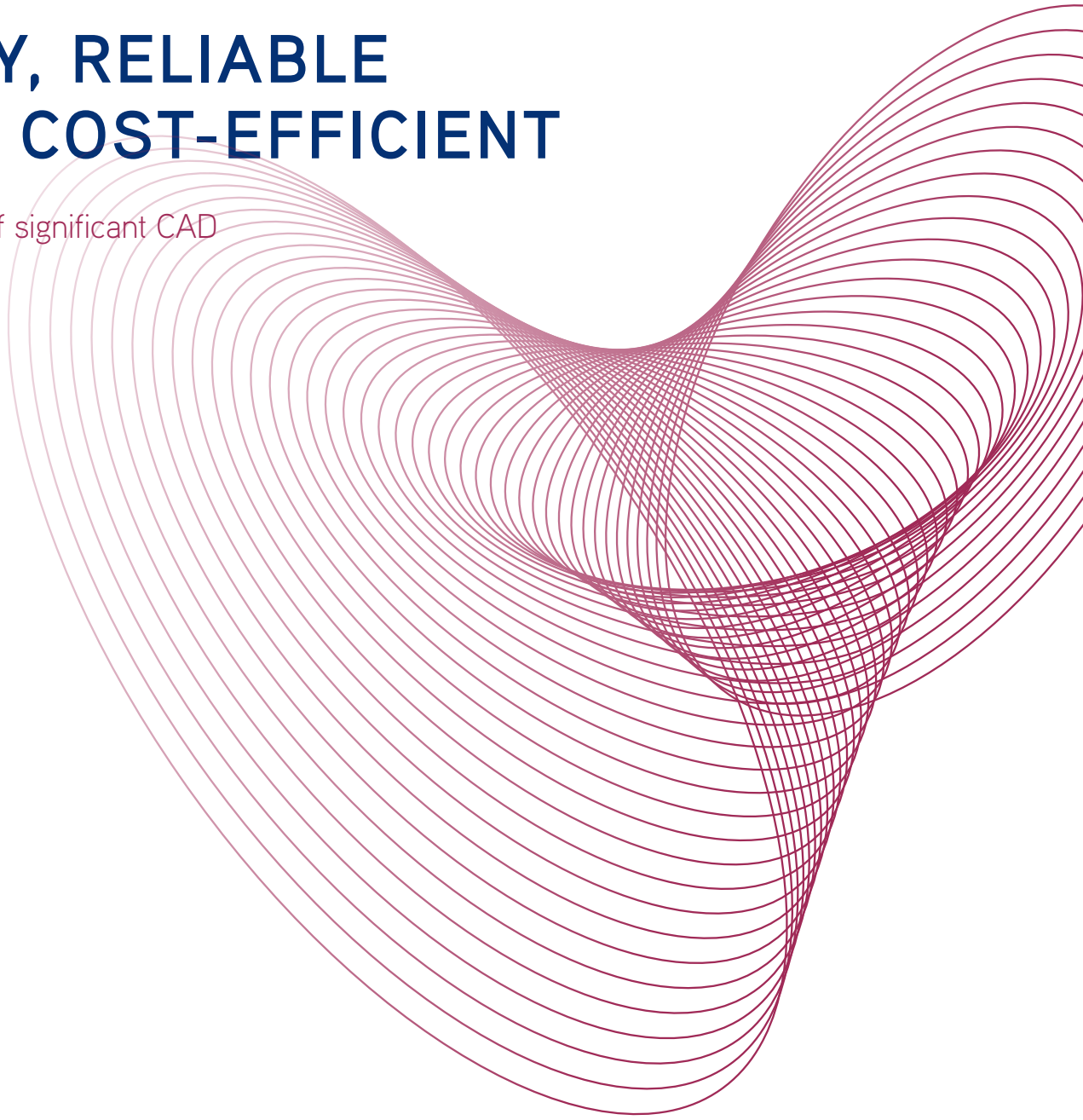
CADScor®System

EASY, RELIABLE AND COST-EFFICIENT

Rule-out of significant CAD



acarix

acoustic cardiac diagnostics

CONTENT

Dear Reader,

in 2003 two young scientists from Aalborg University in Denmark developed the idea to acoustically detect constrictions in the coronary arteries instead of using an invasive cardiac catheter. Samuel Schmidt and Claus Graff, integrated various disciplines, mathematics, physics and medicine into their discourse on detectability of coronary vessel constrictions that cause changes in blood flow.

Heart murmurs have been evaluated acoustically for the last 200 years. The world's first stethoscope, developed in 1818 by René Laennec as well as the binaural stethoscope used today can only perceive "loud" heart murmurs – such as movements of the heart valves and the noise from the blood flow between the heart chambers.

For more than 50 years it has been known that stenosed vessels cause turbulence in the blood flow generating a corresponding noise detectable in the diastole. Early attempts to systematically record these diastolic noises and to make them diagnostically useful failed however due to technological limitations.

The vision of the two young Danish researchers, was able to combine Danish, state-of-the-art, acoustic technology with mathematical algorithms in order to systematically record noises of the flow in the coronary vessels.

The interdisciplinary research group started its work in 2004 and received the "MedicoPrisen" award from the Danish Medtech Trade Association in 2007. A research and development cooperation between Aalborg University and the medical device company Coloplast A/S was founded. The group also received public support from the Danish National Advanced Technology Foundation in 2008.

A prototype was successfully developed and in 2015 the CADScor®System received the CE mark. The first CADScor®System was sold and placed on the market 2017.

Per Persson
CEO Acarix AB

INTRODUCTION

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. The CADScor®System is an acoustic, cost efficient technology for easy, fast and accurate rule-out of coronary artery disease (CAD) in symptomatic patients with chest pain. The device is non-invasive and does not expose the patient to any radiation or stress.

The CADScor®System works with ultrasensitive microphones to record heart sounds of the resting patient (figure 1). Sounds of myocardial movement and blood flow are captured, processed and analyzed to provide a patient specific score. A very high negative predictive value (NPV) allows physicians to exclude CAD with high reliability for patients with a CAD-score ≤20.

FIGURE 1: Heart sound recording with the CADScor®System

The CADScor®System records previously non-detectable heart sounds and vibration for calculation of a patient specific score

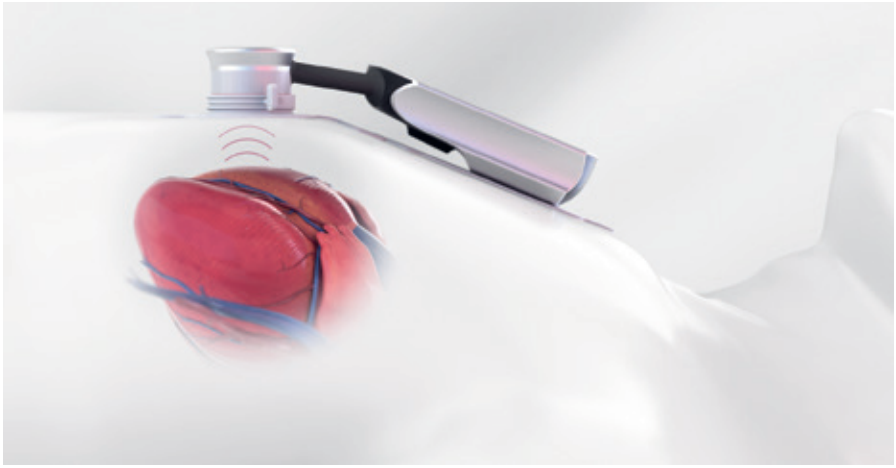
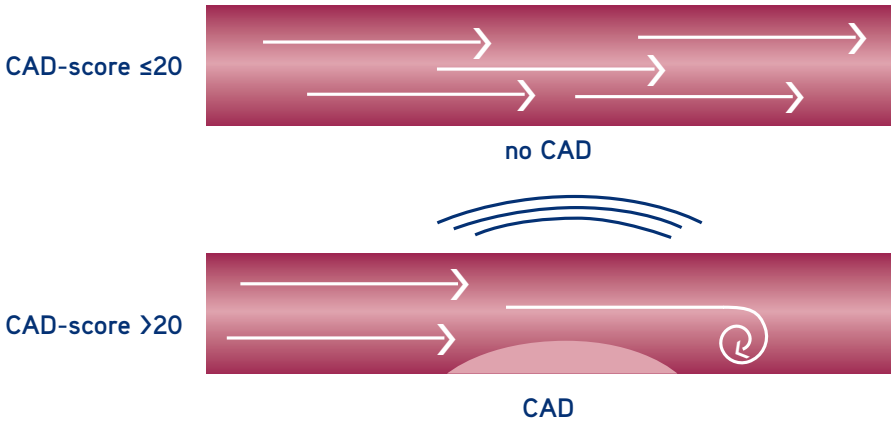


FIGURE 2: Example of cardiac sound abnormality
The disruption of laminar flow by a coronary artery stenosis causes disruption of flow and generates turbulence. Those turbulences cause a detectable acoustic pattern.



Recent technological advancements in the acoustics of the microphones used in the CADScor®Sensor, as well as novel analytic capabilities for data filtering and processing, allow the systematic performance of ultrasensitive audio recordings of the heart (ultrasensitive phonocardiography). Along with substantial miniaturization of the diagnostic technology, a portable, bedside device was developed to exclude suspected CAD easily in less than 10 minutes. The CADScor®System has been commercially available since 2017.

The recordings of the heart sounds allow abnormalities of cardiac sound and myocardial movement to be detected. For example, stenosis in arteries can cause disruption of normal, laminar blood flow and generate turbulence (figure 2). Coronary murmurs originating from turbulence have been described since the 1970s to be correlated with the presence of coronary stenosis[1,2].

The CADScor®System is a new diagnostic aid to exclude CAD non-invasively without radiation or stress

[1] Cheng TO (1970) Diastolic murmur by coronary artery stenosis. Ann Intern Med 72:543-546.
[2] Sangster JF, Oakley CM (1973) Diastolic murmur of coronary artery stenosis. Br Heart J 35:840-844.

We suggest using the CADScor®System as a first-line diagnostic aid for symptomatic patients before any other non-invasive testing

Not only stenosis but also other parameters, such as coronary stiffness, contribute to acoustic characteristics of the diseased heart.

The CADScor®System Algorithm uses eight well described acoustic features adding to a patient specific CAD-score[3]. The result is displayed as a number between 0 and 99 on the device immediately after the short examination. The CAD-score indicates the risk of having CAD (defined as ≥50% diameter stenosis). Three risk categories are defined using the CADScor®System: low risk: CAD-score ≤20; intermediate risk: CAD-score >20 – 30< and high risk: CAD-score ≥30.
A low CAD-score excludes CAD with a NPV of 97% and a sensitivity of 89%. Patients with an intermediate or high-risk CAD-score should be considered for further diagnostic procedures.[4]

This comprehensive overview presents a new technology in its medical context: Limitations in the current diagnostic pathways have the effect that many healthy patients are exposed to costly diagnostic procedures, including risk from radiation, invasive procedures and related stress.

The CADScor®System is a new diagnostic aid to exclude CAD in patients with chest pain through recording and processing of heart sounds in less than 10 minutes.

We suggest using the CADScor®System as a first-line diagnostic aid before any other non-invasive testing is performed for patients with symptoms of stable CAD. Using the CADScor®System as a first in line diagnostic device, will reduce costly diagnostic procedures, which may be associated with additional risk.

[3] Schmidt SE et al. (2015) Acoustic Features for the Identification of CAD. IEEE Transactions on Biomedical Engineering 62.11 2611–2619.
[4] In a population with 10% prevalence: Schmidt SE et al. (2019). Manuscript submitted for publication. Risk-Reclassification of Patients with Suspected CAD Using an Acoustic Score. Circulation. 2018;138: A15761.

CADScor®System

FIRST CHOICE IN NON-INVASIVE RULE-OUT EVALUATION

- Rule-Out CAD in 10 Minutes
- Cost-Efficient and Accurate
- User-Friendly and Reliable

Watch out! The CADScor®System can be used so easily:
vimeo.com/319315725

CHAPTER 1

THE DIAGNOSTIC PATHWAY FOR PATIENTS WITH CHEST PAIN

1 OVERESTIMATION OF CAD IN THE CHEST PAIN PATIENT POPULATION

2 CHEST PAIN PATIENTS AND RECOMMENDATIONS IN CLINICAL GUIDELINES

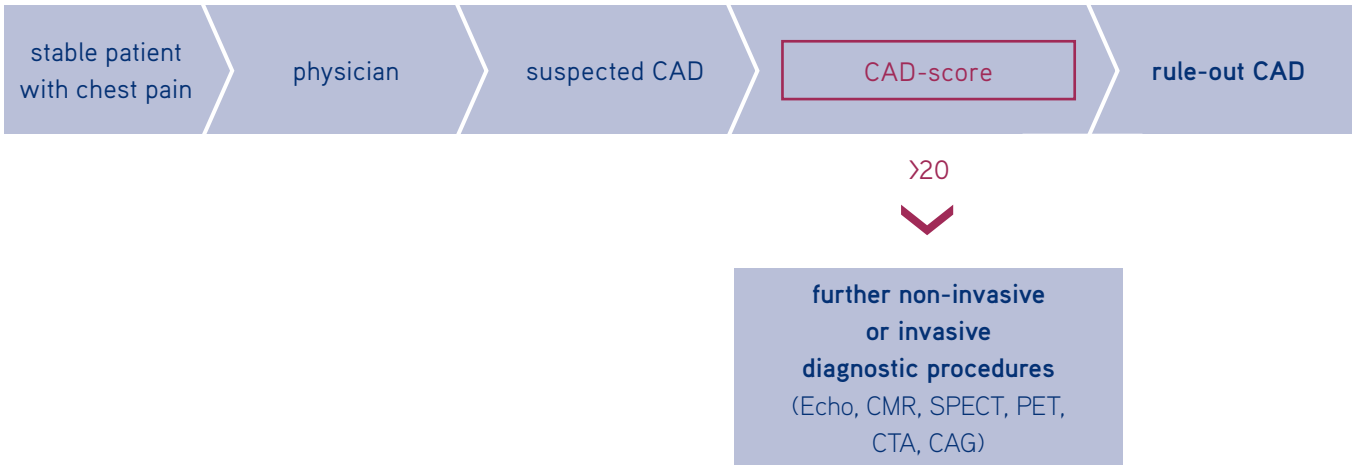
3 THE CONCEPT OF RECLASSIFICATION

4 THE CADScor®System – THE EASY SOLUTION TO BRING DOWN COSTS AND RISKS

OVERESTIMATION OF CAD IN THE CHEST PAIN PATIENT POPULATION

Stable CAD is understood as the condition characterized by episodes of inducible and reversible ischemia commonly associated with transient chest discomfort. The safe and efficient assessment of individuals with chest pain and suspected stable angina is fraught with challenge. In the process of accurately diagnosing stable CAD, physicians must balance the risk of falsely classifying a patient with chest pain and existing CAD as "low risk" against the risk of exposing healthy individuals to non-invasive or invasive diagnostic procedures (figure 3).

