openheart

Diagnostic performance of a device for acoustic heart sound analysis in patients with suspected myocardial infarction

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2022-002090).

To cite: Lehmacher J, Neumann JT, Sörensen NA, *et al*. Diagnostic performance of a device for acoustic heart sound analysis in patients with suspected myocardial infarction. *Open Heart* 2023;**10**:e002090. doi:10.1136/openhrt-2022-002090

Received 19 July 2022
Accepted 10 February 2023

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ABSTRACT

Background As only a small proportion of patients with chest pain suffers from myocardial infarction (MI), safe rule-out of MI is of immense importance. Recently an ultrasensitive microphone performing diastolic heart sound analysis (CADScorSystem) for rule-out of coronary artery disease (CAD) has emerged. In this explorational study, we aimed to evaluate the feasibility of the CADScorSystem for diagnosis of MI in the setting of a large emergency department.

Methods Patients presenting to the emergency department with suspected MI were included. Acoustic heart sound analysis was performed in all patients and automated CAD-score values were calculated via a device-embedded algorithm, which also requires inclusion of three clinical variables: age, sex and presence of hypertension. Patients additionally received serial high-sensitive troponin T measurement measurements to assess the final diagnosis according to third Universal Definition of Myocardial Infarction applying the European Society of Cardiology 0 hour/3 hours algorithm. Diagnostic parameters for MI, considering different CAD-score cut-offs, were computed.

Results Of 167 patients, CAD-scores were available in 61.1%. A total of eight patients were diagnosed with MI. At a cut-off value of <20, CAD-score had a negative predictive value (NPV) of 90.7 (78.4–96.3). The corresponding positive predictive value (PPV) was 6.8 (2.7–16.2). For the adjusted CAD-score (age, sex, hypertension), at a cut-off value of <20, NPV was 90.0 (59.6–99.5) with a PPV of 10.8 (5.3–20.6).

Conclusion In this explorative analysis, a transcutaneous ultrasensitive microphone for heart sound analysis resulted in a high NPV analogous to the findings in rule-out of stable CAD in elective patients yet inferior to serial high-sensitivity cardiac troponin measurements and does not seem feasible for application in an emergency setting for rule-out of MI.

Trial registration number NCT02355457.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ As only a small proportion of patients with acute chest pain actually suffer myocardial infarction rapid and safe diagnosis of myocardial infarction is crucial. Ultrasensitive microphones have recently proven their potential to rule out stable coronary artery disease by performing diastolic heart sound analysis, yet it is unknown, whether rule-out of myocardial infarction in patients with acute chest pain is possible.

WHAT THIS STUDY ADDS

⇒ Use of an ultrasensitive microphone does not seem feasible for application in an emergency setting for diagnosis of myocardial infarction and is inferior to serial high-sensitivity cardiac troponin measurements as standard of care regarding diagnostic performance.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Serial measurement of high-sensitivity cardiac troponin proves high diagnostic accuracy in patients with suspected myocardial infarction. Yet, ultrasensitive microphones may be used in an outpatient setting for rule-out of stable coronary artery disease as previous works have shown.

INTRODUCTION

Coronary artery disease (CAD) is a common diagnosis in western countries with estimated raising prevalence in the years coming.[1 2] Potential symptoms suggestive of CAD such as angina pectoris and dyspnoea are rather unspecific and thus, several potential differential diagnoses have to be considered in the individual. The diagnostic procedures involved in the workup of CAD still bind substantial healthcare resources due to the need for non-invasive and invasive testing.[3] According to the 2019 European Society of Cardiology (ESC) guidelines for management of chronic coronary syndrome, after initial assessment, determining whether patients have symptoms of acute myocardial infarction (MI), requiring a different diagnostic workup and therapy, evaluation of clinical likelihood for obstructive CAD is of crucial importance.[3] Depending on clinical

