor-based and not a sole inherent property of the acoustic algorithm. In addition, the presence of any risk factor (eg, age, sex, smoking, diabetes) increases obstructive CAD identification.[18] However, the acoustic signal itself has a moderate AUC for obstructive CAD discrimination,[9] and the combined use of risk factors and acoustic features by the CAD score potentially serves as a clinically feasible tool to modify patient-specific CL which is recognised as a 'gap in evidence' in the recent ESC guidelines.[5] Overall, ESC-PTP 5% to >15% patients constitutes one-third of patients with de novo chest pain,[3 4] where a clinically feasible tool estimating the CL of obstructive CAD to increase test deferral rates is warranted.[5]

Diagnostic performance

For discrimination of obstructive CAD, the CAD score V.3.1 showed high NPV for CAD rule-out (table 3). The diagnostic performance of the CAD score has previously been investigated with sensitivities ranging from 81% to 98%, specificities from 18% to 41%, PPVs from 11% to 41% and NPVs from 91% to 97%.[9 13 19]

In the Dan-NICAD 1 study,[9 20] which was a prospective, multicentre study investigating very-low/low likelihood patients referred for a primary examination by coronary CTA, the ability to rule out obstructive CAD using the CAD score V.3.0 was good and similar to the results from our study; NPV 96.2% for haemodynamically obstructive CAD.[10] The present study and the Dan-NICAD 1 cohort had a similar mean baseline likelihood of CAD, and the obstructive CAD prevalences were comparable between the studies (10.0% vs 11.7%).[9] The present study confirmed the performance of CAD score V.3.1, showing similar results as for the Dan-NICAD 1 study on which the CAD score V.3.1 was developed, and where an NPV of 96.1% at a 10.4% prevalence of anatomically obstructive CAD was shown.[13]

In the study by Schmidt *et al*,[13] which consisted of three previous studies all comprising very-low/low likelihood patients undergoing coronary CTA, approximately one out of four of the study participants were asymptomatic (n=572). Compared with our study, the ability to rule out anatomically obstructive CAD by CAD score V.3.1 was similarly good (NPV 97.2%) and the mean pretest likelihood and obstructive CAD prevalence (9.4% vs 11.7%) was comparable.[13]

Recently, Renker *et al*[19] reported from a study of high-risk patients referred for ICA. The obstructive CAD rule-out power

Table 2 Prevalence of obstructive CAD, non-obstructive CAD and no CAD according to 2019 ESC-PTP and CAD-score subgroups

	ESC-PTP ≤5		ESC-PTP 5 to ≤15		ESC-PTP >15	
	CAD score ≤20	CAD score >20	CAD score ≤20	CAD score >20	CAD score ≤20	CAD score >20
Patient, total	166 (9.9%)	47 (2.8%)	316 (18.8%)	343 (20.4%)	146 (8.7%)	665 (39.5%)
No CAD	117 (70.5%)	26 (55.3%)	197 (62.3%)	122 (35.6%)	58 (39.7%)	132 (19.8%)
Non-obstructive CAD	45 (27.1%)	18 (38.3%)	108 (34.2%)	200 (58.6%)	74 (50.6%)	387 (58.3%)
Obstructive CAD	4 (2.4%)	3 (6.4%)	11 (3.5%)	21 (5.8%)	14 (9.6%)	146 (21.8%)

Prevalence of obstructive CAD, non-obstructive CAD and no CAD according to ESC-PTP and CAD-score subgroups.
CAD, coronary artery disease; ESC, European Society of Cardiology; PTP, pretest probability.

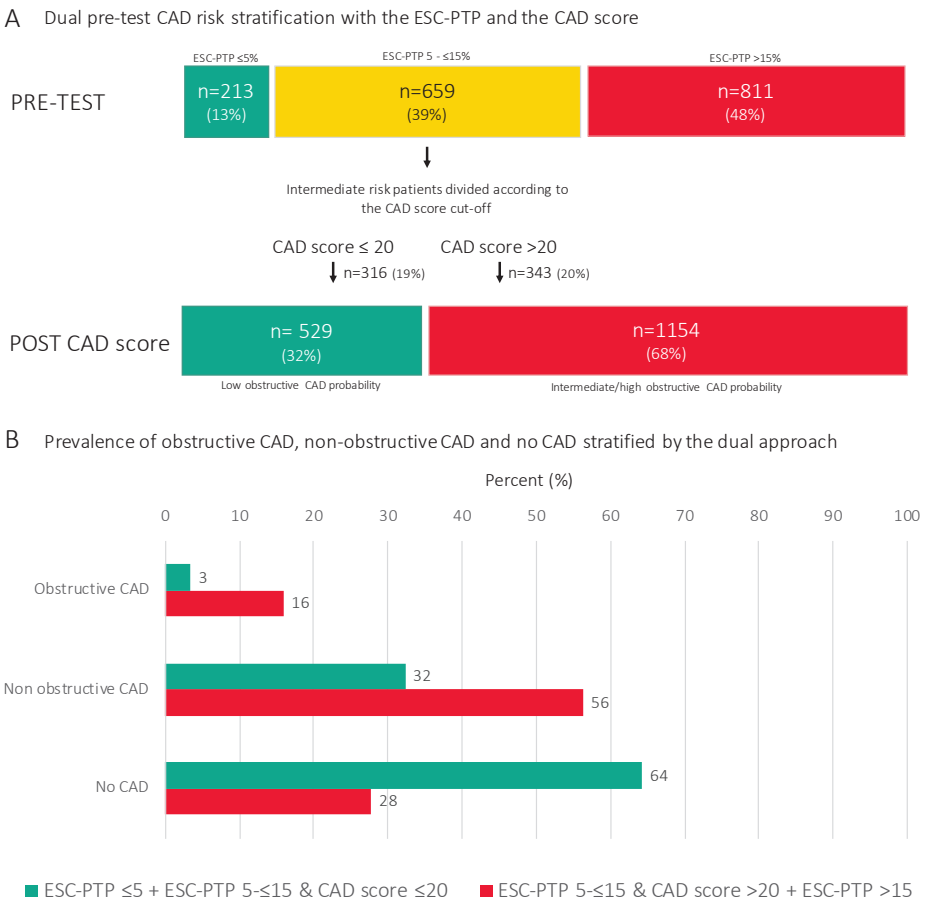

Figure 3 Risk reclassification of patients with angina symptoms and low likelihood of obstructive CAD, the grey zone, using a novel method of combining likelihood of obstructive CAD with the acoustic CAD score (A). According to the present CAD-score cut-off, nearly half of grey zone patients can be down-classified to a likelihood of obstructive CAD ≤5% (B). CAD, coronary artery disease; CTA, CT angiography; ESC, European Society of Cardiology; FFR, fractional flow reserve; ICA, invasive coronary angiography; PTP, pretest probability.

by the CAD score V.3.1 was the lowest of all three studies (NPV 90.5%). The prevalence of obstructive CAD (anatomically defined) was higher than in our study (38.5% vs 11.7%). As the diagnostic performance of a test depends on the disease prevalence in the cohort examined, the CAD score rule-out power is expected to decline in high prevalence populations as reported by Renker *et al*.[19] This is in line with our findings (table 3).

CAD score and reference standard for obstructive CAD

In general, FFR is considered the gold standard for physiological assessment of coronary stenoses.[21] Originally, the CAD score was calibrated towards a QCA-based endpoint overestimating lesion severity.[22] However, the Dan-NICAD 1 study demonstrated similar diagnostic performance applying an end point of

Table 3 Diagnostic performance of the CAD score stratified by 2019 ESC-PTP subgroups using an FFR-based end point of obstructive CAD

	All n=1683 (95% CI)	ESC-PTP ≤5% n=213 (95% CI)	ESC-PTP 5% to ≤15% n=659 (95% CI)	ESC-PTP >15% n=811 (95% CI)	ESC-PTP >5% n=1470 (95% CI)
Sensitivity	85.4% (79.7–90.0)	42.9% (9.9–81.6)	65.6% (46.8–81.4)	91.3% (85.8–95.1)	87.0% (81.4–91.4)
Specificity	40.4% (37.9–42.9)	78.6% (72.4–84.0)	48.6% (44.7–52.6)	20.3% (17.3–23.6)	34.2% (31.6–36.9)
PPV	16.1% (13.9–18.5)	6.4% (1.3–17.5)	6.1% (3.8–8.2)	22.0% (18.9–25.3)	16.6% (14.3–19.0)
NPV	95.4% (93.4–96.9)	97.6% (93.9–99.3)	96.5% (93.9–98.2)	90.4% (84.4–94.7)	94.6% (92.1–96.5)

Diagnostic performance of the CAD score stratified by 2019 ESC-PTP subgroups using an FFR-based end point of obstructive CAD. Number of true positives, true negatives, false positives and false negatives are shown in online supplemental table 1.
CAD, coronary artery disease; ESC, European Society of Cardiology; FFR, fractional flow reserve; NPV, negative predictive value; PPV, positive predictive value; PTP, pretest probability.

QCA versus FFR,[9] which is in line with our findings (table 3, online supplemental figure 1).