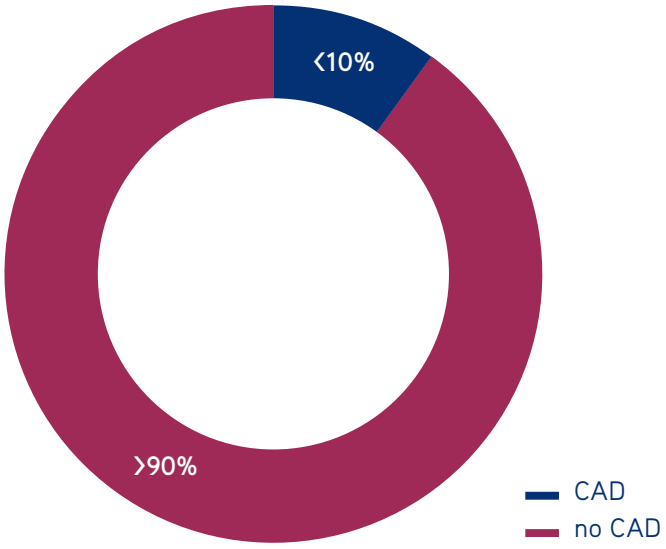
FIGURE 3: Diagnostic flow for chest pain patients



Commonly used risk stratification strategies like the Diamond Forrester score (DF-Score) for patients with chest pain and suspected stable CAD are known to overestimate the likelihood of the disease. Recent studies have shown that as few as 6 – 10% of patients referred to non-invasive testing suffer from significant CAD[5,6]. This means that 9 out of 10 patients referred to non-invasive diagnostic procedures do not suffer from significant CAD. Hence the testing of those patients could be seen as futile (figure 4).

Less than 10%
of patients undergoing non-invasive testing are suffering from CAD

FIGURE 4: Overestimation of significant CAD in current risk stratification
Nine out of ten patients referred to complex diagnostic procedures do not suffer from CAD (red). The burden is twofold: patients are exposed to procedures, live in anxiety while waiting for test results, and the health care system has to pay for many futile procedures.



[5] Winther S et al. (2018) Diagnostic performance of an acoustic-based system for CAD risk stratification. Heart: 104, 928-935 & Douglas PM et al. (2015) Outcomes of anatomical versus functional testing for CAD. N Engl J Med: 372, 1291-1300.
[6] Therming C et al. (2018) Low Diagnostic Yield of Non-Invasive Testing in Patients with Suspected CAD: Results from a Large Unselected Hospital-Based Sample. Eur Heart J – Qual Care Clin Outcomes 4: 301-308.

In case of invasive procedures, despite over half a century of experience, two thirds of the patients undergoing elective diagnostic angiograms do not have significant CAD[7]. Consequences include high cost and potential risk of complications[8]. In Germany, for example, 8 – 11% of patients with chest pain at the primary care level have stable CAD. According to the German Heart Report, over 900,000 diagnostic invasive coronary angiograms are performed in Germany each year. 1% of the patients are suffering from an incident, and 0,19% are dying during the intervention[9]. With more than 900,000 interventions, this results in a significant number of patients put at risk every year.

Summarized, a large proportion of patients evaluated with invasive diagnostics do not suffer from significant CAD. The question arises of how to improve the selection of patients with chest pain for further cost intensive cardiac diagnostic procedures. The need to reduce the number of non-invasive and invasive diagnostic procedures while maintaining diagnostic reliability seems obvious. This should be achieved through better identification and rule-out of patients not suffering from significant CAD early in the diagnostic pathway while ensuring reliability of diagnosis[10].

[7] Patel MR et al. (2010) Low diagnostic yield of elective coronary angiography. N. Engl. J. Med. 362, 886–895.

[8] Tavakol M, Salman A, Brener SJ (2010): Risks and Complications of Coronary Angiogrphy: A comprehensive Review. Global Journal of Health Science, 4,1; 65-93.

[9] German Heart Report 2015, 2016, 2017, 2018.

[10] Albus C et al. (2017) The Diagnosis of Chronic Coronary Heart Disease. Dtsch Arztebl Int. 114 (42):712-719

CHEST PAIN PATIENTS AND RECOMMENDATIONS IN CLINICAL GUIDELINES

Optimizing the balance of safety and efficiency underpins the principles of international clinical guidelines for how to classify patients with chest pain into low risk with no further diagnostic procedures, and higher risk patients who may need further treatment. The European guidelines for the assessment of stable chest pain from the European Society of Cardiology (ESC) and the British National Institute for Health and Care Excellence (NICE) both discourage non-invasive testing in low risk patients with chest pain. However, the approach for how to define those patients differs (figure 5). The updated Diamond-Forrester score was published in 2011. The ESC proposes a risk-based approach based on the updated Diamond-Forrester (DF) classification published in 1979 and 2011.[11,12].

FIGURE 5: Different approaches to define low risk patients

A: Risk-based suggested by the European Society of Cardiology.[13]

	Typical angina		Atypical angina		Non-anginal chest pain	
Age	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
30 – 39	59	28	29	10	18	5
40 – 49	69	37	38	14	25	8
50 – 59	77	47	49	20	34	12
60 – 69	84	58	59	28	44	17
70 – 79	89	68	69	37	54	24
› 80	93	76	78	47	65	32

B: Symptom-based suggested by the UK NICE-Guideline[14]

Typical stable angina symptoms

- Constricting discomfort in the front of the chest, in the neck, shoulders, jaw or arms
- Precipitated by physical exertion
- Relieved by rest or glyceryl trinitrate within about 5 minutes

Typical angina:
all of the above

Atypical angina:
two of the above

Non-anginal chest pain:
one or none of the above

[11] Diamond GA Forrester JS (1979) Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med 300: 1350 – 1358.
[12] Genders TS et al. (2011) A clinical prediction rule for the diagnosis of CAD: validation, updating, and extension. Eur Heart J 32: 1316 – 1330.

The extensive group of patients classified as **intermediate risk** undergoes diagnostic procedures

The risk-based strategy uses the pre-test probability (PTP)[13]. Knowledge of the PTP is used to categorize patients into one of three diagnostic risk groups: low, intermediate, or high.

The NICE guideline[14] recommends since its 2016 edition that the previously used PTP risk score should no longer be used. Instead, following clinical evaluation, patients adjudged to have typical or atypical symptoms, or an abnormal resting electrocardiogram, are categorized into a possible angina group for whom additional non-invasive imaging with coronary computed tomography angiography (CTA) is recommended. The remaining patients are classified as non-anginal, and no further testing is recommended.

Both guidelines agree that non-invasive testing for CAD has the greatest utility (Class I recommendation) in the intermediate risk group, which is arbitrarily defined as 15% to 85% PTP in Europe. This large group of patients seen as intermediate risk should undergo further diagnostic procedures (figure 6).

[13] 2013 ESC Guidelines on the Management of Stable CAD. Eur Heart J 34: 2949–3003.

[14] Chest pain of recent onset Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin (update) NICE guideline CG95 November 2016.

FIGURE 6: Available non-invasive diagnostic procedures adapted from Andrew[15]

Imaging	Stress	Contrast agent/ tracer	Readout(s)	Comments
Echocardiography	Exercise or inotropes	Microspheres may be needed	Regional wall motion	Widely available, needs good echo windows, operator dependent
SPECT-MPI	Exercise, vasodilators or inotropes	Thallium-201 technetium-99 tetrofosmin	Photon emission from tracer distribution	Reasonably widely available, relatively low spatial/temporal resolution with high radiation dose
CTA	None for anatomy, vasodilators used for perfusion assessment	Iodinated contrast	Coronary anatomy, first-pass perfusion	Increasingly available, low radiation dose for anatomy, high dose for perfusion
CMR	Vasodilators or inotropes	Gadolinium-based contrast agent	First-pass perfusion (also regional wall motion if inotropes used)	Increasingly available, high spatial/temporal resolution, not routinely used in patients with cardic devices
PET	Exercise, vasodilators or inotropes	Rubidium-82, oxygen-15, nitrogen-13, and others	Photon emission from tracer distribution	Expensive, not widely available, high spatial resolution, intermediate radiation dose
CADScor®System	Not needed	none	Coronary murmurs, coronary stiffness, myocardial movement	Available since 2017, operator and location independent usage

CMR = cardiac magnetic resonance; CTA = computet tomography angiography; PET = positron emission tomography; SPECT-MPI = single-photon emission computet tomography-myocardial perfusion imaging

[15] Andrew J M (2017) The age of diagnostic coronary angiography is over. J Cardiol 24:105–7.

General Examination | Stress Test (Treadmill or Stress Echo) | MPI, Nuclear Imaging, (CTA) | Invasive Coronary Angiography | Invasive Treatment

Current guidelines[16] do not assign preference to one non-invasive testing modality over another. However, the German national guideline for chronic CAD[17] recommends for patients with a PTP of 15 – 50% computed tomography and for patients with a PTP of 15 – 85% a functional test (stress-echocardiography, perfusions-SPECT or stress-cardiac magnetic resonance CMR). A stress ECG is only recommended for patients with a PTP of 15 – 30%. Given the recently shown reclassification potential from stress ECG for contributing with information only for patient with a PTP of <19%, a margin of 30% PTP seems high[18]. The most radical change in the British NICE 2016 guidelines is the recommendation that all patients with new onset chest pain should be examined with a CTA angiogram as a first-line examination. Whether UK hospitals can fundamentally reconfigure their chest pain investigation pathways, based on current finances and staffing levels, is discussed critically in the UK[19a].

A powerful pre-screening tool to reduce the now overwhelming number of patients recommended for CTA could unwind this situation. NICE published an innovation briefing on CADScor®System 2019 in which „the potential to release resources and provide cost-savings by reducing the need for more complex investigations, such as CTCA and ICA, was identiPed as a key benefit to the healthcare system. The potential to reduce the use of ionising radiation was also identiPed as a benefit".[19b]

16 2013 ESC Guidelines on the Management of Stable CAD. Eur Heart J 34: 2949–3003.

17 Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale Versorgungsleitlinie chronische KHK – Kurzfassung, 4. Auflage. Version 1. 2016. Available from: www.khk.versorgungsleitlinien.de; DOI: 10.6101/AZQ/000323.

18 Knuuti J et al. (2018) The Performance of Non-Invasive Tests to Rule-in and Rule-Out Significant Coronary Artery Stenosis in Patients with Stable Angina Alfakih K a Meta-Analysis Focused on Post-Test Disease Probability. Eur Heart J 39: 3322-3330

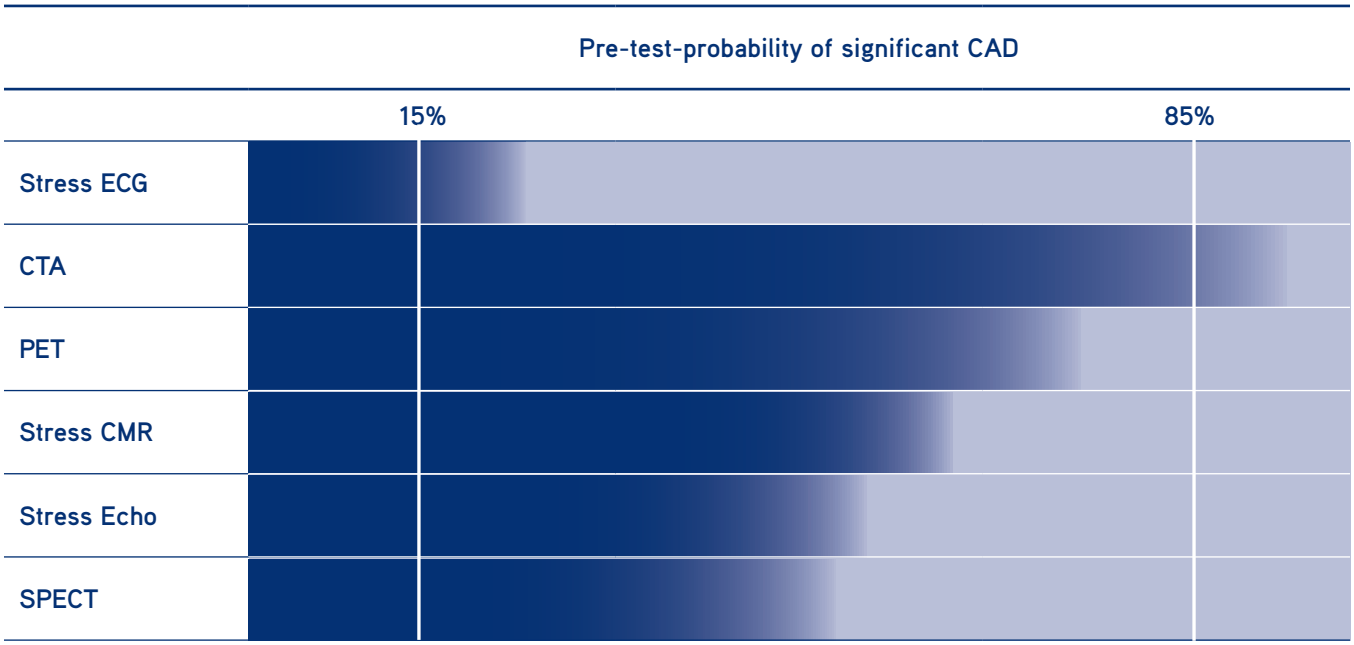
19a Alfakih K et al. (2017) The 2016 update to NICE CG95 guideline for the investigation of new onset stable chest pain: more innovation, but at a cost? Clin Med 17:209-211.