likelihood of significant CAD, guidelines recommend different testing modalities such as CT-angiography, cardiac MR tomography, stress electrocardiography, cardiac perfusion scintigraphy or invasive coronary angiography.[3] Recently, a new non-invasive method based on ultrasensitive microphone recording of diastolic low frequency murmurs has been approved for the rule-out of stable CAD (CADScorSystem, Acarix A/S, Denmark), after a large clinical study showed a negative predictive value (NPV) of 96% with coronary CT and invasive coronary angiography serving as the gold standard.[4] The target population was patients with low to intermediate pretest probability of significant CAD in an outpatient setting.[5] The device is a highly sensitive electronic microphone, recording cardiac sounds, not hearable by the human ear. In particular, the key feature of the device is the detection and interpretation (via an integrated algorithm and learning via a sound database) of specific patterns of diastolic murmurs linked to CAD as well as poststenotic flow turbulences caused by coronary stenosis.[6–8] A concept of detecting diastolic murmurs, caused by poststenotic coronary turbulences, was already proposed in the 1960s as a possible cost-effective alternative to identify patients with suspected significant CAD.[9–12] Technical advances in computers, acoustic technology and processing speed have enabled several research groups to develop algorithms for automated detection and analysis of heart sounds to assess risk of CAD within 5–10 min.[13–15] Yet these tests all have been performed with patients already having received clinical risk assessment.[4 16 17] In emergency departments (EDs), unselected patients presenting with chest pain constitute a clinical challenge identifying those in need for early invasive diagnostic and therapy. Although the above-mentioned device (CADScorSystem) hitherto was tested in unselected elective patient cohorts for diagnosis of stable CAD. As MI, in contrast to stable CAD, is an acute and potentially life-threatening condition, requiring urgent treatment, safe and fast diagnosis is of crucial importance. Certain patients with MI (especially those with type 2 MI), do not show full coronary artery occlusion, whereas acoustic findings of poststenotic murmurs may occur also in some patients with MI.[18–21] In previous works, poststenotic murmurs occurred frequently in patients with up to 95% vessel stenosis.[22] In addition, earlier works detected auscultatory sounds of papillary dysfunction, which may occur in patients with acute MI.[23] To this point, the above-mentioned device has not been tested for ability to rule-in or rule-out MI. The utilisation in the ED of a chest pain unit could prove as an alternative to other non-invasive tests to rule-in or rule-out MI. If feasible and accurate in this setting, the possible ability for diagnosis of MI could offer an easy, fast and safe alternative to other contemporary non-invasive tests, possibly discriminating patients in need for invasive coronary angiography versus early discharge without further diagnostic workup. In this study, we aimed to evaluate, whether the microphone-based rule-out of MI is safe and feasible in the ED in a population with a wide range of pretest probability.

METHODS

We included consecutive patients of the Biomarkers in Acute Cardiac Care (BACC) cohort presenting with angina pectoris or other cardinal symptoms of MI to the ED of the University Hospital Hamburg-Eppendorf between June 2016 and November 2017. As an observatory study, the main goal of the BACC study is the evaluation of new and established cardiac biomarkers for the diagnosis of MI as well as improvement of risk scores for ACS and to assess impact on patient outcome. The detailed inclusion criteria have been described in previous publications.[24 25] Patients had to be over 18 years old and had to give written, informed consent.

Patients received high-sensitive troponin T measurement (Elecsys troponin T high-sensitive; Roche Diagnostics) at admission and after 3 hours according to the 0/3-hour algorithm of the ESC.[26] Patient characteristics such as age, gender, pre-existing cardiovascular conditions and cardiovascular risk factors, were documented as well.

CAD-score measurements were performed by trained personnel in the ED of the University Hospital Hamburg-Eppendorf. Acoustic heart sounds were recorded with patients resting in a supine position with the acoustic sensor system placed in the fourth left intercostal space using the CADScorPatch. Total recording time was 3 min with patients holding their breath for 8 s in four cycles. A numerical CAD-score was automatically calculated immediately after recording via an integrated algorithm.[4 7 8 27] In total, the examination time was up to 10 min per patient (including device preparation, placement of sensor, 1 min prerecording time and 2 min the device needed to calculate the CAD-score). If unsuccessful the device demanded a second recording, in which cases another attempt should be made.