Validating reclassification

The CAD score showed strong reclassification properties in grey zone likelihood (ESC-PTP 5% to ≤15%) patients where decision on deferral or referral should be based on 'CL'.[5] In this subcohort, the CAD score would down-classify 316 patients (48%) with an obstructive CAD prevalence of 3.5% (table 3, figure 3) while sensitivity of obstructive CAD was only moderate. This is in accordance with previous studies using an overcalibrated CL model and a reference standard anatomically obstructive CAD.[2 10 15] Thus, on a patient-level, the CAD score should be seen as a supplement for likelihood refinement by a dual approach, not as a test equivalent to coronary CTA, in combination with the ESC-PTP, taking the overall likelihood profile of the patient into account. This approach is currently being tested in the Cost-effectiveness and Safety of the CADScorSystem in Patients With Symptoms Suggestive of Stable Coronary Artery Disease (FILTER-SCAD) study.[23] Additionally, other dual approaches of combining likelihood stratification tools have recently been suggested.[24]

Based on the recommended 'CL' assessment in grey zone likelihood patients, Winther *et al* suggested a new tabulated model to assess the CL of CAD.[18] This model adds risk factors to a basic age-gender-symptom approach and optimises reclassification of patients to very-low likelihood of CAD. However, the proposed model classified 41.2% of the patients in the validation cohort as grey zone likelihood of whom 10% had obstructive CAD. Hence, there is a potential for combining the CAD score with even more advanced CL models to reduce the number of grey zone patients in whom a clear testing strategy is currently uncertain.

The guideline-endorsed cut-offs for pretest likelihood assessment (ESC-PTP ≤5%, 5% to ≤15%, >15% to 50% and >50%) are arbitrary.[5] In our cohort, obstructive CAD prevalence was 5.4% in all patients with ESC-PTP >5% and CAD score ≤20 (tables 2 and 3). From both a patient-related and a clinical perspective, a low CAD score classification should not overrule moderate likelihood ESC-PTPs above a certain threshold which currently is unknown.

The CAD score is calibrated towards an end point of obstructive CAD. However, data from the Scottish Computed Tomography of the Heart (SCOT-HEART) trial showed that identification of non-obstructive lesions improve prognosis due to more targeted preventive interventions,[25 26] and, in general, data from several large, clinical trials suggest that patients with non-obstructive CAD have increased event rates.[25 27 28] The CAD score has an inherent limitation of not being able to identify non-obstructive lesions, and across ESC-PTP categories, we found non-obstructive CAD prevalences ranging from 27% to 51% (table 2). Using the follow-up data in Dan-NICAD 1, however, Winther *et al* recently reported low annual event rates in patients with a CAD score ≤20 compared with >20 but the cohort also underwent subsequent coronary CTA enabling targeted medical therapy.[29] The prognostic implication of test deferral based on a CAD score ≤20 and no coronary CTA to guide initiation of medical therapy is currently being investigated.[23] In light of the ISCHEMIA trial,[30] one could argue that high-risk CAD should be ruled out by coronary CTA with revascularisation only in patients with medically refractory symptoms regardless of other coronary lesions and lesion severity. Patient selection for ISCHEMIA enrolment, however, was based on moderate/severe ischaemia on non-invasive stress testing which is infrequent in patients with de novo chest pain.[12] In our study, no down-classified patients from the ESC-PTP 5% to ≤15% subgroup had prognostic disease, and the enigma of whether one-third of patients with non-obstructive/obstructive CAD and annual event rates <2%[24] should be deferred from testing based on a CAD score ≤20 or 197/316 (62.3%) patients with normal coronary arteries should undergo coronary CTA yields further improvements in CL stratification in general (table 2).

Limitations

Our cohort was based on patients with de novo chest pain referred for a primary investigation by a coronary CTA. Overall, the likelihood was very-low/low, comorbidities were infrequent and our results should only carefully be extrapolated to higher likelihood cohorts with higher disease prevalences.

CONCLUSIONS

A novel sound-based recording device enables CL stratification in patients with suspected CAD. With a strong reclassification potential and an NPV of 95.4%, an acoustic rule-out strategy could supplement currently recommended CL strategies.

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Contributors LDR, SW and MB designed the study. LDR and SW enrolled patients. Coronary CTA scans were read by SW, JKJ, HMS, OH. Invasive coronary angiographies were conducted by SRK, JW, EC, AE, NRH. MN and SES provided statistical support to LDR. All authors have read and commented on the manuscript in detail. LDR is responsible for the overall content as guarantor.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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REFERENCES

1 Nissen L, Winther S, Schmidt M, *et al*. Implementation of coronary computed tomography angiography as nationally recommended first-line test in patients with suspected chronic coronary syndrome: impact on the use of invasive coronary angiography and revascularization. *Eur Heart J Cardiovasc Imaging* 2020;21:1353–62.
2 Juarez-Orozco LE, Saraste A, Capodanno D, *et al*. Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2019;20:1198–207.
3 Winther S, Schmidt SE, Rasmussen LD, *et al*. Validation of the European Society of cardiology pre-test probability model for obstructive coronary artery disease. *Eur Heart J* 2021;42:1401–11.
4 Bing R, Singh T, Dweck MR, *et al*. Validation of European Society of cardiology pre-test probabilities for obstructive coronary artery disease in suspected stable angina. *Eur Heart J Qual Care Clin Outcomes* 2020;6:293–300.
5 Knuuti J, Wijns W, Saraste A, *et al*. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2019;41:407–77.
6 Gulati M, Levy PD, Mukherjee D, *et al*. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of CHEST pain: a report of the American College of cardiology/american heart association joint committee on clinical practice guidelines. *Circulation* 2021;144:e368–454.
7 Thomas JL, Winther S, Wilson RF, *et al*. A novel approach to diagnosing coronary artery disease: acoustic detection of coronary turbulence. *Int J Cardiovasc Imaging* 2017;33:129–36.
8 Schmidt SE, Holst-Hansen C, Graff C, *et al*. Segmentation of heart sound recordings by a duration-dependent hidden Markov model. *Physiol Meas* 2010;31:513–29.
9 Winther S, Nissen L, Schmidt SE, *et al*. Diagnostic performance of an acoustic-based system for coronary artery disease risk stratification. *Heart* 2018;104:928–35.
10 Schmidt SE, Winther S, Boettcher M. Coronary artery disease risk reclassification using an acoustic-based score in view of the new European Society of cardiology 2019 guidelines on chronic coronary syndromes. *Int J Cardiovasc Imaging* 2020;36:383–4.
11 Rasmussen LD, Winther S, Westra J, *et al*. Danish study of non-invasive testing in coronary artery disease 2 (dan-NICAD 2): study design for a controlled study of diagnostic accuracy. *Am Heart J* 2019;215:114–28.
12 Rasmussen LD, Winther S, Eftekhari A, *et al*. Second-line advanced myocardial perfusion imaging to detect functionally obstructive stenosis: head-to-head comparison of magnetic resonance and positron emission tomography. *JACC Cardiovasc Imaging* 2022.
13 Schmidt SE, Winther S, Larsen BS, *et al*. Coronary artery disease risk reclassification by a new acoustic-based score. *Int J Cardiovasc Imaging* 2019;35:2019–28.
14 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.
15 Winther S, Nissen L, Westra J, *et al*. Pre-test probability prediction in patients with a low to intermediate probability of coronary artery disease: a prospective study with a fractional flow reserve endpoint. *Eur Heart J Cardiovasc Imaging* 2019;20:1208–18.
16 Genders TSS, Steyerberg EW, Hunink MGM, *et al*. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. *BMJ* 2012;344:e3485.
17 Wasfy MM, Brady TJ, Abbara S, *et al*. Comparison of the diamond-forrester method and duke clinical score to predict obstructive coronary artery disease by computed tomographic angiography. *Am J Cardiol* 2012;109:998–1004.
18 Winther S, Schmidt SE, Mayrhofer T, *et al*. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. *J Am Coll Cardiol* 2020;76:2421–32.
19 Renker M, Kriechbaum SD, Schmidt SE, *et al*. Prospective validation of an acoustic-based system for the detection of obstructive coronary artery disease in a high-prevalence population. *Heart Vessels* 2021;36:1132–40.
20 Nissen L, Winther S, Isaksen C, *et al*. Danish study of non-invasive testing in coronary artery disease (dan-NICAD): study protocol for a randomised controlled trial. *Trials* 2016;17:262.
21 Tonino PAL, De Bruyne B, Pijls NHJ, *et al*. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213–24.
22 Yong ASC, Ng ACC, Brieger D, *et al*. Three-dimensional and two-dimensional quantitative coronary angiography, and their prediction of reduced fractional flow reserve. *Eur Heart J* 2011;32:345–53.
23 Bjerking LH, Hansen KW, Biering-Sørensen T, *et al*. Cost-effectiveness of adding a non-invasive acoustic rule-out test in the evaluation of patients with symptoms suggestive of coronary artery disease: rationale and design of the prospective, randomised, controlled, parallel-group multicenter FILTER-SCAD trial. *BMJ Open* 2021;11:e049380.
24 Rasmussen LD, Fordyce CB, Nissen L, *et al*. The PROMISE minimal risk score improves risk classification of symptomatic patients with suspected CAD. *JACC Cardiovasc Imaging* 2022;15:1442–54.
25 Newby DE, Adamson PD, Berry C, *et al*. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;379:924–33.
26 Adamson PD, Williams MC, Dweck MR, *et al*. Guiding therapy by coronary CT angiography improves outcomes in patients with stable chest pain. *J Am Coll Cardiol* 2019;74:2058–70.
27 Min JK, Dunning A, Lin FY, *et al*. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International multicenter confirm (coronary CT angiography evaluation for clinical outcomes: an international multicenter registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011;58:849–60.
28 Ferencik M, Mayrhofer T, Bittner DO, *et al*. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. *JAMA Cardiol* 2018;3:144–52.
29 Winther S, Nissen L, Schmidt SE, *et al*. Advanced heart sound analysis as a new prognostic marker in stable coronary artery disease. *Eur Heart J Digit Health* 2021;2:279–89.
30 Maron DJ, Hochman JS, Reynolds HR, *et al*. Initial invasive or conservative strategy for stable coronary disease. *N Engl J Med* 2020;382:1395–407.