19b CADScor system for ruling out coronary artery disease in people with symptoms of stable coronary artery disease. Medtech innovation briefing. Published: 4 March 2019. www.nice.org.uk/advice/mib174.

THE CONCEPT OF RECLASSIFICATION

A recent meta-analysis[18] showed that the described non-invasive testing modalities have different optimal PTP ranges for reclassifying patients into a post-test probability that defines (PTP >85%) or excludes (PTP <15%) significant CAD. This meta-analysis, for the first time, provides guidance of what non-invasive diagnostic approach (NID) to be used for which patient. When significant CAD was used as a reference standard for reclassification, the best performance in ruling-out CAD was achieved using CTA and least effective with stress ECG. The functional imaging techniques (PET, CMR, and SPECT) had moderate power to rule-out (47 – 58%) significant CAD (figure 7).

FIGURE 7: Reclassification potential
Non-invasive diagnostic procedures (NID) vary in their potential to re-classify patients with initially intermediate risk to low risk. The CADScor®System is the only easily accessible device offering significant and immediate re-classification of patients.



[18] Knuuti J et al. (2018) The Performance of Non-Invasive Tests to Rule-in and Rule-Out Significant Coronary Artery Stenosis in Patients with Stable Angina Alfakih K a Meta-Analysis Focused on Post-Test Disease Probability. Eur Heart J 39: 3322-3330

Stress ECG can rule-out significant CAD only when PTP ≤19%. With this performance it adds only marginal benefit, as only a narrow range of patients with PTP between 15% and 19% are reclassified to the low risk group. CTA is able to rule-out at a PTP of ≤80%. This means that for reclassifying patients to low risk, all individuals with a PTP between 15 and 80% can be ruled out from further testing by a negative CTA[18].

Most procedures capable of reclassifying a very large group of intermediate-risk patients require significant investment in equipment and trained personal.

With the CADScor®System, a user-friendly point of care device is, for the first time, available to rule-out patients from further non-invasive or invasive and expensive diagnostic approaches. The reclassification of the CADScor®System is shown on page 28 and 29.

The CADScor®System **reclassifies a large group** of intermediate risk patients to low risk

THE CADScor®System – THE EASY SOLUTION TO BRING DOWN COSTS AND RISKS

The innovative, completely non-invasive and cost-efficient technology of the Acarix CADScor®System has been commercially available since July 2017. The CADScor®System is to be used as a diagnostic aid for patients suspected with stable CAD. The device consists of a sensor to capture heart sounds and a disposable patch to fix the sensor on the patient's chest (figure 8).

FIGURE 8: The CADScor®System attached to IC4-L
A disposable patch ensures fixation of the sensor to the patient's chest. Heart sounds are detected and analysed in a all-in-one device. A patient-specific CAD-score is displaced after the ten-minute examination to indicate if the patient can be ruled out from further diagnostic procedures or not.

The CADScor®System represents a non-invasive ultra-sensitive method detecting turbulent arterial blood flow and myocardial movement to rule-out significant CAD early in the diagnostic pathway. A portable all-in-one device captures heart sounds and provides a patient specific score to assess the risk for CAD in less than ten minutes. This provides physicians with a rapid first-line tool for early assessment before moving on to more expensive methods.

The CADScor®System is based on acoustic detection of atypical myocardial movement and flow to non-invasively rule out of CAD. It has shown to have a 97% NPV at 9.4% prevalence of CAD. The detection of acoustic features correlated to CAD is delicate, since their energies (amplitudes) are very low. Detection and recording require not only an advanced sensor but also proper attachment above the heart to optimize the recorded signal. First, the sensor records coronary sounds for a few minutes (phonocardiography). Subsequently the sound is analyzed and segmented. Advanced algorithms identify a variety of acoustic parameters associated with CAD, for example murmurs during diastasis. The algorithm combines eight acoustic features into a combined CAD-score, (see chapter "technology"). The CAD-score is calculated within two minutes and displayed immediately as a number between 0 and 99. The cut-off threshold for excluding significant CAD is defined as a CAD-score of 20 or below. In a patient population with 9.4% prevalence, the NPV was found to be 97%.

In addition to its accuracy the CADScor®System offers several advantages: It is fast, radiation-free, non-invasive and applicable in any normal working environment. Handling of the device is easy to learn. The examination can be performed effortlessly and managed by all medical and paramedical staff in less than ten minutes. Results are easily interpreted and delivered instantly, allowing for immediate decisions on how to proceed.

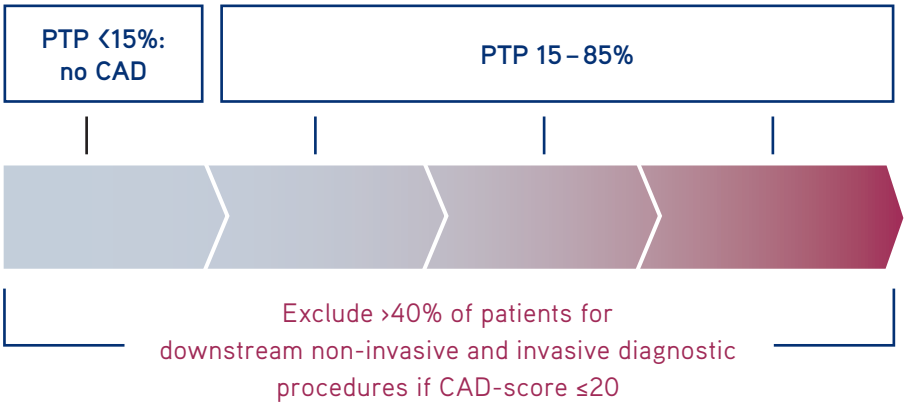
Accurate, fast, radiation free, non-invasive
rule-out of CAD
in symptomatic patients

>40% of patients with low or intermediate risk **can be ruled out** for further diagnostics

With the CADScor®System many patients can be ruled out at an early stage[21]. In a recently published cost model for ruling out symptomatic CAD patients in the German ambulatory sector, 41% of the patients with low to intermediate risk could be reclassified as low risk. This led to a cost reduction of more than 21%, triggered mainly by an exclusion from further diagnostic procedures (figure 9).

With the CADScor®System, coronary angiograms and non-invasive tests can be avoided in patients without CAD[22], resulting in a relief for the patient and the health care system. In case the CADScor®System does not reliably exclude CAD (CAD-score >20), further non-invasive or invasive examinations might be appropriate.

FIGURE 9: CAD continuum
Only 6 – 10% of stable, symptomatic CAD patients presenting for non-invasive diagnostics are diagnosed with CAD. Many of those patients receive CTA, stress ECG, stress echo or coronary angiography. The CADScor®System can rule-out non CAD patients early in the health care process.



[21] Wahler S et al. (2018) Cost model for ruling out CAD in symptomatic patients with ultra-sensitive phonocardiography in the German ambulatory sector, Value in Health 21 PMD46.
[22] Winther S et al. (2017) Cost model for a new acoustic diagnostic aid to rule-out CAD, Value in Health 20 A399–A811 CV4.

CHAPTER 2

THE CADScor®System

CLINICAL STUDIES OVERVIEW

After the successful completion of various technical studies for general research into the procedure carried out on over 750 patients[23], the first major clinical study was AdoptCAD, conducted in Denmark with 228 participants in 2012[24]. This resulted in the granting of the CE mark in August 2015. The CADScor®System is approved in Europe as a diagnostic aid for symptomatic patients with suspected CAD and has been available for purchase and use since 2017. The participants in the registration study were patients, who due to clinical symptoms were referred for CTA or invasive coronary angiography (ICA), as part of their evaluation of suspected obstructive CAD. Before further diagnostic procedures were carried out, a CAD-score was determined for all participants using the CADScor®System. Although these results of the study were sufficient for approval due to the NPV of 93%, the system was not yet made available. The aim was to achieve a further improvement of the NPV in order to optimize the CADScor®System as a safe exclusion diagnostic method.

A patient from a negative test result should not suffer from significant CAD with a high degree of certainty[25].
A larger clinical study, Dan-NICAD, was conducted at two cardiology centers in Denmark[26]. A total of 1,675 patients who had been referred with suspected CAD were included in this study. A CAD-score was obtained from 1,437 patients and further diagnostics carried out according to a defined protocol, up to coronary CTA or ICA.

After the diagnostic procedure had been completed, it was determined that 10% suffered from significant CAD (stenosis ≥50% of vessel diameter). At the pre-determined threshold value for the CAD-score of ≤20, the NPV was 96%[27].

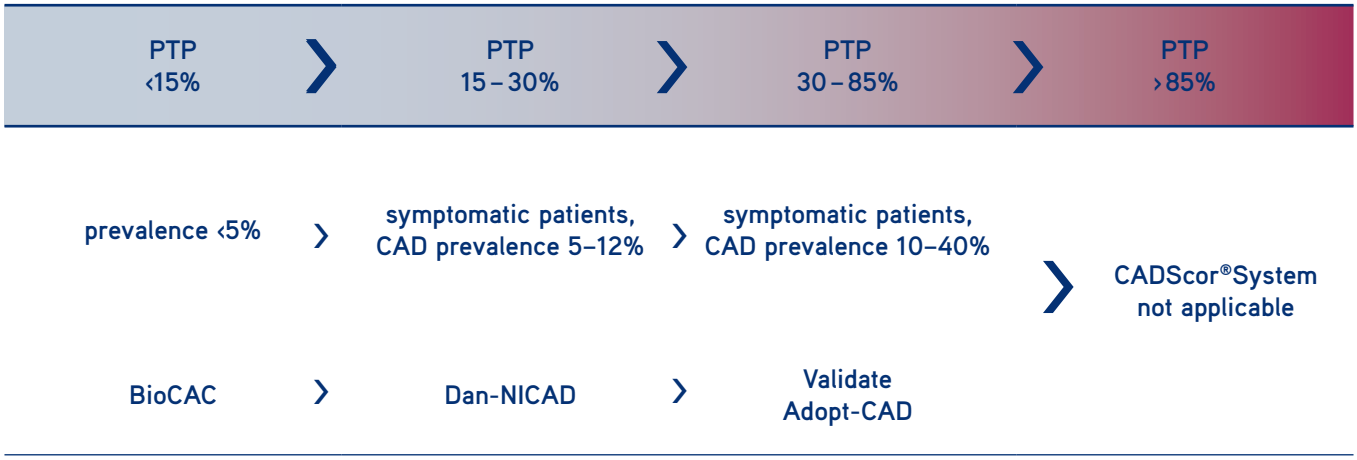
As a result, the algorithm used in the device has been further improved.
The NPV for the total population of 2245 patients and healthy controls from the clinical database used in the algorithm is 97% (prevalence 9.4%) figures 10a and 10b[28].

[23] Schmidt SE et al. (2015) Acoustic Features for the Identification of CAD, Transactions on Biomedical Engineering 62: 2611-9.
[24] Winther S et al. (2015) Diagnosing CAD by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris, Int J Cardiovasc Imaging 32 (2): 235-245.
[25] Thomas JL et al. (2016) A novel approach to diagnosing CAD: acoustic detection of coronary turbulence. Int J Cardiovasc Imaging 33 (1): 129-136.
[26] Nissen L et al. (2016) Danish study of Non-Invasive testing in CAD (Dan-NICAD): study protocol for a randomized controlled trial. Trials. 17(1):262.
[27] Winter S et al (2018) Diagnostic performance of an acoustic-based system for CAD risk stratification, Heart 104 (11): 928-935.
[28] Schmidt SE etal. (2019) Coronary artery disease risk reclassification by a new acoustic-based score. The International Journal of Cardiovascular Imaging https://doi.org/ 10.1007/s10554-019-01662-1.

FIGURE 10A: Clinical trial overview

CADScor®Algorithm Database						
Study	**Summary**	**Pre-valence**	**N**	**Published**	**Sensitivity**	**NPV%**
Reclas-sifica-tion	Combined analysis of 2245 patients from AdoptCAD, BIO-CAC and Dan-NICAD.	9.4%	2245	submitted for publication	89	97
Dan-NICAD	1675 Patients with low to intermediate PTP referred for CTA with suspicion of CAD. Patients with at least one obstructive stenosis identified in CTA were referred to ICA.	10%	1675	2018	80	96
Adopt-CAD	255 subjects referred for either CTA or ICA. Patients where CTA identified a stenosis were further referred to ICA. A total of 249 patients had heart sounds recorded prior to other examinations using a prototype device.	28%	255	2016	90	93
Vali-date	From 226 subjects referred for ICA, CAD-scores were collected prior angiography and also after potential coronary stenting/FFR. The data were collected to confirm the predicted NPV in a high prevalence population.	publication in preparation				
Bio-CAC	CAD-scores of 661 subjects as suple-mentary test in a subset of asymptom-atic subjects undergoing CACS scoring in the 5-year follow-up of the DanRisk study.	–	661	–	–	-

FIGURE 10B: Clinical trials prevalence



A smaller research outside the intended patient group was performed in Germany in 2017. In order to research prevalence-dependent NPV in a higher prevalence population, The Validate study included 226 patients referred for coronary angiography[29].