The device-embedded algorithm takes into account four features of acoustic aspects from diastolic heart sounds, relating to poststenotic murmurs as well as other characteristics to calculate a numeric score ranging from 0 to 99.[4 12 28] Also, an updated score, using a modified algorithm (CAD-score algorithm V.3.1), was calculated.[16] The algorithm used postprocessing of the acoustic data obtained with the CADScorSystem. The CAD-score algorithm version 3.1 considers eight acoustic features extracted from the heart sounds, combined with cardiovascular risk factors (age, gender, hypertension).[13 14] Hypertension was defined as documented systolic blood pressure ≥140 mm Hg or prescribed antihypertensive drugs. The updated algorithm was developed in a previous work by Winther *et al* and the final algorithm V.3.1 is described by Schmidt *et al*.[16 17] The study group used a heart sound database (Acarix A/S, Denmark) with acoustic data obtained in previous pilot studies, already published data, and a training cohort from the

Dan-NICAD study.[4 17] The latter work of Winther *et al* showed a good diagnostic performance for detection of stable CAD at a cut-off value of ≤20.[17]

The final diagnosis was adjudicated independently by two cardiologists in a blinded fashion considering all available data (clinical, laboratory and imaging data), except from the CAD-score results, according to the third Universal Definition of MI.[21] In cases of incongruent diagnosis, a third cardiologist was consulted. Following categories were defined for final diagnosis: ST-elevation MI, non-ST-elevation MI, unstable angina pectoris, stable angina pectoris, cardiac non coronary chest pain and non-cardiac chest pain. The final MI diagnosis consisted of the categories ST-elevation MI and non-ST-elevation MI, and the final non-MI diagnosis consisted of the categories unstable angina pectoris, stable angina pectoris, cardiac non-coronary chest pain and non-cardiac chest pain.

For continuous variables median (25th percentile, 75th percentile) is given. For binary variables absolute numbers and relative frequencies are shown. For between group comparison, the Mann-Whitney U test and the χ^2 test, respectively, were performed. All analyses were performed twice, once for unadjusted CAD-score and once for adjusted CAD-score (CAD-score algorithm version 3.1). Diagnostic parameters were calculated (NPV, positive predictive value (PPV), sensitivity and specificity) for different CAD-score values as cut-off (<10, <20, <30, <40, <50, <60, <70, <80, <90 and <100). Whereas an individual will be classified as having MI if the CAD-score value is greater equal the cut-off. The area under the ROC curve (AUC) was computed using the CAD-score as a continuous variable for the diagnosis of MI. For further analyses (comparing baseline characteristics of patients for unadjusted and adjusted CAD-score) we used a cut-off value of <20 vs ≥20. Statistical significance was defined as p<0.05. All statistical analyses were performed using R-Statistics V.3.5.2 (R Foundation for Statistical Computing).[29]

RESULTS

Figure 1 shows a detailed overview of the study population as well as reasons for recording failures. In total, 548 consecutive chest pain unit individuals were included in the main BACC study in the above-mentioned time period from 2016 to 2017. Of these individuals, 321 patients were not evaluated for eligibility for CAD-score measurement. In 167 individuals, a CAD-score measurement was performed. An unadjusted CAD-score value was available in 102 patients (8 MI, 94 non-MI), adjusted CAD-score values were available in 75 patients (8 MI, 67 non-MI). Non-eligibility for CAD-score measurement (60 patients) most often resulted from dyspnoea or other patient distress incompatible with the recumbent position for the time required for recording (25 patients). Lack of understanding the measurement procedure (16 patients) or not being able to rest (19 patients) were also reasons for