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ORIGINAL ARTICLE

Advanced heart sound analysis as a new prognostic marker in stable coronary artery disease

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Aims Recent technological advances enable diagnosing of obstructive coronary artery disease (CAD) from heart sound analysis with a high negative predictive value. However, the prognostic impact of this approach remains unknown. To investigate the prognostic value of heart sound analysis as two scores, the Acoustic-score and the CAD-score, in patients with suspected CAD which is treated according to standard of care.

Methods and results Consecutive patients with angina symptoms referred for coronary computed tomography angiography (CTA) were enrolled. The Acoustic-score was developed from eight acoustic CAD-related features. This score was combined with risk factors to generate the CAD-score. A cut-off score >20 was pre-specified for both scores to indicate disease. If coronary CTA raised suspicion of obstructive CAD, patients were referred to invasive angiography and revascularized when indicated. Of 1675 enrolled patients, 1464 (87.4%) were included in this substudy. The combined primary endpoint was all-cause mortality and myocardial infarction ($n = 26$). Follow-up was 3.1 (2.7–3.4) years. Of patients with primary endpoints, the Acoustic-score was >20 in 25 (96%); the CAD-score was >20 in 22 (85%). In an unadjusted Cox analysis of the primary endpoints, the hazard ratio for scores >20 under current standard clinical care was 12.6 (1.7–93.2) for the Acoustic-score and 5.4 (1.9–15.7) for the CAD-score. The CAD-score contained prognostic information even after adjusting for lipid-lowering therapy initiation, stenosis at CTA, and early revascularization.

Conclusion Heart sound analysis seems to carry prognostic information and may improve initial risk stratification of patients with suspected CAD.

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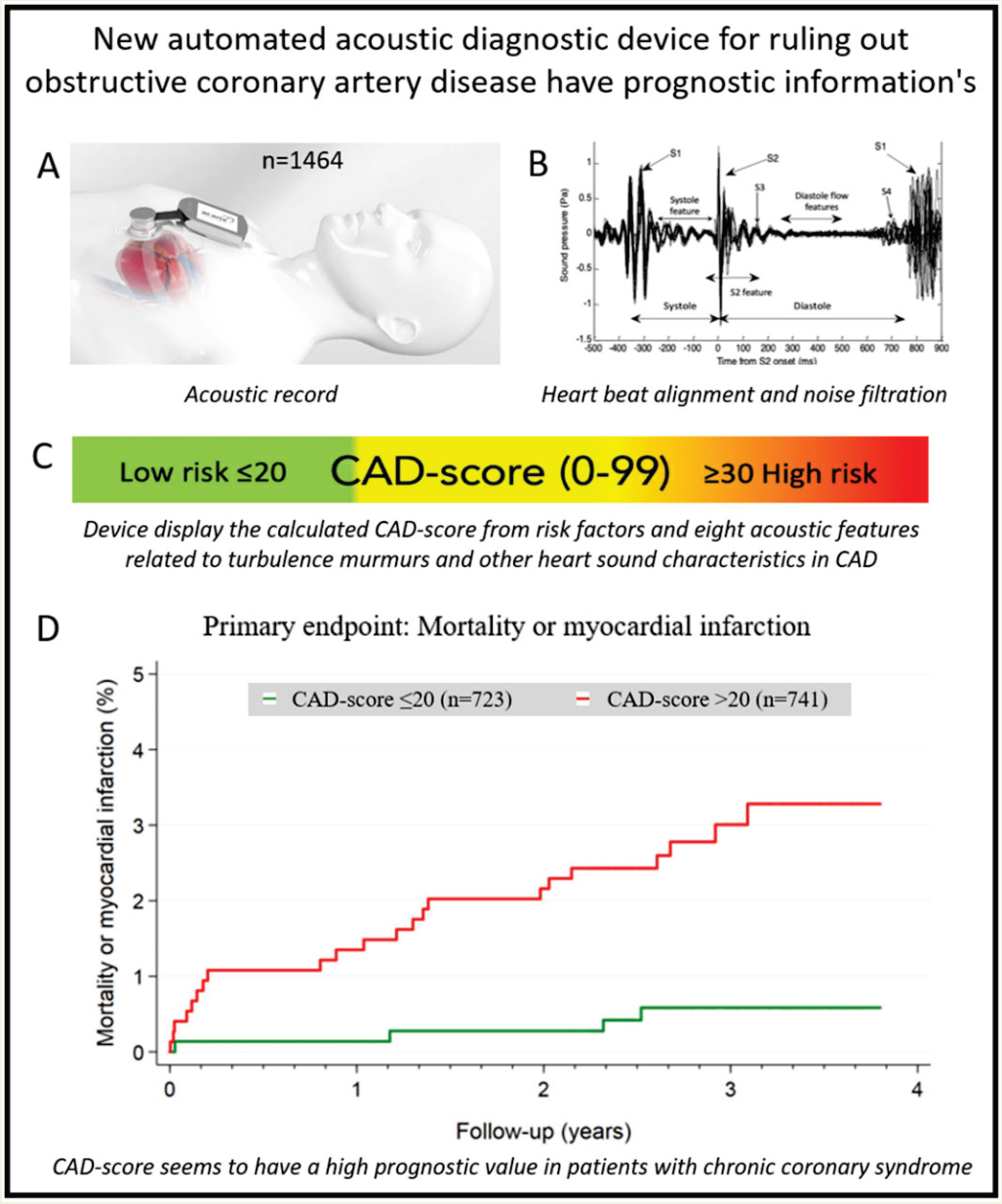
Graphical Abstract



Keywords Prognosis • Coronary stenosis • Cardiovascular diagnostic technique • Heart sound • Acoustic cardiography

Introduction

Pre-test probability stratification of patients with suspected obstructive coronary artery disease (CAD) has been suboptimal for many years. Hence, most diagnostic tests to rule out CAD show normal conditions.[1–3]

Acoustic devices measuring the heart sound originating from turbulent blood flow in the coronary circulation and altered myocardial relaxation have therefore been developed. These devices have been shown to be effective in ruling out CAD, and to outperform other methods by being faster, risk-free and more cost-effective.[4]

The diagnostic performance of two acoustic algorithms was recently tested in two large studies of patients presenting with symptoms suggestive of obstructive CAD.[5–7] The studies demonstrated that these algorithms were positively correlated with the extent of CAD in terms of coronary artery calcium score, maximal diameter

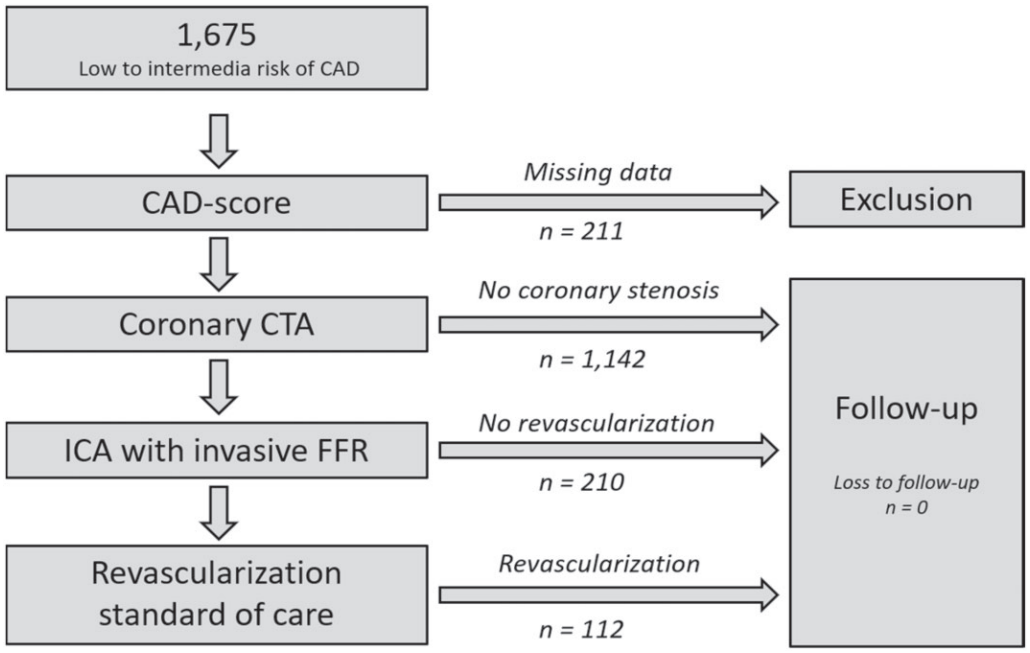


Figure 1 Flow chart of patients in the study. CAD, coronary artery disease; CTA, computed tomography angiography; FFR, fractional flow reserve; ICA, invasive coronary angiography.

stenosis, and number of vessels with disease. The studies demonstrated high sensitivities of 78–81%, moderate specificities of 35–53% but a high negative predictive value of 91–96%. It is therefore possible that these algorithms may serve as rule-out tests in patients with suspected stable CAD.