The CADScor®System was commercially launched in July 2017. A further major study was initiated in 2018. The first patients were included in the Dan-NICAD2 study in January 2018. Dan-NICAD2 fundamentally resembles the previous Dan-NICAD study and collects data for further algorithm improvement.

[29] Prospektive, konsekutive und verblindete Evaluation des nicht-invasiven CADScor®Systems im Vergleich zur invasiven Koronarangiographie bei Patienten mit stabilen koronarer Herzerkrankung (KHK) DRKS00010492: https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00010492

THE CAD-SCORE

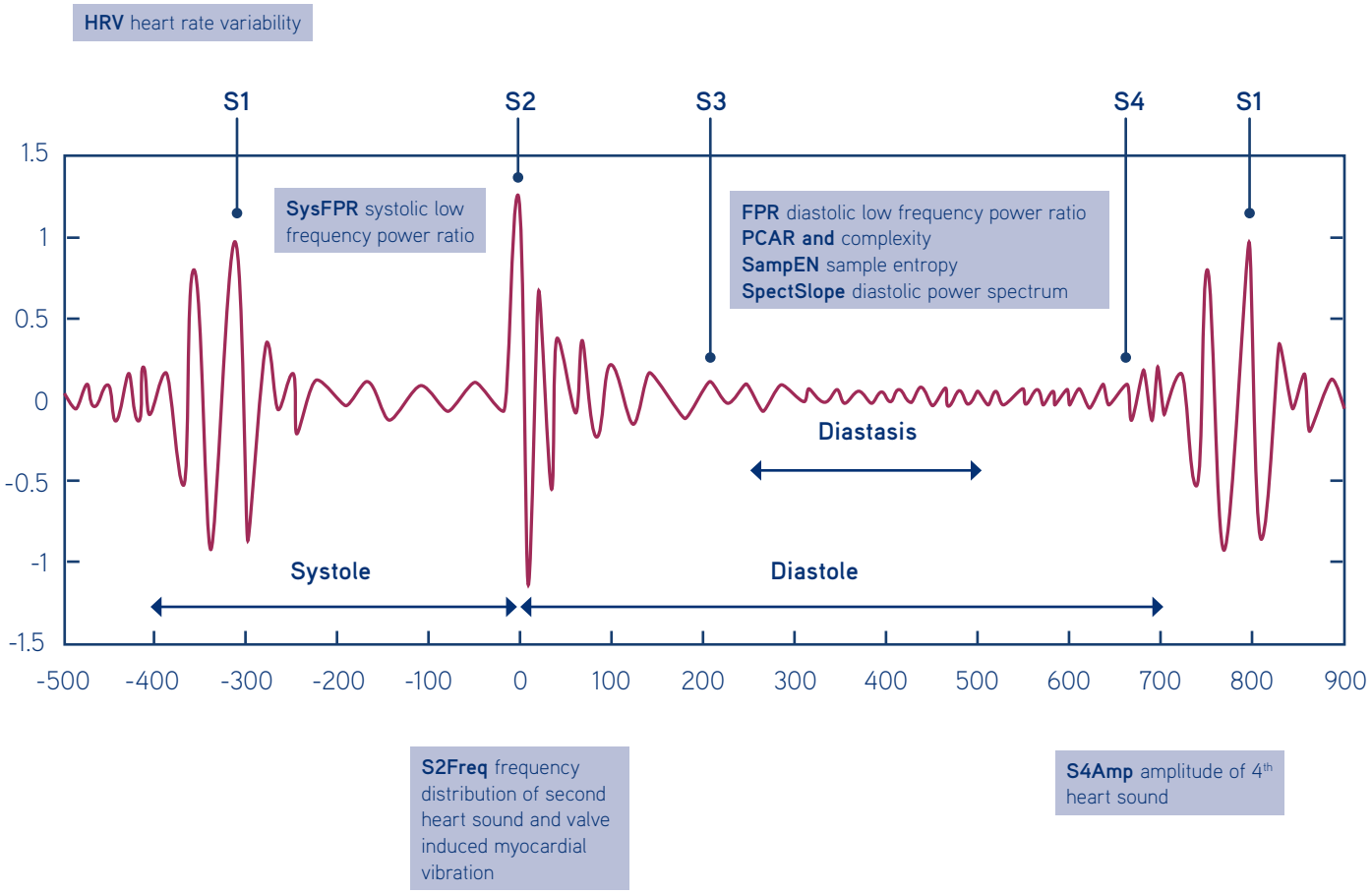
The CADScor®Algorithm has been continuously developed, from the first clinical studies to the launch of the CADScor®System. AdoptCAD used algorithm 2 which combined four acoustic features to calculate a CAD-score. In Dan-NICAD, algorithm 3 was developed in a subset of 1201 patients. The combined database leads to the final algorithm version 3.1. which is embedded in the CADScor®System.

The device's main microphone is attached to the fourth left intercostal space to capture heart sounds. Additionally, a microphone facing outwards captures ambient noise. The examination starts with a pre-recording of 30 seconds to validate sound quality, including analysis of ambient noise. Once the pre-recording passes the internal sound quality control, the patient is asked to hold his or her breath four times, for eight seconds each time. These four "loops" are used for the final analysis, in which first the heart sounds are segmented into systolic and diastolic periods[30]. Next, sounds are filtered, and ambient noise is subtracted from the heart sounds. Eight acoustic features are extracted which describe acoustic properties correlated to CAD[26, 27] (figure 11).

The acoustic features quantify the frequency distribution and the degree of randomness of the diastolic sound, the amplitude of the fourth heart sound, the frequency distribution of the second heart sound, and the frequency distribution of the mid-systolic period. These features are combined into an acoustic score using a linear discriminant function (see chapter software). Using logistic regression, the acoustic score is combined with gender, age, and hypertension, defined as systolic blood pressure of ≥140 mmHg or receiving antihypertension medicine. The CAD-score was scaled such that 90% of subjects with CAD had a CAD-score above 20. Hence, a CAD-score >20 was categorized as abnormal. As a safety measure all patients with an updated DF-Score above 85% are automatically classified as having a minimum CAD-score of 21 in order to adhere to clinical guidelines.

[26] Nissen L et al. (2016) Danish study of Non-Invasive testing in CAD (Dan-NICAD): study protocol for a randomized controlled trial. Trials. 17(1):262.
[27] Winter S et al (2018) Diagnostic performance of an acoustic-based system for CAD risk stratification, Heart 104 (11): 928-935.
[30] Schmidt SE et al. (2010) Segmentation of heart sound recordings by a duration-dependent hidden Markov model. Physiol. Meas. 31, 513–529.

FIGURE 11: Acoustic features captured in a phonocardiogram



THE CADScor®System PERFORMANCE AND RECLASSIFICATION POTENTIAL

Instead of 13.6%
41.8% of patient could be ruled out

Three clinical studies set the foundation of the current heart sound database: The Acoustic Data collection for Optimizing CAD-score Algorithm study (AdoptCAD)[31], the DanRisk five-year follow-up study (BIO-CAC)[32,33], and the Danish Study of Non-Invasive Diagnostic Testing in CAD (Dan-NICAD)[26,27] (figure 10A)

Of the 2245 patients, 212 (9.4%) had significant CAD confirmed by ICA (≥50% diameter stenosis). The average CAD-score of 38.4 for patients with significant CAD was significantly higher versus the CAD-score of 25.1 of the remaining patients ($p<0.001$). [34]

With respect to the important question whether the CADScor®System can reclassify a significant group of intermediate-risk patients, all symptomatic patients of the database were checked. 1673 patients were referred to testing due to suspected CAD (patients from the AdoptCAD and Dan-NICAD studies). 227 (13.6%) of them were classified as having a low likelihood of CAD, PTP <15%. The PTP was calculated using the updated DF-Score[35] according to the ESC guidelines: low <15%, intermediate 15 – 85% and high PTP >85%. Patients with low PTP (<15%) were kept in the low PTP group and patients with a high PTP (>85%) were kept in the high PTP group (figure 12). Only the intermediate PTP group (15 – 85%) was re-classified using the CAD-score. Patients with an intermediate PTP and a CAD-score below or equal to 20 were reclassified to low post-test probability, while patients from the intermediate PTP with a CAD-score above 20 were kept as intermediate probability.

Prior to the CADScor®Test, 227 patients were scored as low risk, and 1395 (83.4%) as intermediate risk. CADScor®System could reclassify 472 out of 1395 patients to “low risk”. The overall low risk group was increased from 227 to 699 patients. Expressed in percentages, initially only 13.6% of the total patient population were classified as low risk. Post-test with CAD-scoring, 41.8% were classified as low risk and could be ruled out from further diagnostics. This reduced the proportion of intermediate risk patients from 1395 to 923, or from 83.4% to 55.2%. Instead of 13.6% of the global patient group, 41.8% could be ruled out, avoiding further testing post CADScor®Testing[34] (figure 12).

[31] Winther S et al. (2015) Diagnosing CAD by sound analysis from coronary stenosis induced turbulent blood flow: diagnostic performance in patients with stable angina pectoris. Int. J. Cardiovasc. Imaging 32 (2): 235-245

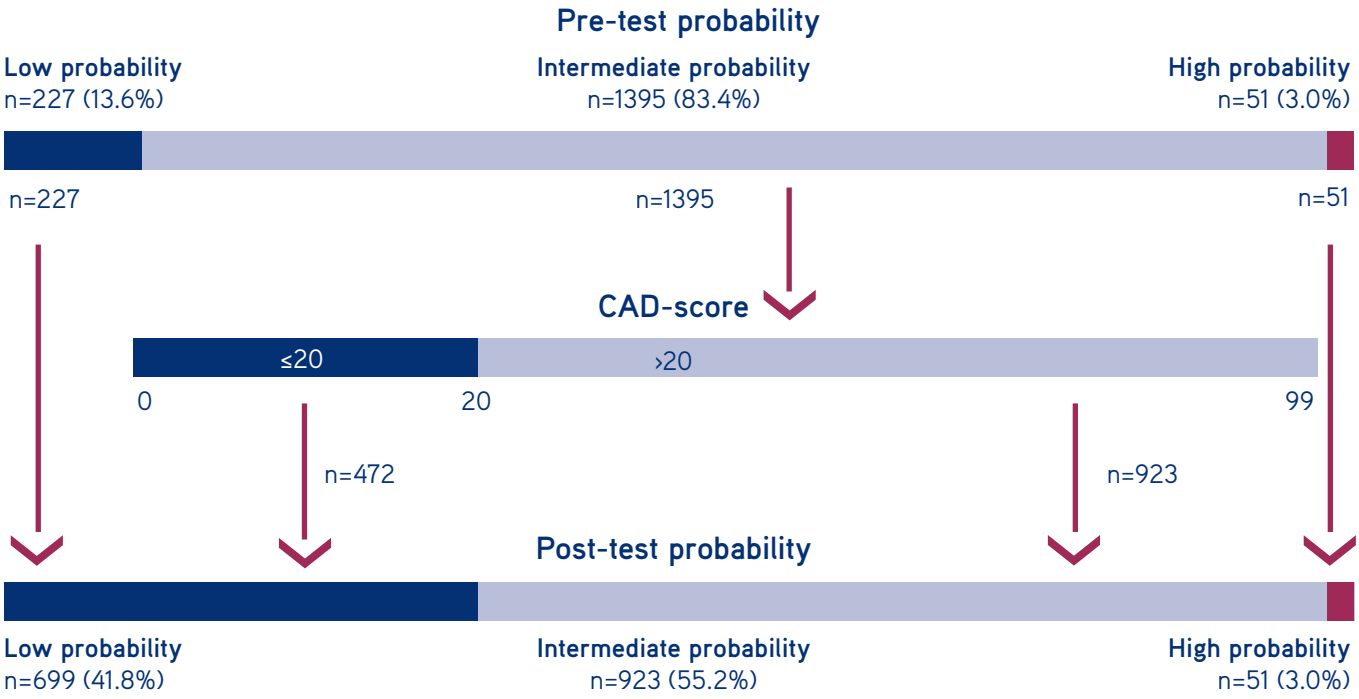
[32] Grønhøj MH et al. (2018) External validity of a cardiovascular screening including a coronary artery calcium examination in middle-aged individuals from the general population. Eur. J. Prev. Cardiol. 2047487318774850 doi:10.1177/2047487318774850

[33] 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 doi:10.1016/j.jcmg.2017.05.010

[34] Schmidt SE etal. (2019) Coronary artery disease risk reclassification by a new acoustic-based score. The International Journal of Cardiovascular Imaging https://doi.org/10 . s10554-019-01662-1.

[35] Genders T. S. S. et al. (2011) A clinical prediction rule for the diagnosis of CAD: Validation, updating, and extension. Eur. Heart J. 32, 1316–1330.

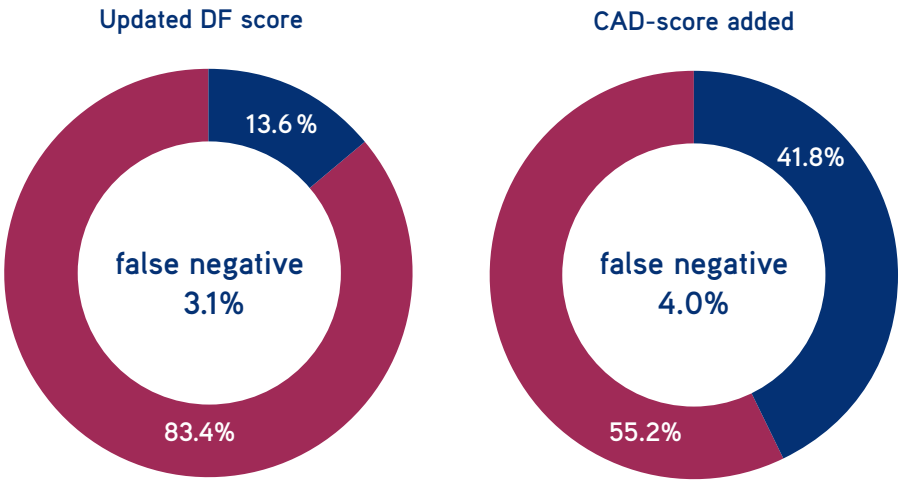
FIGURE 12: Reclassification potential of the CADScor®System



Most importantly the prevalence of CAD did not increase significantly in the enlarged low risk group. Prior to testing, seven patients with low PTP (3.1%) suffered from significant CAD; after the reclassification this number of patients increased to 28 patients (4.0%) (p=0.52).

The incremental increase in CAD-prevalence in the low-risk group was not significantly different and allows for early rule-out of low-risk patients with an NPV of 97% in a population with a 9.4% prevalence of significant CAD (figure 13).

FIGURE 13: Rule-out potential of the CADScor®System



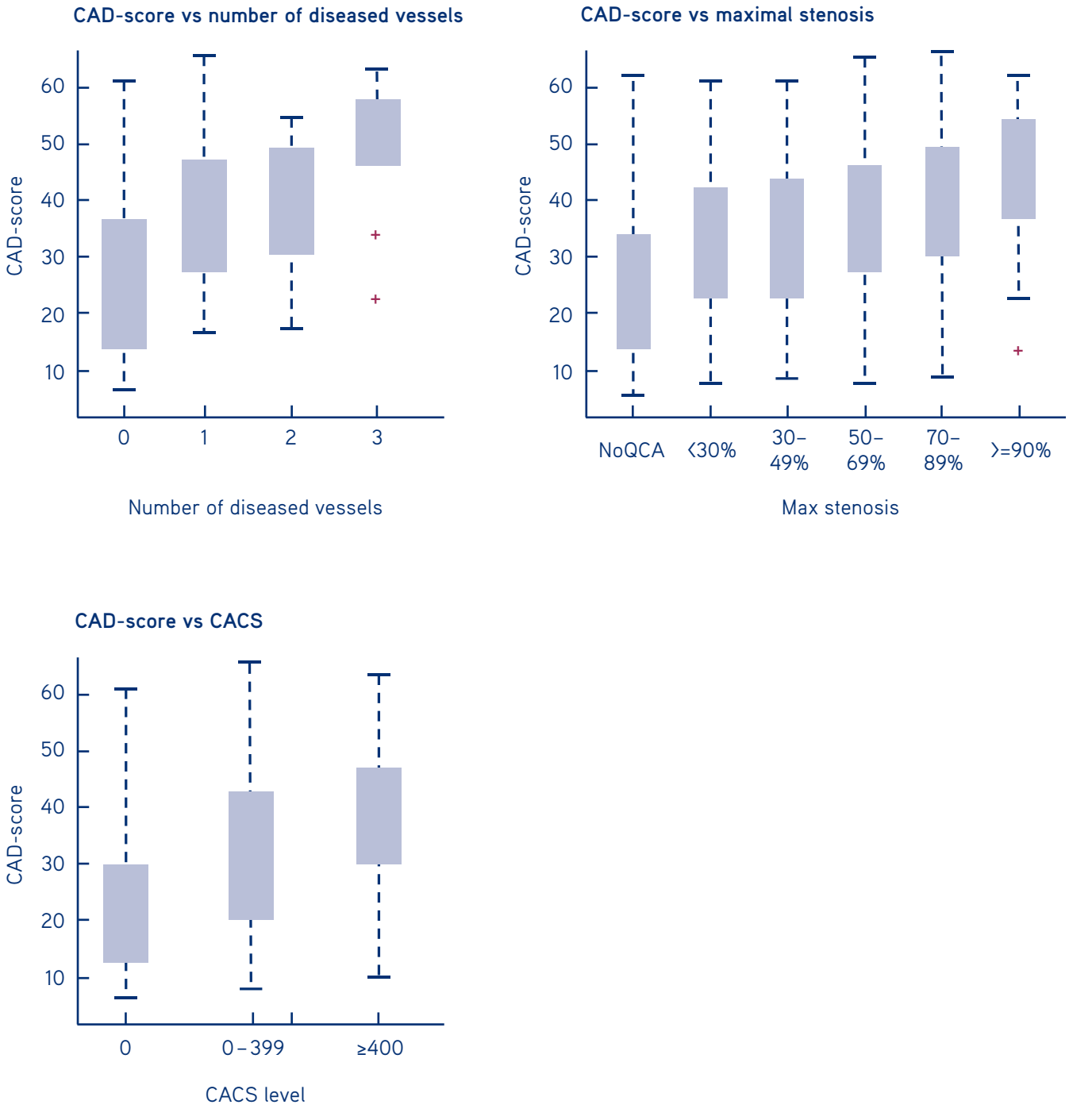
The strength of the CADScor®System is the reliable rule-out of patients without significant CAD. A CAD-score below or equal 20 rules out CAD with a very high likelihood.

The CAD-score also correlates to disease severity: The CAD-score increases with the number of vessels diseased, increasing obstruction and coronary calcium score CACS (figure 14).

In summary, with post-test reclassification and the CADScor®System, the number of low-risk patients increased from 13.6% to 41.8% in a symptomatic patient population. The number of patients classified as intermediate risk was reduced from 83.4% to 55.2%. This impressive reduction was achieved at the expense of a small, but non-significant increase of false negative (FN) patients (3.1 vs 4.0%, p=n.s.).

FIGURE 14: CAD-score correlates to disease severity

Boxplots of CAD-scores show an increasing CAD-score with increasing number of diseased vessels, degree of stenosis and CACS



THE CADScor®System TECHNOLOGY: HARDWARE

FIGURE 15: The CADScor®Sensor and its docking station

The CADScor®System (figure 15) is a device for recording and quantifying acoustic noise arising from coronary artery stenosis micro-turbulence and myocardial movement.

The CADScor®System calculates a patient-specific CAD-score by computational processing of a heart sound recording obtained from the chest surface of the patient. The system consists of two physical units: the CADScor®Sensor and the docking station with a power adaptor for charging and qualification of the sensor.

The CADScor®Sensor records heart sounds at the fourth left inter costal region and carries the software to calculate the CAD-score based on the acoustic recording. The sensor has one physical button and is operated by a graphical touch-screen interface.

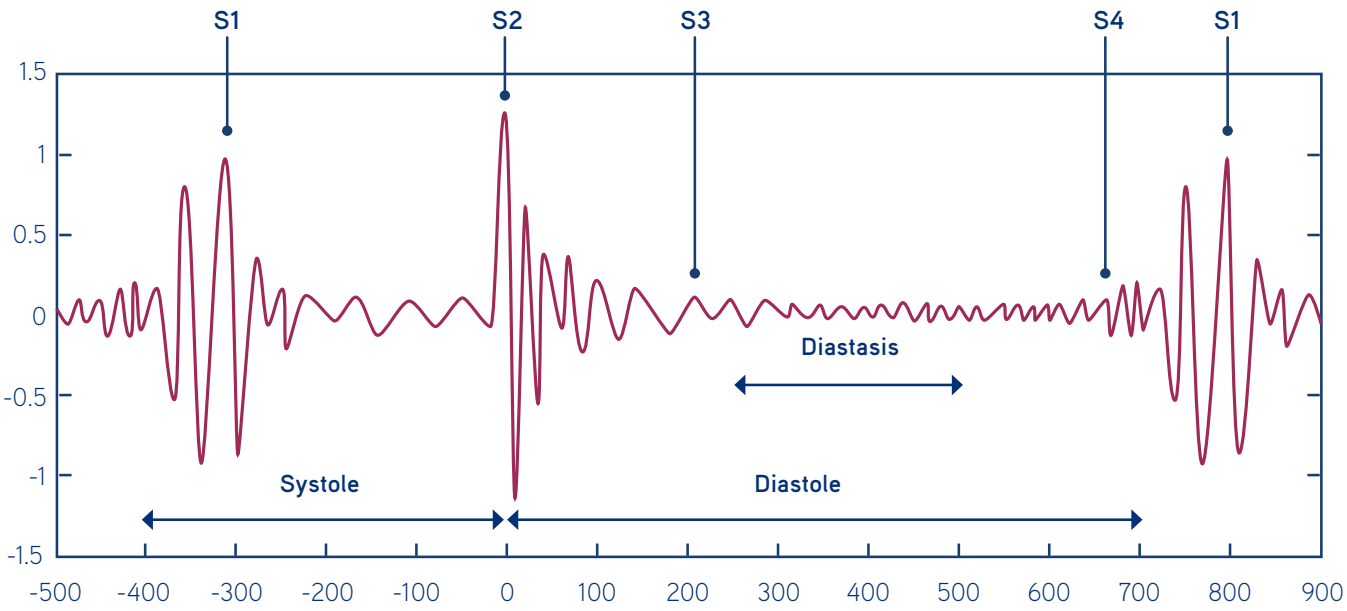
The patch for anchoring the sensor to the chest of the patient is a crucial accessory for the proper functioning of the CADScor®System. It ensures fixation of the microphone over the heart of a patient for recording without vibration from external physical handling of the device which would add acoustic parameters captured by the ultrasensitive sensor (figure 16).

FIGURE 16: Usage of the CADScor®Patch
CADScor®Sensor is attached with a disposable patch onto the patient's chest at the fourth left intercostal space.

THE CADScor®Algorithm

The CAD-score is calculated by the built-in scoring algorithm, processing the audio recordings combined with clinical risk factors. The acoustic analysis is initiated by segmentation of the heart sounds into systolic and diastolic periods (figure 17).

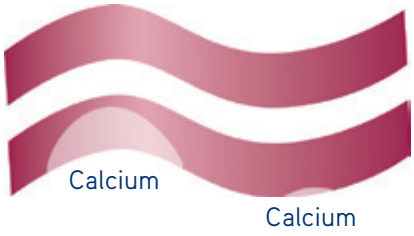
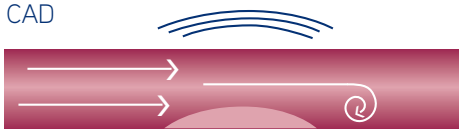
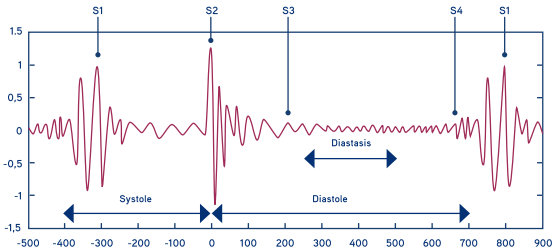
FIGURE 17: Segmentation of heart sounds as first part of the algorithm



Furthermore, the timing of the third and fourth heart sounds is used to define onset and end of the mid-diastolic period. Next, the ambient noise is suppressed by subtracting the recorded ambient noise from the heart sound signal using an adaptive filtering method. Heart beats containing noise are discharged, and an automated quality control algorithm validates the recording quality. Eight acoustic features are extracted from the recorded heart sound: a low frequency power ratio (FPR), the amplitude of the fourth heart sound (S4Amp), low frequency power ratio from the systolic period (SysFPR), the estimated slope of diastolic frequency spectrum (SpecSlope), a simple measure of heart rate variability (HRV), a principle component analysis-based measure of the randomness of the diastolic sound (PCARand), Sample Entropy of the diastolic sound (SampEn) and a frequency distribution of the second heart sound (S2freq), see figure 11.

Using acoustics as the basis for the CADScor®System proposes similar interpretation options as based on imaging techniques, as summarized in figure 18. CT-imaging collects information about the calcium and stenotic burden in coronary arteries, an indirect measure of coronary stenosis.

FIGURE 18: Algorithm features compared to other techniques

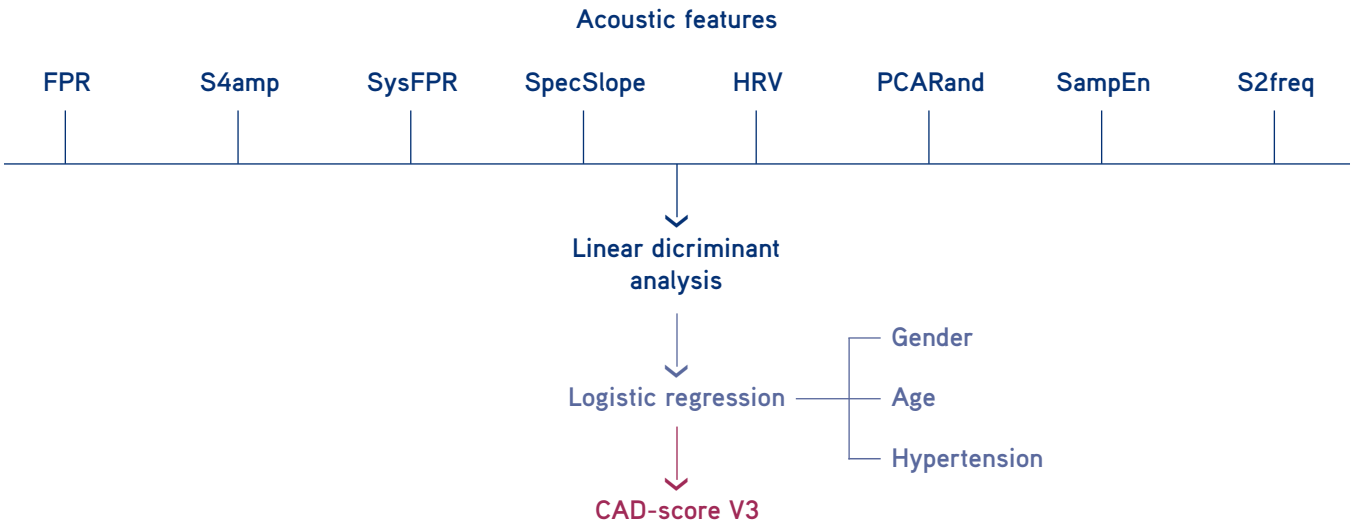
Other techniques	CAD-score	Algorithm features
CT-imaging • stenosis • calcium deposit	 no CAD  CAD 	diastolic phase; predominant coronary murmurs Spec Slope, FPR, PCARand, sampEN, sysFPR
Echocardiography • myocardial movement • verticular filling • valve opening/closing		sound   	S2; valve closing. S4Amp, S2Freq, myocardial stiffness (Calcium)
Electrocardiogram ECG • timing • slopes • amplitude			heart signal seqmentation S4AmP HRV

The CADScor® Algorithm collects audible information originating from turbulent blood flow and myocardial movement. Four features – SpecSlope, FPR, PCAR and SampEn – quantify the mid-diastolic sound where coronary murmurs are expected to be the loudest. The systolic feature SysFPR is included to capture subjects with right coronary artery stenosis where the blood flow is expected to peak during the systolic period.