However, no study has investigated whether heart sound carries any prognostic information. The acoustic features included in these acoustic algorithms have been linked to coronary stenosis degree, coronary flow volume and velocity, vascular stiffness, left ventricular diastolic, and systolic dysfunction—all markers which are predictive of a poor prognosis.[6,8–14]

The aim of this study was to investigate the prognostic value of pre-specified heart sound analysis (Acoustic-score) and an acoustic pre-test probability score (CAD-score) in patients with symptoms suggestive of CAD referred for coronary computed tomography angiography (CTA) and subsequently treated according to standard of care.

Materials and methods

Study design and population

The present predefined substudy used patients from the Danish study of the Non-Invasive Testing in Coronary Artery Disease (Dan-NICAD) trial 1.[15,16] Patients referred to coronary CTA due to symptoms suggestive of obstructive CAD were enrolled consecutively between September 2014 and March 2016. Patients were referred to coronary CTA after evaluation by a cardiologist in an outpatient cardiology unit. Decisions regarding referral to coronary CTA were based on patients' history, symptoms, risk profile, and echocardiographic findings according to national and European Society of Cardiology guidelines. Exclusion criteria were: (i) age <40; (ii) previous known CAD; (iii) estimated glomerular filtration <40 mL/min; (iv) pregnancy; and (v) contra-indication for iodine-containing contrast medium, magnetic resonance imaging, or adenosine (severe asthma, advanced atrioventricular block, or critical aorta stenosis). All patients signed a written informed consent form. The Central Denmark Region Committees on Health Research Ethics, The Danish Medicines Agency, and The Danish Data Protection Agency approved the study, including the present 10-year follow-up substudy.

All included patients underwent a systematic interview to assess risk factors and symptoms and underwent coronary CTA. During their visit for coronary CTA, an examination with the acoustic microphone, CADScor®System (Acarix A/S, Denmark) was performed. Patients with suspicion of a coronary stenosis at coronary CTA all underwent invasive coronary angiography (ICA) with fractional flow reserve (ICA-FFR) measurement approximately 4 weeks after the coronary CTA. Patients without stenosis at coronary CTA did not undergo further testing. Follow-up data were obtained from electronic patient records and Danish national health registries (*Figure 1*).

The study design, imaging protocols, and analysis strategy have been published.[16]

CAD-score

Heart sound recordings were obtained with the CADScor®System which is a small transportable electronic stethoscope device consisting of microphones and a micro-computer with a display. The microphone is mounted at the 4th intercostal space just to the left of the sternum with a dedicated adhesive patch during 5 min of rest. During the 3-min recording, the patient is asked to hold his/her breath for a period of 8 s, four times.

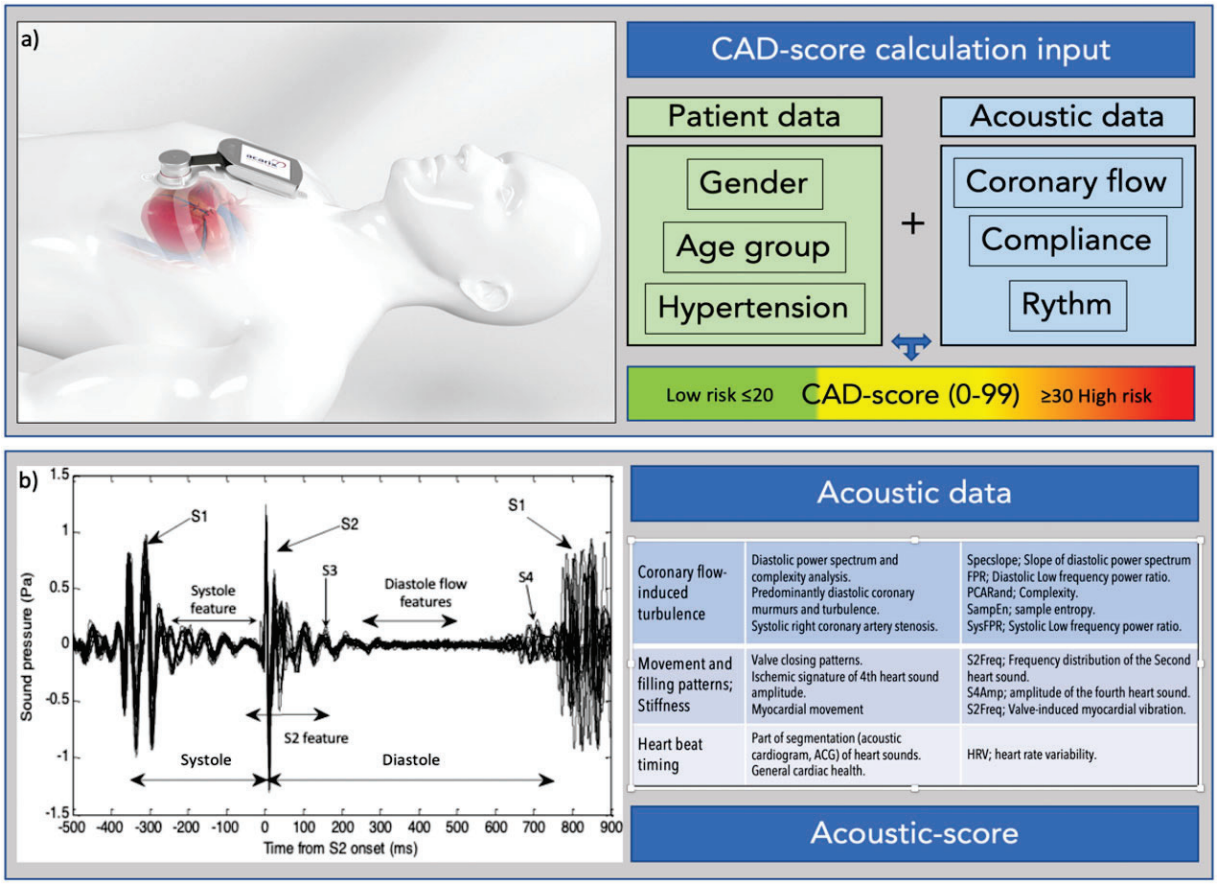


Figure 2 Depiction of the acoustic diagnostic method. (*A*) Coronary artery disease-score is calculated based on a 3-min recording session from the IC4-L region. Three patient risk factors are combined with acoustic derived data to generate a coronary artery disease-score. A score ≤20 is considered low risk and used to substantiate rule-out for coronary artery disease. (*B*) The acoustic data are derived from both the systolic and diastolic periods. The acoustic recording is segmented into discrete heart beats and aligned according to S2. Heart beats containing excess noise are filtered out, and the Acoustic-score is calculated. Several acoustic features having different, distinct coronary and myocardial origins are combined into the Acoustic-score.

Recordings were conducted in an undisturbed room. The CADScor®System analyses the quality of the recording and in case of poor quality, the device requests a second recording.

The CADScor®System algorithm Version 3 (V3) algorithm was utilized to calculate the Acoustic-score *per se* based on post-processing of audio recordings of the heart sound. In total, eight acoustic features related to turbulence murmurs and other heart sound characteristics in CAD were included in the Acoustic-score (*Figure 2*). The CAD-score V3 was generated by combining the Acoustic-score with the risk factors; gender, age, and hypertension (*Figure 2*).

In this paper, we present data from the Acoustic-score version 3 without risk factor modification and the CAD-score version 3. Both an Acoustic-score and a CAD-score value >20 were pre-specified as abnormal.[6]

Coronary computed tomography angiography

All patients in the Dan-NICAD trial underwent coronary CTA scans on a 320-slice volume CT scanner (Aquillion One, Toshiba Medical Systems, Japan) according to clinical guidelines.

CT imaging analysis included an Agatston calcium score and evaluation of CAD including luminal diameter stenosis estimation in each segment of the coronary tree using an 18-segment model. Coronary lesions were evaluated blinded to patient history. Stenosis severity was classified in all segments with a reference vessel diameter >2 mm. Severe stenosis was defined as 50–100% diameter reduction (≈70% to 100% area reduction). Segments with suspected severe stenosis and non-evaluable segments with a reference vessel diameter >2 mm were defined as having obstructive CAD by coronary CTA and referred to ICA.