An echocardiogram analyses myocardial movement, ventricular filling and valve movements. Two features of the CADScor®Algorithm – S4Amp and S2freq – aim at quantifying myocardial stiffness while S2 reflects valve closing.

An ECG gives various pieces of information about the heart function. Timing, slopes and amplitude of the ECG indirectly inform about myocardial performance. Low-frequency HRV is an independent predictor of coronary disease[37].

FIGURE 19: The CADScor®Algorithm

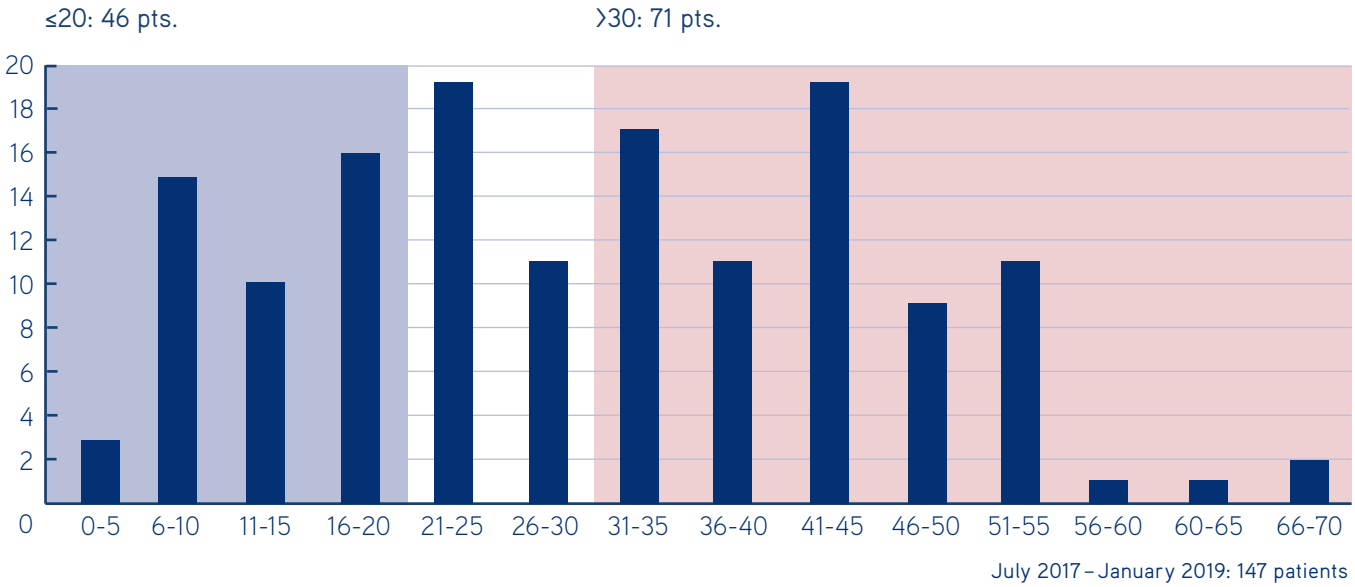


The identified acoustic features are combined into an acoustic score using a linear discriminant function (figure 19) and are combined with clinical features of the patient to build the final CAD-score.

[37] Hayano J et al. (1990) Decreased magnitude of heart rate spectral components in CAD. Its relation to angiographic severity. Circulation 81: 1217-1224

REAL LIFE EXPERIENCES

FIGURE 20A: Real life usage in Austria



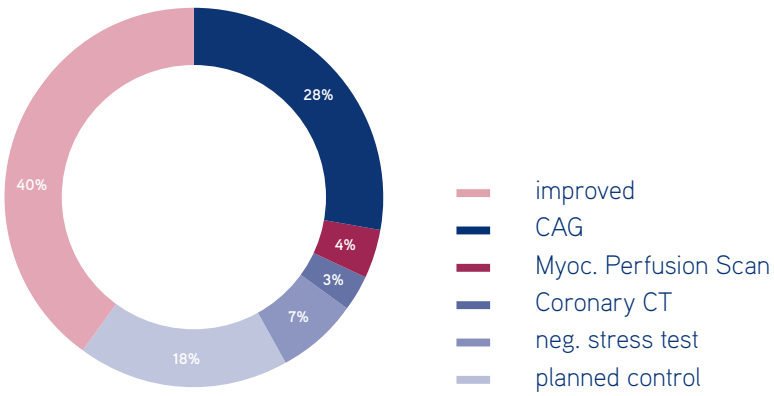
July 2017 – January 2019: 147 patients

We present two examples from the usage of the CADScor®System in clinical practice.
The first example[38] is a case from an Austrian cardiologist with a private practice in which he uses the CADScor®System for the diagnostic pathway. In his private practice, 147 patients were CAD-scored in the period between July 2017 and January 2019 (figure 20A).

From the 71 high-risk patients (CAD-score >30), 40% showed spontaneously improvement of symptoms, the others were referred for further diagnostics or routine follow-ups. Only 20 patients out of 147 were referred to ICA. Remarkably, 60% of patients referred to angiography showed a positive result with respect to the presence of significant CAD.

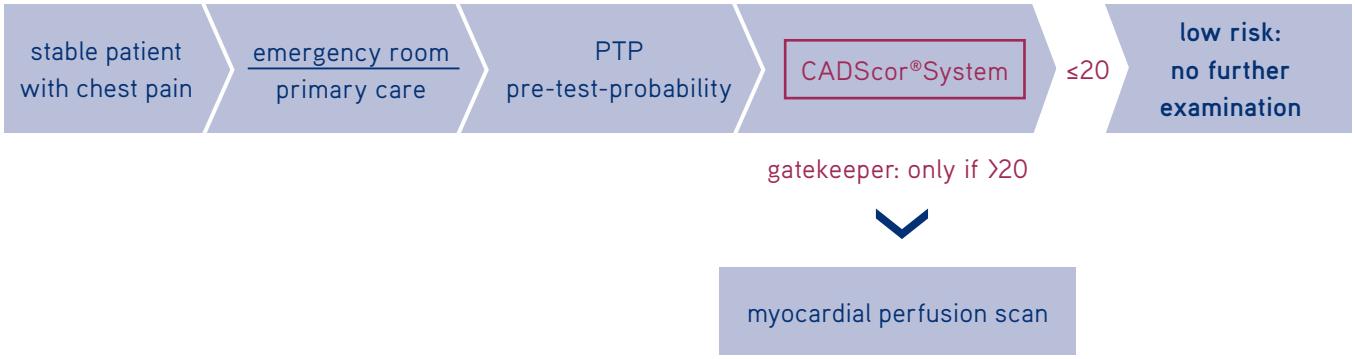
The cardiologist was able to confidently directly exclude one third of his patients for further CAD-related diagnostics. He reports that he feels confident in sending patients with a CAD-score ≤20 home and no incidents regarding those patients have been reported so far.

FIGURE 20B: Pathway of 71 patients with CAD-score >30



[38] Dr. Werner Kommer, personal communication.

FIGURE 21A: Proposed usage of the CADScor®System in a Swedish hospital



The second example describes the evaluation and usage of the CADScor®System in a Swedish hospital[39]. Prior to the integration of the system into the local diagnostic pathway, the hospital intended to verify the performance of the CADScor®System in its own clinical setting.

The related question was, whether the CADScor®System could safely and reliably rule out those patients without CAD.

The objective was to add the CADScor®System as a gatekeeper, prior to a MPS after an inconclusive stress-ECG (figure 21A).

Twenty patients (11 female, 9 male) referred to a MPS received a CAD-score prior to the MPS and the results were validated by comparing the results from CAD-scoring with the results from the MPS (figure 21b). The evaluation was performed in April and May 2018.

[39] Dr. Magnus Simonsson, personal communication.

FIGURE 21B: Results of the MPS

	All patients (n=20)	Patients with no signs of CAD (n=15)	Patients with signs of CAD (n=5)
Female	11	9	2
Male	9	6	3
Age (mean,year)	52.9	58.4	61.4

Substantial reduction of healthy patients exposed to invasive and non-invasive diagnostics in clinical practice

In the MPS, 5 patients showed signs of CAD, 15 patients did not show any signs of CAD. Four of the five patients were correctly scored as diseased with a CAD-score >20, one patient was initially scored false negative (5%), due to an inconclusive myocardial perfusions scan, but turned out to be true negative.

This corresponds to a sensitivity of 80% in this patient population, including the false negative patient. 9/15 patients without CAD was correctly diagnosed by the CADScor®System as disease free (60%), corresponding well to the specificity of our database of 42% (figure 21c). 50% of the patients had a CAD-score ≤20. To safely rule-out patients, the NPV of 90% in a low-risk population is seen as sufficiently high to include the CADScor®System in the clinical setting as gatekeeper for MPI for patients with an inconclusive stress ECG.

In both cases the CADScor®System has in clinical practice proven to reduce the number of healthy patients exposed to further invasive or non-invasive diagnostic procedures.

FIGURE 21C: Results from the CADScor®System

Number of patients, total	20 (100%)
True positive	4 (20%)
True negative	9 (45%)
False positive	6 (30%)
False negative*	1 (5%)
Diagnostic performance	
Sensitivity	80%
Specificity	60%
PPV	40%
NPV	90%

* **False negative patient:** Inconclusive Myocardial Perfusion Scan, referred to ICA; decision later not to perform ICA; no ischemia

CHAPTER 3

APPENDIX

1 FREQUENTLY ASKED QUESTIONS

2 COMPUTED CARDIAC TOMOGRAPHY AND THE CADScor®System

3 HOW TO PERFORM A CAD-SCORE MEASUREMENT

4 ABBREVIATIONS

FREQUENTLY ASKED QUESTIONS

How can I use the CADScor®System?
The CADScor®System is intended for use as a diagnostic aid in symptomatic patients suspected of stable CAD. We suggest using the CADScor®System as a first-line non-invasive diagnostic aid to rule-out CAD in patients suspected of stable CAD, to avoid further downstream testing and invasive diagnostic procedures. A patient with a low CAD-score (≤20) is highly unlikely to have CAD. A patient with an intermediate (20 – 29) or high (≥30) CAD-score has an increased likelihood of disease and should be followed more closely or referred for further evaluation.

Where can I not use the system?
Contraindications for use are previous coronary artery bypass graft (CABG), previous coronary stenting, arrhythmia causing non-sinus rhythm, implanted donor heart or mechanical heart, implanted mechanical heart pump, implanted pacemaker or cardioverter defibrillator (ICD), implanted electronic equipment in the area above and around the heart, significant operation scars, fragile or compromised skin, abnormal body shape in the fourth left intercostal (IC4-L)-recording area.
The CADScor®System performance has not been validated outside the indication for use or, for patients younger than 40 years of age.

Can we use the CADScor®System on patients with valve disease/aorta insufficiency?
Patients with heart valves are not contraindicated. In Dan-NICAD, in a low number of patients with heart valve disease, higher CAD-scores were observed. Remarkably, this was only the case when the clinical risk factors were added, and not with the acoustic score only, indicating that patients with heart valve disease are diagnosed accurately. In case the artificial sound of the heart valves disturbs correct segmentation, the device would indicate this, but this has not been reported as a major issue.

What is the performance of the CADScor®System?
Defining CAD as obstructive above 50% diameter stenosis, the sensitivity to identify a patient with CAD is 88.7%. Specificity is 41.3%. Under these conditions the test has a NPV of 97.2% in a 10% CAD prevalence population. Data has been calculated from the CADScor® clinical database using the latest implemented CADScor®System algorithm version.

What is NPV, PPV, Sensitivity, Specificity?
Sensitivity is the ability of a test to correctly classify an individual as ´diseased´. Specificity is the ability of a test to correctly classify an individual as disease-free. Positive Predictive Value (PPV) is the percentage of patients with a positive test who have the disease. Negative Predictive Value (NPV) is the percentage of patients with a negative test who do not have the disease. Positive and NPVs are directly related to the prevalence of the disease in the population. Assuming all other factors remain constant, the PPV will increase with increasing prevalence; and NPV increases with decrease in prevalence.

Can CADScor®System predict where a stenosis is located?
No. The CADScor®System does not indicate the location of stenosis; it predicts with a very high NPV that a patient is unlikely to have CAD. However, we see a correlation of the severity of CAD and the CAD-score. The more vessels show stenosis, the higher the CAD-score.