Invasive coronary angiography

Patients with suspected obstructive CAD at the coronary CTA were referred to ICA. ICA-FFR was measured in lesions with a visually estimated 30–90% diameter stenosis located in vessels with a reference diameter >2.0 mm using a clinical ICA-FFR system (Aeris, St. Jude Medical, Minnetonka, MN, USA). Haemodynamically obstructive CAD was identified in a blinded core lab as: (i) ICA-FFR value <0.80, (ii) luminal diameter stenosis reduction >90%, or (iii) luminal diameter stenosis reduction ≥50% if ICA-FFR was indicated but not performed for technical, anatomical, or other reasons.

Revascularizations were performed according to standard clinical practice after the ICA. Decisions were made blinded for CAD-score and other diagnostic test results.

Follow-up

Clinical endpoint data were extracted from patient records and Danish national health databases. Using the Civil Personal Registration number assigned to each Danish citizen at birth, we obtained information regarding mortality, diagnosed diseases, in-hospital procedures, and medical treatment. The CAD-score remained blinded to clinicians during follow-up. End of follow-up was set to 30 June 2018.

Information on mortality, myocardial infarction, and revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) was obtained from the Western Denmark Heart Registry, the Danish National Patient Registry, and/or Danish Civil Personal Register. Data on Medical treatment and compliance were extracted from reimbursed medical prescriptions at Danish pharmacies through the Danish National Health Service Prescription Database. Changes in lipid lowering therapy after primary cardiac evaluation were defined as continued, discontinued, initiated, or no therapy according to both pre- and post-test-issued prescriptions within a window of 180 days before and 120 days after the examination.

Statistical analysis

The primary study endpoint was defined as a composite endpoint of all-cause mortality and myocardial infarction blinded for the first 120 days after coronary CTA. Secondary endpoints were early and late revascularization with a cut-off of 120 days with death as competing risk, and any coronary events blinded for the first 120 days after coronary CTA (all-cause mortality, myocardial infarction, and late revascularization). Patients who were revascularized early in relation to the baseline cardiac diagnostic evaluation were not excluded from the follow-up.

The primary aim was to compare scores with a cut-off value of 20, however for the CAD-score, we also considered the three groups: CAD-scores ≤20 (reference), CAD-scores 21–29, and CAD-scores ≥30, as well as an increment of the CAD-score of 10 units.

Time-to-event analysis was performed with univariate and multivariate Cox regression of the cause-specific hazard ratios (HRs). Cumulative incidence functions for each endpoint were generated to illustrate the risk over time. For Cox multiple regression analysis, we pre-specified models which included an updated Diamond–Forrester score, coronary disease severity at coronary CTA with stratification for change in medication, and revascularization as part of the Dan-NICAD trial's cardiac evaluation. However, *post hoc* we chose to develop several models with the endpoint of any cardiac event due to the low number of events. Cox multiple regression analysis was pre-specified to be blinded for the period of the first 120 days from baseline to enable adjustment of change in medication and revascularization as part of the baseline cardiac evaluation. In the blinded period, two patients died. They were the only ones excluded in the Cox multiple regression analysis.

For all statistical analyses, 95% confidence intervals (CIs) were reported when appropriate. The statistical analyses were performed using STATA-15.

Results

Of 1675 patients enrolled in the Dan-NICAD trial, 1464 (87.4%) were included in this study. In total, 211 (12.6%) were excluded due to missing CAD-score V3 (characteristics specified in Supplementary material online, *Table S1*). Baseline characteristics are listed in *Table 1*.

The median Acoustic-score was 24 (14–29). The Acoustic-score correlated vaguely with age, Spearman's rho 0.11 ($P < 0.001$), and was higher in males than in females, 27 (21–32) vs. 21 (16–25) ($P < 0.001$). A total of 488 (33%) patients had an Acoustic-score ≤20, indicating low risk.

The median CAD-score was 20 (10–31). The CAD-score was positively correlated with age, Spearman's rho 0.50 ($P < 0.001$), and was higher in males than in females: 28 (15–31) vs. 15 (7–24) ($P < 0.001$), respectively. A total of 723 (49%) patients had a CAD-score ≤20, indicating low risk. The CAD-score was positively correlated with the Acoustic-score, Spearman's rho 0.54 ($P < 0.001$). Furthermore, 2 × 2 tables for the scores are available in Supplementary material online, *Table S2*).

Diagnostic imaging characteristics of the baseline cardiac evaluation including echo, coronary CTA, ICA-FFR measurements, and revascularization related to the baseline cardiac evaluation, which were part of the Dan-NICAD trial, are summarized in *Table 2*. The median inter-test interval between coronary CTA and ICA was 30 days (10th and 90th percentiles: 14 and 50 days).

Treatments initiated at baseline

Lipid-lowering therapy was initiated based on baseline cardiac evaluation in 103 (14.3%) patients with a CAD-score ≤20 and in 184 (24.8%) with a CAD-score >20 (Supplementary material online, *Figure S1*). However, at baseline, plasma cholesterol levels were also higher in patients initiating lipid lowering therapy than in others, 5.8 ± 1.1 vs. 5.3 ± 1.0 mmol/L, $P < 0.001$.

In total, 140 patients were diagnosed with haemodynamically obstructive CAD at ICA based on the baseline cardiac evaluation; and 112 patients were subsequently early revascularized according to standard clinical practice, 62 with PCI and 50 with CABG (secondary endpoint, *Tables 3* and *4*). CAD-scores were significantly higher in the 112 revascularized patients than in the 1352 patients without revascularization related to the primary cardiac evaluation, 31 (21–40) vs. 19 (10–30) ($P < 0.001$), respectively. A detailed description of clinical information and imaging characteristics of the 26 patients who were revascularized and had a CAD-score ≤20 is presented in Supplementary material online, *Table S3*.

Prognostic value of heart sound analysis

The combined primary endpoint occurred in 26 patients; 16 patients died and 10 patients had a myocardial infarction within a median follow-up time of 3.1 (2.7–3.4) years. In total, nine patients had late revascularization (>120 days after inclusion) (Supplementary material online, *Table S4*).

The isolated Acoustic-score without inclusion of risk factors was >20 in 25 out of 26 (96%) patients with the primary endpoint, mortality and myocardial infarction (*Table 3*). The unadjusted HR was 12.6 (1.7–93.2), $P < 0.05$. The HR of the Acoustic-score did not increase for Acoustics-scores ≥30 compared with scores in the 21–29 range. Acoustic-score >20 had an HR for early revascularization within 120 days of 2.3 (1.4–3.6) but did not predict late revascularization (*Figure 3*, Supplementary material online, *Figure S2*).

The CAD-score was >20 in 22 of 26 (85%) patients with the combined primary endpoint—in 12 of 16 (75%) of patients who died, and in all 10 patients who had myocardial infarction. In addition, CAD-

Table 1 Baseline characteristic of included patient demographics (*N* = 1464)

	Total	CAD-score ≤20	CAD-score >20
Number of patients	1464	723 (49.3%)	741 (50.7%)
Characteristic			
Race, Caucasian	1454 (99.3%)	717 (99.2%)	737 (99.5%)
Sex, male	716 (48.9%)	257 (35.6%)	459 (62.9%)
Age (years)	57.1 ± 8.7	53.3 ± 8.0	60.8 ± 7.8
Body mass index (kg/m^2)	26.6 ± 4.1	26.3 ± 4.1	27.0 ± 4.1
Abdominal circumference (cm)	93.0 ± 12.6	90.6 ± 12.3	95.3 ± 12.5
Blood pressure			
Systolic	138 ± 19	129 ± 14	148 ± 18
Diastolic	83 ± 11	79 ± 10	86 ± 11
Heart rate[a]	65 ± 11	65 ± 11	66 ± 11
Smoking			
Never	697 (47.6%)	343 (47.4%)	354 (47.8%)
Former	536 (36.6%)	245 (33.9%)	291 (39.3%)
Active	231 (15.8%)	135 (18.7%)	96 (13.0%)
Diabetes	79 (5.4%)	24 (3.3%)	55 (7.4%)
Symptoms			
Typical chest pain	407 (27.8%)	203 (28.1%)	204 (27.5%)
Atypical chest pain	493 (33.7%)	259 (35.8%)	234 (31.6%)
Non-specific	564 (38.5%)	261 (36.1%)	303 (40.9%)
Updated Diamond Forrester score	39% (20–54%)	28% (16–45%)	42% (29–59%)
Low risk (<15%)	210 (14.3%)	168 (23.2%)	42 (5.7%)
Moderate risk (≥15% to 85%)	1220 (83.3%)	555 (76.8%)	665 (89.7%)
High risk (≥85%)	34 (2.3%)	0 (0.0%)	34 (4.6%)
Medication			
Hypertension	491 (33.8%)	86 (12.1%)	405 (45.9%)
Mean number of antihypertensives	1.9 ± 1.0	1.9 ± 0.9	1.8 ± 1.0
Hypercholesterolaemia	398 (27.2%)	145 (20.0%)	253 (34.1%)
Biochemistry[b]			
Cholesterol (total, mmol/L)	5.4 ± 1.1	5.4 ± 1.1	5.3 ± 1.1
HbA1c (mmol/mol)	37.7 ± 7.2	37.1 ± 7.0	38.3 ± 7.2
Creatinine (mmol/L)	75.4 ± 14.6	72.4 ± 12.8	78.3 ± 15.6

Values are *n* (%) or mean ±SD or median (IQR).
[a]Mean heart rate at the time of CAD-score measurement was: 54 ± 7 b.p.m. and at the time of CTA: 56 ± 7 b.p.m.
[b]Data available in: cholesterol 94%, glucose fasting 8%, HbA1c 78%, and creatinine 99% of the cohort.

score was >20 in all patients who underwent late revascularization (>120 days after inclusion) (*Table 4*).

In an unadjusted Cox regression analysis of the combined primary endpoint, CAD-scores >20 had an HR of 5.4 (1.9–15.7), $P < 0.01$. The HR increased significantly with higher CAD-score; with CAD-scores ≤20 as reference, CAD-scores 21–29 and CAD-scores ≥30 had a HR of 3.0 (0.9–10.8), $P = 0.09$, and 7.7 (2.6–22.9), $P < 0.001$, respectively (*Figure 4* and Supplementary material online, *Figure S2*).

It was not possible to calculate the HR for late revascularization as there were no events in patients with CAD-scores ≤20. However, the log-rank test for late revascularization was significant, $P < 0.001$ (*Figure 4*).

In Cox regression analysis of any cardiac events after 120 days (secondary endpoint: death, myocardial infarction, or revascularization >120 days), a CAD-score increment of 10 units had an HR of 1.8 (1.3–2.5) $P < 0.01$, which was not influenced by adjustment for sex and age. In contrast to the updated Diamond–Forrester score, the CAD-score remained significant after including the updated Diamond–Forrester score in the model. Finally, the CAD-score remained significantly associated with events after adjusting for (i) coronary stenosis at coronary CTA and (ii) lipid lowering therapy initiation and revascularization (*Table 5*).

In a stratified analysis of patients not revascularized as part of the baseline cardiac evaluation ($n = 1352$), a CAD-score >20 had an HR of 3.9 (1.1–13.9), $P < 0.05$, and a CAD-score increase of 10 units had an HR of 1.5 (1.0–2.3), $P = 0.05$, for events after 120 days (dead, myocardial infarction or revascularization >120 days). Similarly, in patients ($n = 112$) who were revascularized, all patients who died or had myocardial infarction or revascularization >120 days had a CAD-score >20, and a CAD-score increment of 10 units had an HR of 1.5 (0.8–2.6), $P = 0.17$, for events after 120 days.

Table 2 Imaging study characteristics from the baseline cardiac evaluation which were protocolized in the Dan-NICAD trial

	Total	CAD-score ≤20	CAD-score >20
Number of patients	1464	723 (49.3%)	741 (50.7%)
Echo (*n* = 1438)			
Left ventricular ejection fraction	59.9% ± 3.4	60.0% ± 2.6	59.5% ± 4.0
Cardiac valve disease, any	69 (4.7%)	23 (3.2%)	46 (6.2%)
Coronary artery calcium score (*n* = 1459)			
Median	0 (0–81)	0 (0–13)	25 (0–192)
Coronary artery calcium score (CACS) groups			
None (CACS = 0)	747 (51.2%)	472 (65.7%)	275 (37.2%)
Low/moderate (CACS: 1–399)	564 (38.7%)	219 (30.5%)	345 (46.6%)
High (CACS ≥400)	148 (10.1%)	28 (3.9%)	120 (16.2%)
Cardiac computed tomography angiography (*n* = 1457)			
Coronary artery disease severity			
Non (stenosis 0% and CACS = 0)	696 (47.8%)	449 (62.5%)	247 (33.5%)
Mild (stenosis 0–30%)	306 (21.0%)	126 (17.5%)	180 (24.4%)
Moderate (stenosis 30–50%)	111 (7.6%)	51 (7.1%)	60 (8.1%)
Severe (stenosis 50–100%)	344 (23.6%)	93 (12.9%)	251 (34.0%)
Radiation dose per coronary CTA (mSv)	2.7 ± 1.7	2.4 ± 1.5	2.9 ± 1.8
Invasive coronary angiography with fractional flow reserve (*n* = 321)[a]			
Coronary artery disease severity			
Obstructive stenosis	140 (9.7%)	27 (3.8%)	113 (15.6%)
Number of coronary vessels with severe stenosis			
One-vessel disease	85 (5.9%)	16 (2.3%)	69 (9.5%)
Two-vessel disease	37 (2.6%)	8 (1.1%)	29 (4.0%)
Three-vessel disease or left main disease	18 (1.3%)	3 (0.4%)	15 (2.1%)

Values are *n* (%) or mean ± SD or median (IQR).
CACS, Coronary artery calcium score.
[a]ICA were only indicated in patient with severe stenosis at coronary CTA.

Table 3 Tables of events during follow-up according to the Acoustic-score

	Total	Acoustic-score ≤20	Acoustic-score >20
Number of patients	1464	448 (33.3%)	667 (66.7%)
Primary endpoint			
Mortality and myocardial infarction	26 (1.8%)	1 (0.2%)	25 (2.6%)
Secondary endpoints			
Mortality, all-cause	16 (1.1%)	1 (0.2%)	15 (1.5%)
Myocardial infarction	10 (0.7%)	0 (0.0%)	10 (1.0%)
Procedure related/spontaneous	2/8	0/0	2/8
Early/late (cut-off 120 days)	7/3	0/0	7/3
Early revascularization (≤120 days)	115 (7.9%)	21 (4.3%)	94 (9.6%)
Part of the primary Dan-NICAD evaluation	112	21	91
Acute	3	0	3
Late revascularization (>120 days)	9 (0.6%)	3 (0.6%)	6 (0.6%)

Values are *n* (%).

In a 'worst case scenario' simulation, an event was assigned to all patients with early revascularization as part of the primary baseline cardiac evaluation and with a false negative CAD-score ≤20 (*n* = 26). In this scenario, CAD-scores >20 had similarly 5-year events rates, for any mortality, myocardial infarction, late revascularization not part of the primary baseline evaluation, and early revascularization as

Table 4 Tables of events during follow-up according to the CAD-score

	Total	CAD-score ≤20	CAD-score >20
Number of patients	1464	723 (49.3%)	741 (50.7%)
Primary endpoint			
Mortality and myocardial infarction	26 (1.8%)	4 (0.6%)	22 (3.0%)
Secondary endpoints			
Mortality, all-cause	16 (1.1%)	4 (0.6%)	12 (1.6%)
Myocardial infarction	10 (0.7%)	0 (0.0%)	10 (1.4%)
Procedure related/spontaneous	2/8	0/0	2/8
Early/late (cut-off 120 days)	7/3	0/0	7/3
Early revascularization (≤120 days)	115 (7.9%)	26 (3.6%)	89 (12.0%)
Part of the primary Dan-NICAD evaluation	112	26	86
Acute	3	0	3
Late revascularization (>120 days)	9 (0.6%)	0 (0.0%)	9 (1.2%)

Values are *n* (%).