Can the system detect significant plaques in the three major arteries equally well?
Yes. The algorithm detects signals from all coronary arteries and the low frequency sound passes with no significant loss organs and bones.

Can I use the system in calcified arteries?
Yes, you can use the CADScor®System in this case. High calcification is neither excluded nor do we have specific data for it. We know that the higher the CACS, the higher the CAD-score.

Does the CADScor®System detect total occlusions?
A total occlusion does not generate heart sounds from turbulent flow. Most patients with total occlusion do not have an isolated total occlusion but a generalized CAD. Accordingly, heart sounds generated from the ischemic heart will contribute to the CAD-score. Patients with total occlusions in our database have been diagnosed as "diseased" with a CADScor >20 in the majority of cases (96%).

Can collateral arteries be detected?
No. Collateral arterial supply is the biological response to decreased blood supply to a specific area in the heart. Collateral supply may have overcome the original supply defect, and as such have decreased turbulent flow patterns and aberrant myocardial movement. We do not include specific sound features from collateral arterial supply in the CAD-score.

Do soft plaques and the plaque composition have any effect on the CAD-score?
We do not have specific data on plaque composition. A plaque, irrespective of its nature, results in a change of coronary flow and changes the acoustic information in such a way that it can be distinguished form a healthy artery.

Can the CADScor®System be used to diagnose high-risk subgroups as diabetic patients?
Diabetic patients were not excluded in the clinical studies, but data on subgroups is limited. However, it is important to stress that the CADScor®System is intended for symptomatic patients only, and not as a screening tool in asymptomatic patients despite belonging to a high-risk group for one or more reasons.

Can I use the CADScor®System in young patients?
No. The current algorithm is only validated for symptomatic patients above 40 years of age.

Does the CADScor®System work in female patients?
Yes. We found no gender difference in our clinical studies.

What about some borderline cases with a CAD-score slightly above 20?
As the CADScor®System has a very high NPV, a CAD-score at or below 20 will effectively rule-out CAD in the patient. A CAD-score above 20 will, on the other hand, indicate that the likelihood of a CAD is increased.

What factors can influence the CAD-score?
Replicate measurements are normally very similar, but some recording parameters are important, like establishing hemodynamic balance (resting prior to CAD-scoring), or not taking vasodilating medicine on the day prior to the measurement (e.g. nitroglycerine spray or tablets).

Can I use Betablockers to achieve a lower heart rate?
Yes, if not of a vasodilating type.

A patient has for a long time been treated for hypertension and has normal BP under medication. Do I consider him hypertensive or not?
For the Algorithm v3 we consider a patient treated for hypertension as a hypertension patient. In future algorithms, there might be a refinement.

Is the CADScor®System approved?
The CADScor®System is approved in Europe (CE mark 2015) and has been marketed since Q2 2017.

In which countries is the CADScor®System used?
Currently (mid 2019), the CADScor®System is used in Denmark, Sweden, Germany and Austria.

To which class of CE mark does it belong?
The CADScor®System is a Class IIa device. The patch is a Class I device.

Where can I find advice for trouble shooting?
In section 11 of the CADScor®System user manual.

What do I do when the battery is low?
The system will indicate if the battery is low. The battery drain is significant during qualifications. Charging it for 15 minutes is sufficient for a couple of recordings, 30 minutes for approx. 10 recordings.

Can I talk to my patient during the recording phase?
Guiding the patient during the CAD-score evaluation is essential. Two parts of each recording loop exists, one in which the patient is breathing normally, and one in which the patient will hold his/her breath. During the breath-holding period no talking (or noisy behavior) can take place.

Can patches be re-used?
No. The patch contains a specific code that is registered and marks the patch as used.

Where should I dispose used patches?
The used patches can be disposed together with other standard clinical waste.

What are the main CADScor®System studies?
In 2015 a study from Winther et al. (Denmark), with 228 patients, led to the approval of the device with algorithm v2 Europe. The study was published in 2016 with a diagnostic performance for

diagnosing >50% stenosis with 90% sensitivity and 92% NPV (prevalence 28%). Dan-NICAD (Denmark), with 1675 patients, was published in 2017 and was the basis for the evolution of algorithm v2 towards algorithm v3.1 which is performing in the commercial device. The Dan-NICAD population showed a diagnostic performance of 81% sensitivity and 96% NPV for diagnosing >50% stenosis (prevalence 9.3%).

The combined database population (prevalence 10%) performs with 88.7% sensitivity and 97% NPV. 2016 and 2017 VALIDATE (Germany) were performed to gain data outside the intended population (high-prevalence population) to contribute to the evolution of the algorithm. Currently (mid 2019), Dan-NICAD II is ongoing.

The CADScor®System Algorithm v3.1 database performance is based on 2245 patients (prevalence 10%). Eight acoustic properties covering four aspects of the heart sound are assessed and subsequently combined with clinical risk factors (age, gender, Hypertension), using logistic regression into a CAD-score.

Examples of the acoustic properties are the amplitude of the fourth heart sound, the characteristics of the systolic and mid-diastolic heart sound and the frequency distribution of the second heart sound. All those sounds have previously described to be predictive of the presence of CAD.

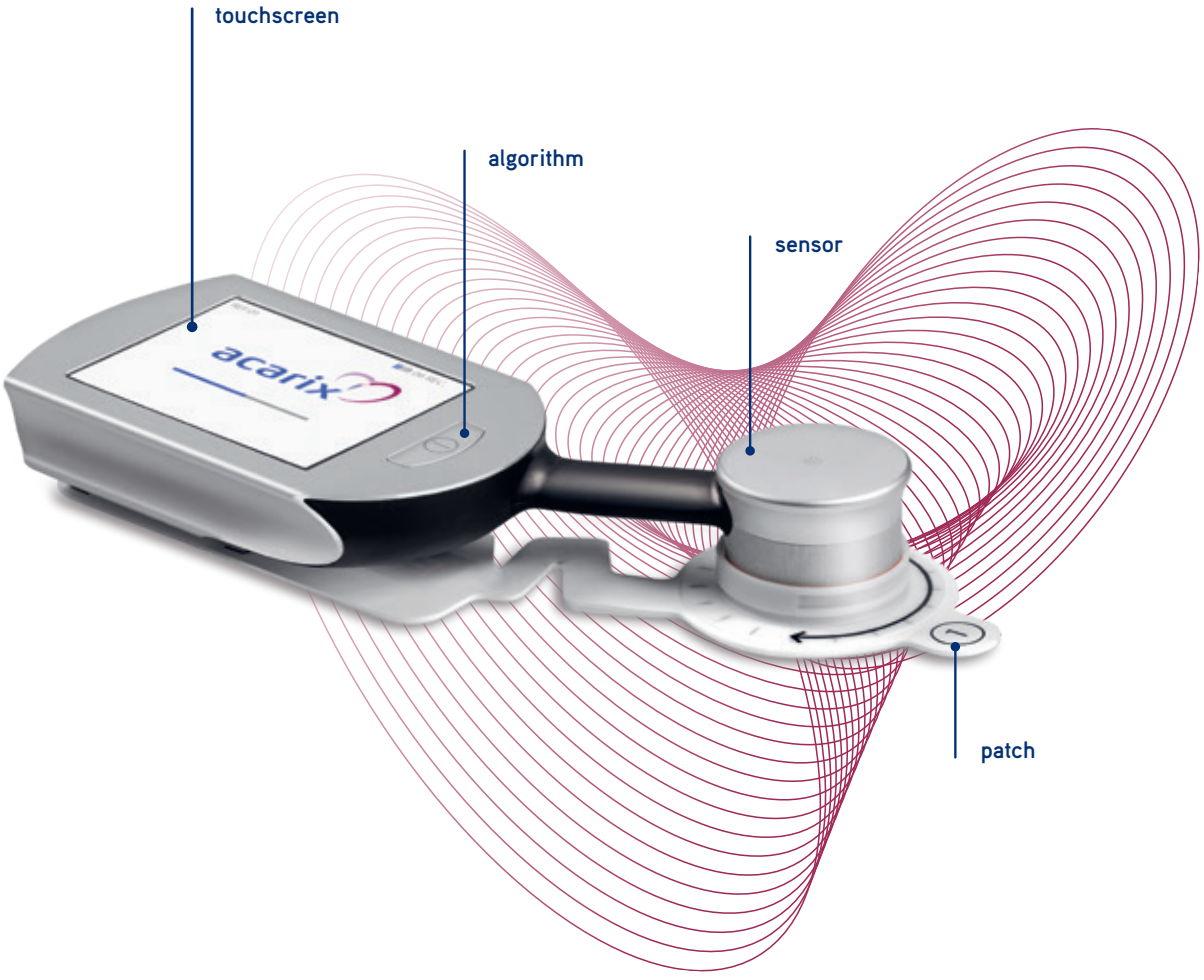


FIGURE 22: Performance overview of the CADScor®System

AUC (%)	Sensivity (%)	Specificity (%)	Study	Algorithm version
75	89	42	Reclassification	3.1 (Device)
72	85	43	Dan-NICAD[C]	3.1
72	80	53	Dan-NICAD*	3.0
58	65	45	Dan-NICAD*	2.0
77	98	31	AdoptCAD[C]	3.1
72	90	45	AdoptCAD*,[C]	2.0

*published [C]calculated

Data on file Acarix

How does the Algorithm v3 perform with/without clinical risk factors?
The Dan-NICAD publication figure 4 illustrates the AUC of the acoustic algorithm version 3 with 62%, whereas the AUC of the "entire" algorithm version 3 (including sound and risk factors) is 71%. When comparing the acoustic algorithm version 3 and the "entire" algorithm version 3, there is no statistically significant difference for the sensitivity and the NPV. The difference for AUC seen in figure 4 is explained by a lower specificity for the acoustic algorithm version 3 compared to the "entire" algorithm version 3. This means that for the intended exclusion of symptomatic patients with suspected CAD both algorithms perform equally well with respect to NPV and sensitivity.

COMPUTED CARDIAC TOMOGRAPHY AND THE CADScor®System

Computed tomography angiography (CTA) offers the best alternative to invasive angiography for the anatomical assessment of epicardial coronary disease. CTA has a sensitivity of 95 – 99% and specificity of 64 – 83% for the detection of CAD. However, concerns have been raised about its generalizability in patients with cardiac disease, with the potential for poor image quality in those with obesity, coronary calcification, or arrhythmia, and the high levels of radiation exposure (about 2 – 5 mSV).

Further, standard CT angiography shares the same inherent limitation as standard invasive angiography: the inability to confidently determine which coronary stenosis of intermediate severity will benefit from intervention. A lesion of intermediate severity on CTA, therefore, frequently results either in an invasive angiogram, with or without fractional flow reserve (FFR) assessment, or a further non-invasive test. Very recently it was suggested that diagnostic potential of routine coronary CTA, augmented with CTA-based FFR analysis, is superior to ICA in patients with intermediate stenosis[40]. However, CTA computational estimates of FFR and perfusion imaging[41] are not yet widely available. As a result, the use of functional imaging tests, which indirectly assess myocardial ischemia by measuring surrogate markers, such as perfusion or regional wall motion during vasodilator, inotropic, or exercise stress, remains high.

The Scott-Heart[42,43], researchers have shown that CT coronary angiography in addition to standard care in patients with stable chest pain resulted in a significantly lower rate of death from coronary heart disease or nonfatal myocardial infarction at five years than standard care alone. Remarkably the result was seen without a significantly higher rate of coronary angiography or coronary revascularization. The positive influence of CTA for the long-term outcome may be due to the fact that more preventive and antianginal therapies were initiated in patients in the CTA group.

Overall, recent evidence and guideline recommendations suggest that the usage of CTA may lead to better outcomes for patients with suspected CAD. If augmented with CTA-based FFR, CTA seems to be superior to the more invasive coronary angiography. A limiting factor of CTA/FFR is the exposure to radiation, the need for a significant investment in the computer tomographic machinery, educated staff to operate it and make diagnoses, waiting times and associated costs. A more precise selection of patients likely to show CAD, and therefore benefiting most from CTA and CTA/FFR, is desirable.

The CADScor®System can reduce the number of patients referred for non-invasive testing without a substantial increase in the false negative rate[44]. It offers a systemic relief for the health care systems that are, for example in the UK, struggling to refer all patients to CTA. Moreover, the CADScor®System improves the cost-effectiveness for patients with suspected stable CAD. Two recent cost models for Danish and German pathways have confirmed this hypothesis. The CADScor®System has led to a cost-reduction in both models, in Denmark mainly due to a reduction of CTAs and in Germany, where the CTA is not reimbursed, due to a reduction in ICA[45].

[40] Wardziak, Ł et al (2018) Coronary CTA Enhanced with CTA Based FFR Analysis Provides Higher Diagnostic Value Than Invasive Coronary Angiography in Patients with Intermediate Coronary Stenosis. Journal of Cardiovascular Computed Tomography 1–6.

[41] Siontis KC et al. (2016) Diagnostic performance of myocardial CT perfusion imaging with or without coronary CT angiography. JACC Cardiovasc Imaging 9: 322–4.

[42] The SCOT-HEART investigators (2015) CT Coronary Angiography in Patients with Suspected Angina Due to Coronary Heart Disease (SCOT-HEART): an Open-Label, Parallel-Group, Multicenter Trial. The Lancet 385.9985: 2383–2391.

[43] The SCOT-HEART Investigators (2018) Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. New England Journal of Medicine 379.10: 924–933.

[44] Schmidt SE et al. (2018) Risk-Reclassification of Patients with Suspected CAD Using an Acoustic Score. Circulation. 2018;138: A15761.

[45] Wahler S et al. (2018) Cost model for ruling out CAD in symptomatic patients with ultra-sensitive phonocardiography in the German ambulatory sector, Value in Health 21 PMD46.

HOW TO PERFORM A CAD-SCORE MEASUREMENT

Preparation, adjustment & fitting
The patient should relax at least five minutes prior to test.

After identifying the IC4-L region and the removal of hair if necessary, a new CADScor®Patch is assembled to the sensor using the assembly tool. Add the clinical factors of the patient into the tool.

Application & recording
Attach sensor with patch on IC4-L. Inform the patient about recording sequence, breathing mode and instruction sounds (guided via screen).

Start recording. After a pre-recording, recording starts. Instruct the patient when to breath and when to hold the breath as guided via the device screen. Do not speak during the recording loops of 4 x 8 seconds.

Data analysis
After the recording, the CAD-score is automatically filtered and processed. The result is displayed in less than two minutes.
In certain cases, the recording needs to be repeated; e.g. in case of unsuitable recording conditions or other errors. The recording can be repeated three times after the initial recording with the same patch if the patch has not been removed.

ABBREVIATIONS

AUC	area under the curve
CAD	coronary artery disease
CAG	coronary angiography
CMR	cardiac magnetic resonance
CTA	computed tomography angiography
ESC	European Society of Cardiology
FFR	fractional flow reserve
FN	false negative
ICA	invasive coronary angiography
MPI	myocardial perfusion imaging
MPS	myocardial perfusion scan
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
PCI	percutaneous coronary intervention
PET	positron emission tomography
PPV	positive predictive value
PTP	pre-test probability
SPECT	single proton computed tomography

CHAPTER 4

UNDERSTANDING THE PERFORMANCE MEASURES OF THE CADScor®System

1 THE PERFORMANCE MEASURES "SENSITIVITY" AND "SPECIFICITY"

2 HOW TO CALCULATE THE NEGATIVE PREDICTIVE VALUE NPV

3 RELEVANCE OF THE AREA UNDER THE CURVE AUC

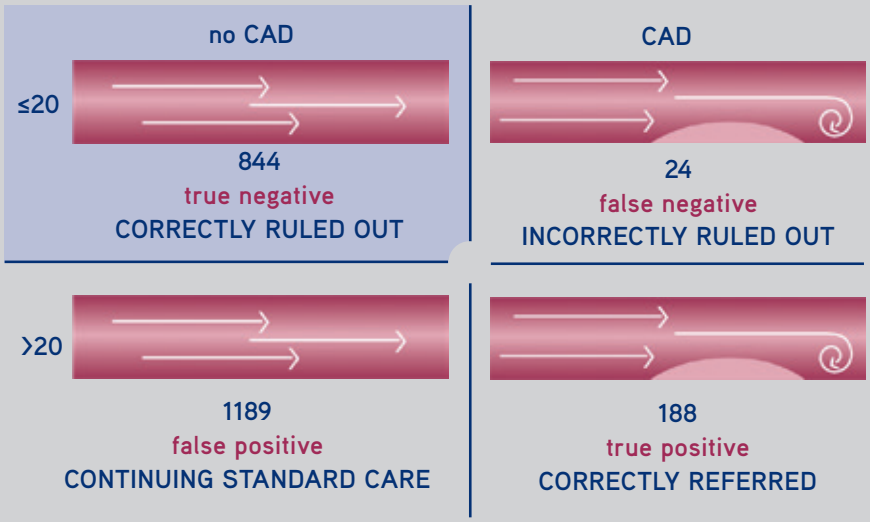
THE PERFORMANCE MEASURES "SENSITIVITY" AND "SPECIFICITY"

Performance algorithm version 3.1

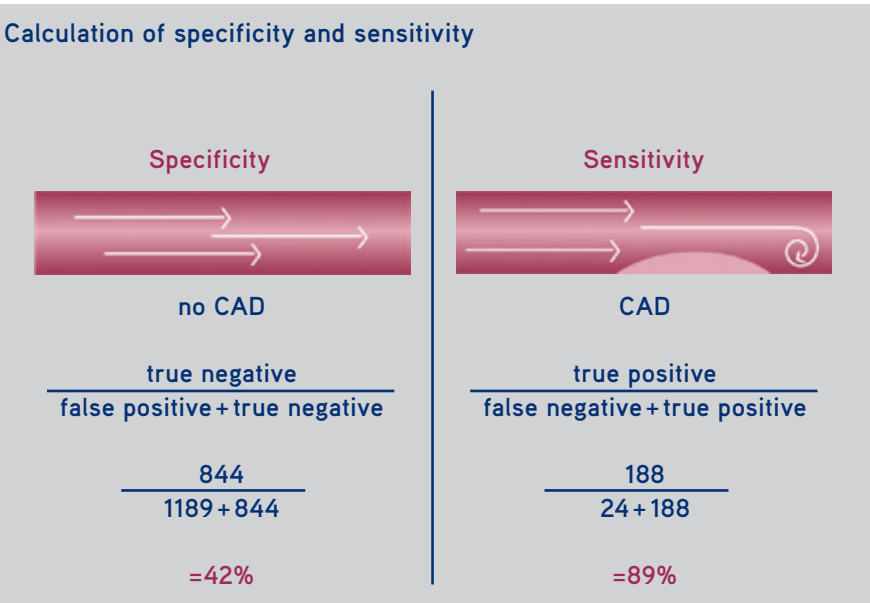
Sensitivity and specificity

The set of 2245 patients in the CADScor®System database is clustered, following their CAD-score and their disease status, into four groups. "true negative" patients are correctly ruled out as they have a CAD-score of ≤20 and do not have significant CAD (≥50% diameter stenosis). Few patients with a low CAD-score of ≤20 have significant CAD and are called "false negative". Patients with a high CAD-score of >20 with significant CAD are called "true positive" and if no significant CAD is present "false positive". The number of patients in each group is used to calculate "sensitivity" and "specificity". These terms describe how well a diagnostic method is able to correctly detect healthy (specificity) or diseased (sensitivity) patients. The CADScor®System has high sensitivity. This means that most diseased patients are correctly defined as diseased. It is relevant for a rule-out device to ensure that the number of non-detected, "false negative" patients is low.

Specificity and sensitivity



Calculation of specificity and sensitivity



HOW TO CALCULATE THE NEGATIVE PREDICTIVE VALUE NPV

Negative Predictive Value NPV
Likelihood for no CAD when ≤20

$$\frac{\text{true negative}}{\text{false negative} + \text{true negative}}$$

$$\frac{844}{24 + 844}$$

$$= 97\%$$

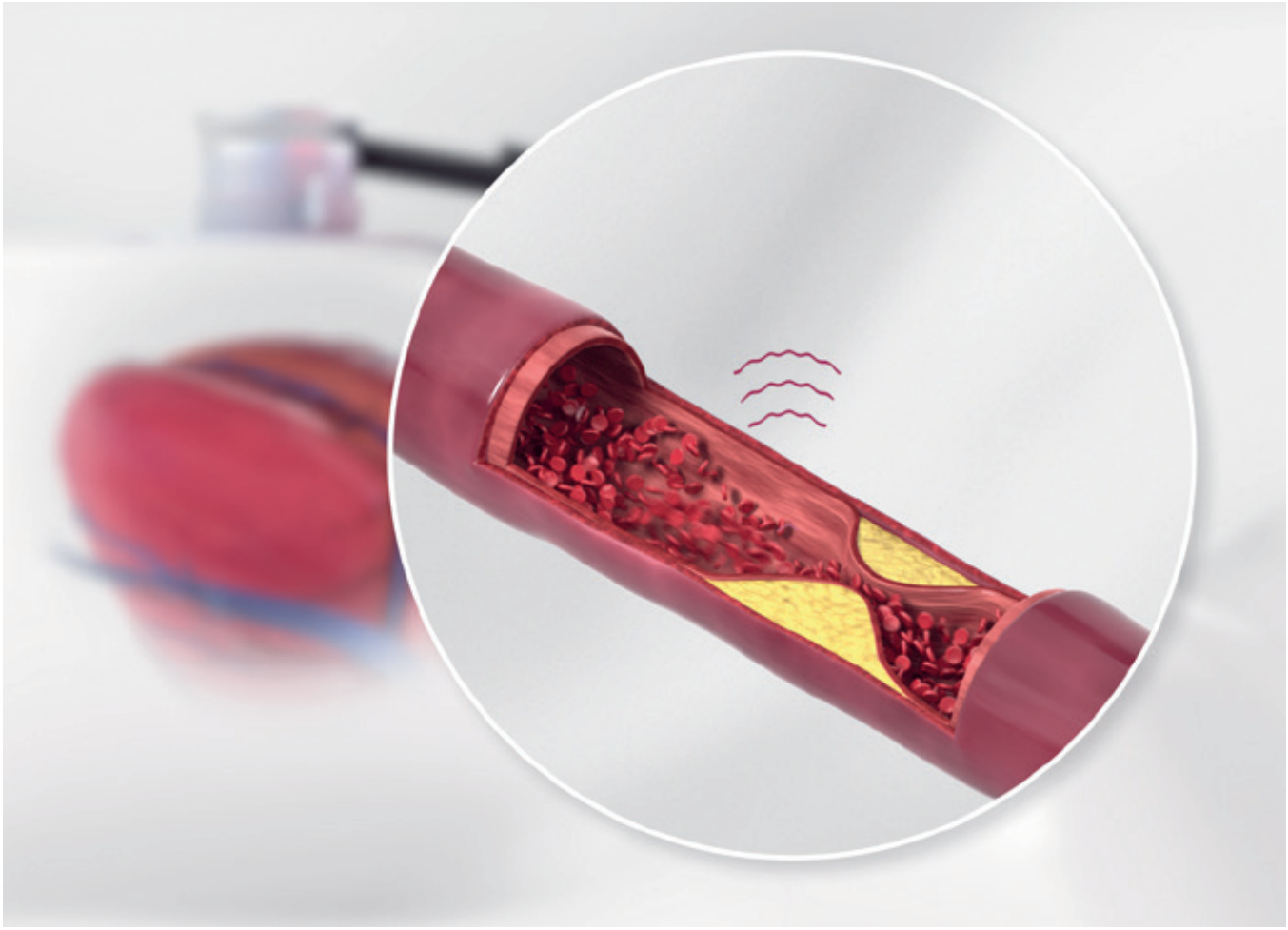
The NPV

To rule-out patients without significant CAD, it is important to know how reliable a CAD-score of ≤20 is.

The NPV describes the likelihood of a patient, ruled out having no significant CAD. The NPV depends on the prevalence of CAD in the patient population.

The lower the prevalence, the higher the NPV.

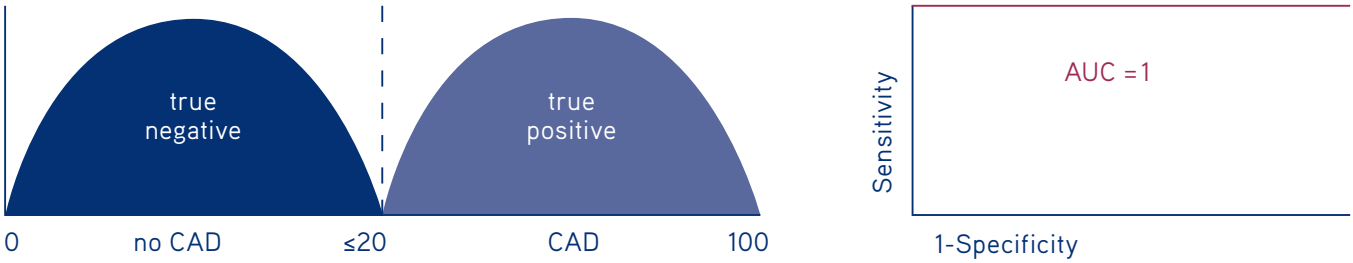
For the CADScor®System the NPV in a patient population with a CAD prevalence of 9.4% is 97%. This means that only 3% of patients with a score ≤20 do have significant CAD.



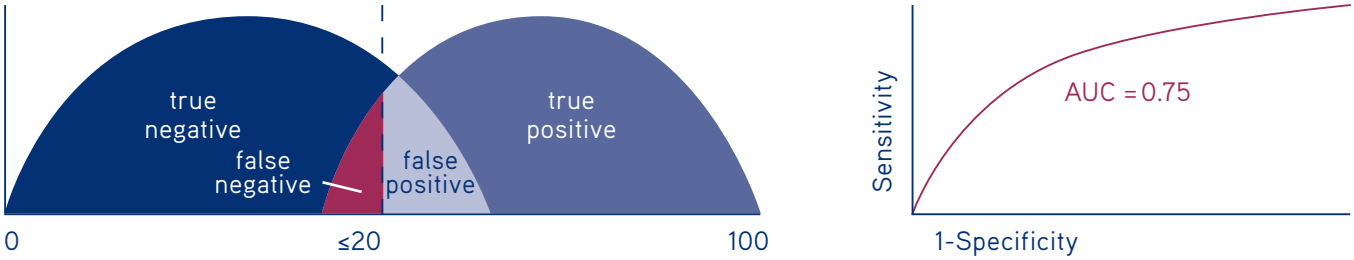
RELEVANCE OF THE AREA UNDER THE CURVE AUC

AUC – Ability to discriminate healthy and diseased patients

perfect test



real world test



The area under the curve

The area under the curve (AUC) is a term to describe the overall performance of a test, describing the ability to discriminate a healthy individual from a diseased patient. specificity and sensitivity are plotted against each other. In a perfect test, all patients not suffering from the disease are described as "true negative", specificity would be 100%. All patients having the disease would be described as "true positive", sensitivity would be 100%. The AUC of a perfect test is 1. With an AUC of 0.5 the chance to be correctly discriminated is 50%. The AUC of the CADScor®System is 0.75.

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