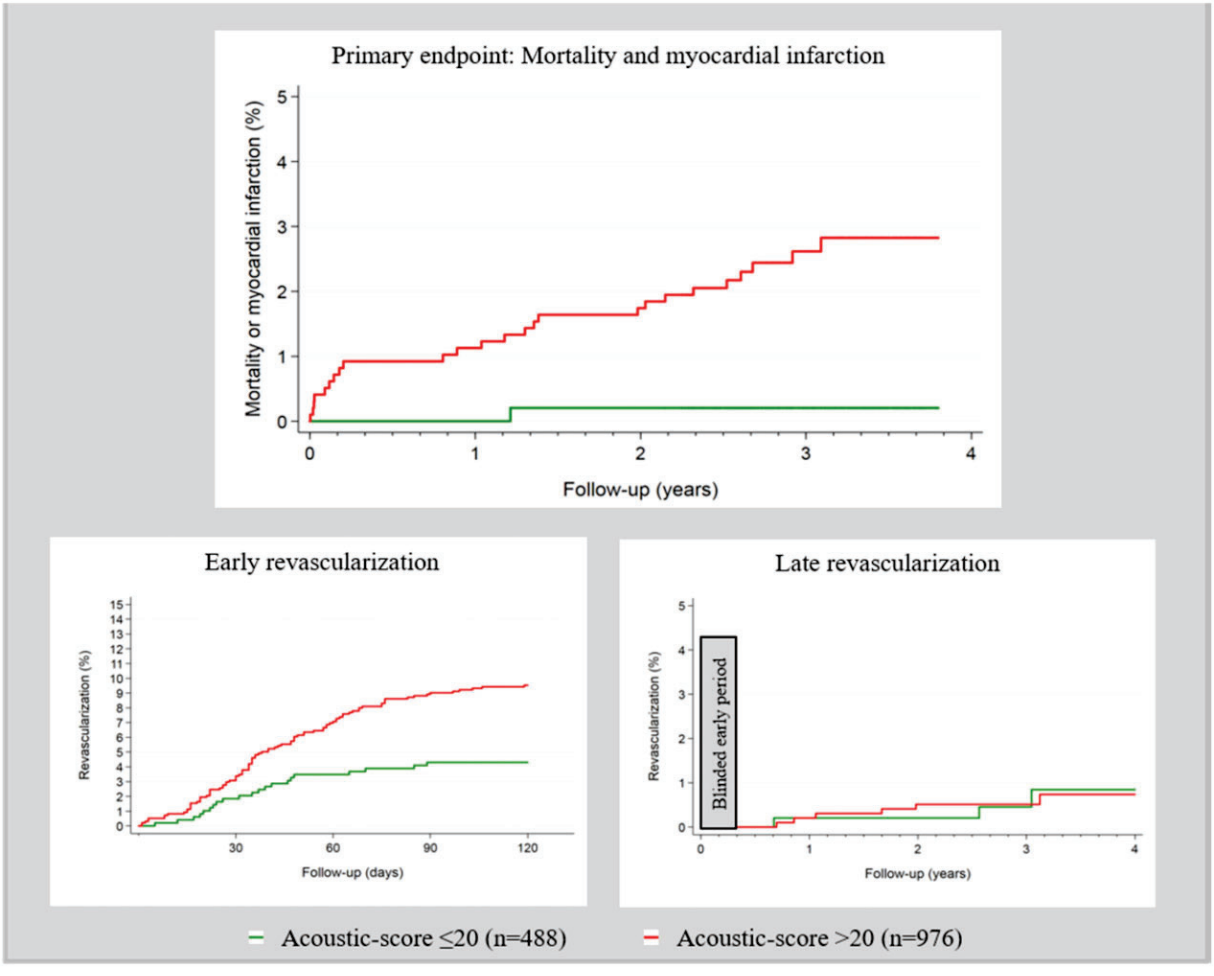


Figure 3 Primary and secondary endpoints according to Acoustic-score with a pre-specified cut-off >20.

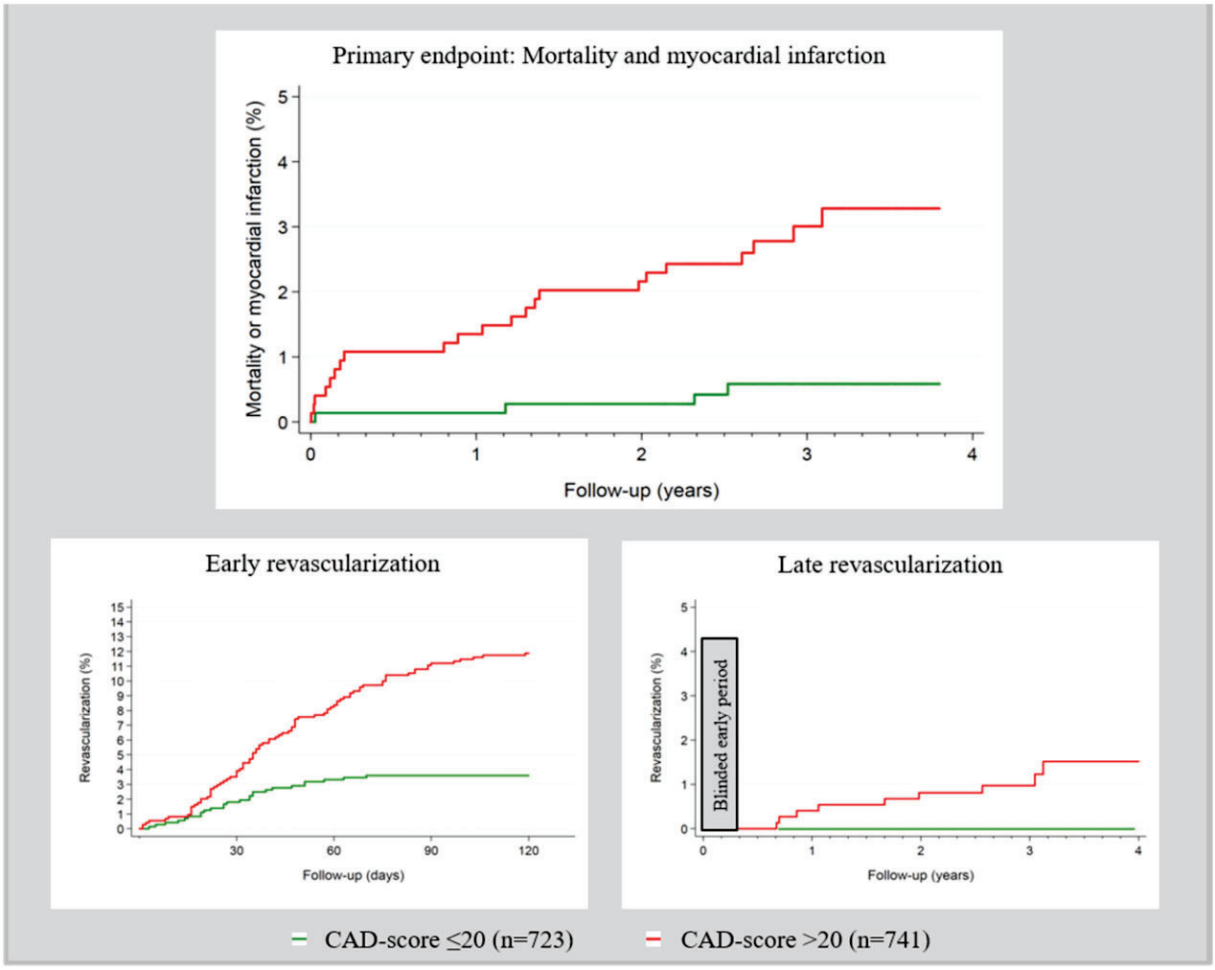


Figure 4 Primary and secondary endpoints according to coronary artery disease-score with a pre-specified cut-off >20.

part of the primary cardiac evaluation with CAD-score ≤20 (Supplementary material online, *Figure S3*).

Discussion

In this study, we present prognostic data showing that an Acoustic-score derived from heart sound has prognostic impact in patients with symptoms suggestive of CAD referred to cardiac CT. This Acoustic-score combined with risk factors, the CAD-score, demonstrated an HR >5 for the primary endpoint, a composite of myocardial infarction and all-cause mortality, at a pre-specified binary cut-point of CAD-score of 20. The prognostic value rose with higher CAD-score, HR >7.5 for CAD-score ≥30 compared with ≤20. In addition, the CAD-core remained a prognostic predictor after adjusting for the updated Diamond–Forrester score and coronary stenosis at coronary CTA.

Acoustic detection of CAD

Acoustic detection of turbulent blood flow in coronary stenosis was first described in 1967 as a high-frequency diastolic murmur.[17] Since then, heart sound analysis has allowed differentiation between no, early, and advanced stages of CAD, as illustrated by diastolic frequency spectrum plots.[5,18] Technological improvements in heart sound recording, segmentation, and analysis have enabled the development of an acoustic device for ruling out obstructive CAD.

Two large studies have tested the diagnostic accuracy of these acoustic rule-out devices in stable CAD. The CADence device was evaluated in the TURBULENCE study, a 21-sites multicentre study in the USA.[7] The CADence device uses multiple recording positions and is handheld during the recording. Patients ($n = 785$) referred for nuclear stress testing due to chest pain symptoms and two or more CAD risk factors were included. Nuclear stress testing was followed by either coronary CTA or ICA as a reference standard with ≥70% diameter stenosis indicating obstructive CAD. Disease prevalence was 15%, and the CADence device had a sensitivity of 78%, a specificity of 35%, and a positive and negative predictive value of 17% and 91%, respectively.

In the Dan-NICAD trial, the CADScor®System was tested in 1,675 patients with predominately intermediate risk of CAD who had been referred for coronary CTA.[6] Patients were referred from five Danish hospitals, and coronary CTA was performed at

Table 5 Cox regression analysis of any cardiac events after 120 days (dead, myocardial infarction or late revascularization >120 days)

	Univariate	Multivariate
Model A		
CAD-score per 10 unit	1.8 (1.3–2.5) $P < 0.01$	1.8 (1.1–2.8) $P < 0.05$
Sex, male	2.1 (0.9–5.0) $P = 0.08$	1.1 (0.4–3.0) $P = 0.84$
Age per 10 years	1.5 (0.9–2.3) $P = 0.11$	1.0 (0.6–1.7) $P = 0.95$
Model B		
CAD-score per 10 unit	1.8 (1.3–2.5) $P < 0.01$	1.7 (1.2–2.4) $P < 0.01$
Diamond–Forrester score 10 unit	1.2 (1.0–1.4) $P < 0.05$	1.1 (0.9–1.3) $P = 0.52$
Model C		
CAD-score per 10 unit	1.8 (1.3–2.5) $P < 0.01$	1.6 (1.1–2.4) $P < 0.05$
Diamond–Forrester score 10 unit	1.2 (1.0–1.4) $P < 0.05$	1.0 (0.8–1.2) $P = 0.88$
Severe stenosis at coronary CTA	6.1 (2.6–14.3) $P < 0.001$	4.2 (1.7–10.4) $P < 0.01$
Model D		
CAD-score per 10 unit	1.8 (1.3–2.5) $P < 0.01$	1.5 (1.1–2.1) $P < 0.05$
Lipid lowering therapy initiated	4.1 (1.9–9.2) $P < 0.01$	2.0 (0.8–4.9) $P = 0.13$
Revascularization at baseline	8.9 (3.9–20.0) $P < 0.001$	4.6 (1.8–11.6) $P < 0.01$

CAD-score and updated Diamond–Forrester scores are analysed as a continuous variable per 10 units.
Values are hazard ratios (CI 95%).

two high-volume centres. Patients with a coronary stenosis at coronary CTA underwent ICA with FFR, and haemodynamically obstructive CAD was defined as ICA-FFR <0.80. In Denmark, coronary CTA is the first-line test for ruling out CAD in *de novo* patients, which results in a low disease prevalence of 10% in the Dan-NICAD trial compared with 15% in TURBULENCE. The CADScor®System had sensitivity of 81%, a specificity of 53%, and a positive and negative predictive value of 16% and 96%, respectively; hence, similar sensitivities and positive predictive values but higher specificities and negative predictive values than the TURBULENCE study.

Prognostic value of acoustic analysis of heart sound

The present study is the first study to evaluate the prognostic value of an acoustic analysis of heart sounds. An isolated Acoustic-score of eight heart sound features related to CAD predicted 25 out of 26 myocardial infarctions or deaths. Combining the Acoustic-score with risk factors to obtain the CAD-score increased the proportion of patients with a score ≤20, and thus a low probability of CAD, from 33% to nearly 50%. Nonetheless, the CAD-score remains highly predictive for both deaths, myocardial infarctions, and late revascularization.

The prognostic value of the CAD-score remained significant after adjustment for coronary stenosis, which is a very strong prognostic predictor in stable CAD. This is due to specific acoustic features related to, e.g. high-risk plaque characteristic. However, further research is needed regarding the origin of these acoustic features and their correlation with specific pathologies.

The Dan-NICAD trial was designed to evaluate the diagnostic accuracy of the CAD-score with a reference of haemodynamic coronary stenosis at ICA.[6] Decisions regarding medical treatment and revascularization were based on standard clinical care; thus, no decision was taken based on the CAD-score. In patients with a CAD-score ≤20, lipid lowering therapy was initiated in 103 (14.3%) and 26 (3.6%) were revascularized. These patients had a therapy that might have altered their prognosis and affected the outcome of the present study. We performed multiple regression and stratified analyses to adjust for this confounder, and the conclusion on the prognosis was unaffected.

Finally, we performed a 'worst case scenario' presuming the situation that all early revascularized patients with CAD-scores ≤20 had an event of death, myocardial infarction, or late revascularization—as mimic the most severe consequence if we had not offered early revascularization to these patients due to rule-out based on CAD-score. In this scenario, a CAD-score >20 was no longer a predictor of prognosis. Contradict, 723 patients with a CAD-score ≤20 would not have need coronary CTA for ruling out obstructive CAD. Hence, a reduction in contrast agent and iodinated radiation of >1700 mSv (723 patients with an averaged radiation dose of 2.4 mSv per coronary CTA) could be achieved in this study despite we used newer generations of CT scanners.

Limitations

This cohort comprised almost exclusively Caucasians with low to intermedia pre-test probability of CAD and none had previously documented CAD. Patients were referred to coronary CTA as the first-line diagnostic test according to Danish standard of care. This approach might have introduced referral bias base on pre-test probability and due to the limitations of coronary CTA, e.g. irregular heart rate and severe obesity.

The development of CAD-score V3 required splitting the cohort into a consecutive training ($n = 593$) and a blinded validation

($n = 1082$) cohort, which might have over-fitted the results in the total cohort analysis. However, diagnostic accuracy in the validation vs. training cohort indicated no over-fitting.[6]

The CAD-score does not distinguish between diastolic murmurs origination. Hence, diastolic valve disease may decrease CAD-score specificity as it increases the false positive rate but sensitivity remains high.[19]

Finally, this study is limited by the low event rates reflecting an overall favourable prognosis of patients with stable CAD. Hence, the results of this study are promising but should be interpreted with caution and final conclusions regarding the safety of acoustic rule-out strategies should await results of randomized controlled strategy trials.

Conclusion

The Acoustic-score derived from heart sound seems to give prognostic information about mortality, myocardial infarction, and late revascularization in patients with symptoms suggestive of CAD which is treated according to standard of care. Diagnostic algorithms of this Acoustic-score combined with risk factors developed for ruling out CAD, the CAD-score, risk-stratified patients even further. These findings are useful as new automated acoustic diagnostic devices have emerged for ruling out obstructive CAD.

Supplementary material

Supplementary material is available at *European Heart Journal is available at* online.

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Data availability

Data can be shared on request to the corresponding author with permission from Acarix A/S.

References

1. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;**362**:886–895.
2. SCOT-HEART investigators. CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial. *Lancet* 2015;**385**:2383–2391.
3. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL; PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med* 2015;**372**:1291–1300.
4. Thomas JL, Winther S, Wilson RF, Bottcher M. A novel approach to diagnosing coronary artery disease: acoustic detection of coronary turbulence. *Int J Cardiovasc Imaging* 2017;**33**:129–136.
5. Winther S, Schmidt SE, Holm NR, Toft E, Struijk JJ, Botker HE, Bottcher M. Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. *Int J Cardiovasc Imaging* 2016;**32**(2):235–245.
6. Winther S, Nissen L, Schmidt SE, Westra JS, Rasmussen LD, Knudsen LL, Madsen LH, Kirk Johansen J, Larsen BS, Struijk JJ, Frost L, Holm NR, Christiansen EH, Botker HE, Bottcher M. Diagnostic performance of an acoustic-based system for coronary artery disease risk stratification. *Heart* 2018;**104**:928–935.
7. Thomas JL, Ridner M, Cole JH, Chambers JW, Bokhari S, Yannopoulos D, Kern M, Wilson RF, Budoff MJ. The clinical evaluation of the CADence device in the acoustic detection of coronary artery disease. *Int J Cardiovasc Imaging* 2018;**34**:1841–1848.
8. Thomas JL, Winther S, Wilson RF, Bottcher M. A novel approach to diagnosing coronary artery disease: acoustic detection of coronary turbulence. *Int J Cardiovasc Imaging* 2017;**33**:129–136.
9. Azimpour F, Caldwell E, Tawfik P, Duval S, Wilson RF. Audible coronary artery stenosis. *Am J Med* 2016;**129**:515–521.e3.
10. Schmidt S, Holst-Hansen C, Hansen J, Toft E, Struijk J. Acoustic features for the identification of coronary artery disease. *IEEE Trans Biomed Eng* 2015;**62**:2611–2619.
11. Becker M, Roehl AB, Siekmann U, Koch A, de la Fuente M, Roissant R, Radermacher K, Marx N, Hein M. Simplified detection of myocardial ischemia by seismocardiography. Differentiation between causes of altered myocardial function. *Herz* 2014;**39**:586–592.
12. Silvestre A, Sandhu G, Desser KB, Benchimol A. Slow filling period/rapid filling period ratio in the apexcardiogram: relation to the diagnosis of coronary artery disease. *Am J Cardiol* 1978;**42**:377–382.
13. Akay M, Semmlow JL, Welkowitz W, Bauer MD, Kostis JB. Noninvasive detection of coronary stenoses before and after angioplasty using eigenvector methods. *IEEE Trans Biomed Eng* 1990;**37**:1095–1104.
14. Wang JZ, Tie B, Welkowitz W, Semmlow JL, Kostis JB. Modeling sound generation in stenosed coronary arteries. *IEEE Trans Biomed Eng* 1990;**37**:1087–1094.
15. Nissen L, Winther S, Westra J, Ejlersen JA, Isaksen C, Rossi A, Holm NR, Urbonaviciene G, Gormsen LC, Madsen LH, Christiansen EH, Maeng M, Knudsen LL, Frost L, Brix L, Botker HE, Petersen SE, Bottcher M. Diagnosing coronary artery disease after a positive coronary computed tomography angiography: the Dan-NICAD open label, parallel, head to head, randomized controlled diagnostic accuracy trial of cardiovascular magnetic resonance and myocardial perfusion scintigraphy. *Eur Heart J Cardiovasc Imaging* 2018;**19**:369–377.
16. Nissen L, Winther S, Isaksen C, Ejlersen JA, Brix L, Urbonaviciene G, Frost L, Madsen LH, Knudsen LL, Schmidt SE, Holm NR, Maeng M, Nyegaard M, Botker HE, Bottcher M. Danish study of Non-Invasive testing in Coronary Artery Disease (Dan-NICAD): study protocol for a randomised controlled trial. *Trials* 2016;**17**:262.
17. Dock W, Zoneraich S. A diastolic murmur arising in a stenosed coronary artery. *Am J Med* 1967;**42**:617–619.
18. Semmlow J, Rahalkar K. Acoustic detection of coronary artery disease. *Annu Rev Biomed Eng* 2007;**9**:449–469.
19. Schmidt SE, Winther S, Larsen BS, Groenhoej MH, Nissen L, Westra J, Frost L, Holm NR, Mickley H, Steffensen FH, Lambrechtsen J, Norskov MS, Struijk JJ, Diederichsen ACP, Boettcher M. Coronary artery disease risk reclassification by a new acoustic-based score. *Int J Cardiovasc Imaging* 2019;**35**:2019–2028.

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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www.nice.org.uk/guidance/mib174

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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