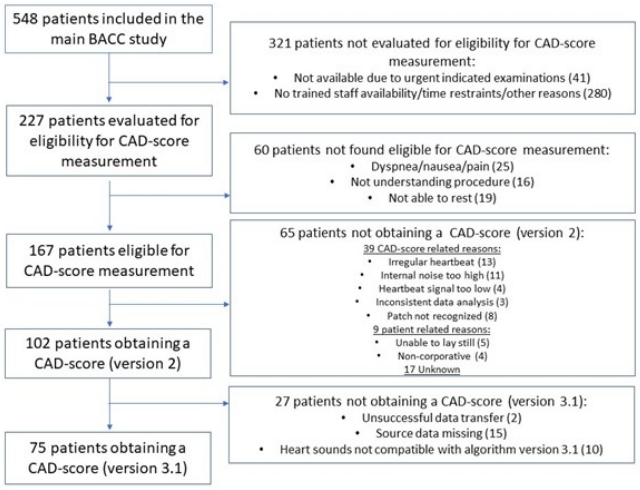

Figure 1 Displays the flow of patients in the study, including reasons for exclusion; version 2=unadjusted CAD-score; version 3.1=adjusted CAD-score (CAD-score version 3.1) adjusted for gender, age and sex. BACC, biomarkers in acute cardiac care; CAD, coronary artery disease.

patients not being eligible for measurement. In the 58 patients where the attempt of measuring a CAD-score was unsuccessful, device related reasons accounted for 32 cases: 'irregular heartbeat' (13 patients), 'internal noise level too high' (11 patients), patch not recognised by the device (8 patients), 'heartbeat signal too low' (4 patients) and 'inconsistent data analysis' (3 patients). Patient-related reasons accounted for nine cases; unable to lay still (five patients) and patients being non-cooperative (four patients). In 17 patients, we were not able to document the reason for recording failure. In total, 41 patients had an error message obtained in first CAD-score measurement. Of those participants, 16 (39%) received a second attempt of calculating CAD-score, of which 7 finally got a calculated CAD-score (44%).

The median age was 58.5 years (range: 46.9–72.1) and 66.7% were male (table 1). Hypertension was documented in 61 patients (59.8%), hyperlipoproteinaemia in 29 (28.4%) and diabetes in 8 (7.8%) patients. In total, 40 (39.6%) participants were active or former smokers. Twenty-four (24.2%) patients had a known family history of CAD and 25 (24.5%) individuals already had documented CAD, coronary artery bypass grafting or percutaneous coronary intervention (PCI). Angiography was performed in 18 (17.6%) of all individuals, of which 14 (77.8% of patients receiving angiography, 13.7% of the study population) receiving PCI (table 2). Coronary artery bypass graft operation was done in 2 (2.0%) patients. Median CAD-score value was 22.5 (14.0, 31.0) and median adjusted CAD-score value was 39.4 (24.8, 49.1). For a detailed description of patients with final diagnosis of MI, please see online supplemental table S3.

In patients with unadjusted CAD-score <20, hypertension was documented more frequently than in those with values above 20 (74.4% vs 49.2%; p=0.018). Also, significantly more patients with CAD-score values below 20

Table 1 Baseline characteristics of the study population

	All (N=102)	CAD-score <20 (N=43)	CAD-score ≥20 (N=59)	P value	Adjusted CAD-score <20 (N=10)	Adjusted CAD-score ≥20 (N=65)	P value
Age, years (range)	58.5 (46.9–72.1)	61.0 (53.0– 73.8)	55.0 (43.2– 71.0)	0.17	42.5 (34.0– 46.2)	62.0 (52.3– 73.3)	<0.001
Male no (%)	68 (66.7)	26 (60.5)	42 (71.2)	0.36	4 (40.0)	50 (76.9)	0.041
Hypertension no (%)	61 (59.8)	32 (74.4)	29 (49.2)	0.018	2 (20.0)	43 (66.2)	0.015
Hyperlipoproteinaemia no (%)	29 (28.4)	14 (32.6)	15 (25.4)	0.57	0 (0)	23 (35.4)	0.059
Ever smoker no (%)	40 (39.6)	19 (44.2)	21 (36.2)	0.55	4 (40.0)	26 (40.0)	1.00
Diabetes no (%)	8 (7.8)	8 (18.6)	0 (0)	0.0021	0 (0)	6 (9.2)	0.71
Family history of CAD no (%)	24 (24.2)	9 (20.9)	15 (26.8)	0.66	5 (50.0)	16 (25.4)	0.22
History of CAD/bypass/PCI no (%)	25 (24.5)	12 (27.9)	13 (22.0)	0.65	0 (0)	20 (30.8)	0.096

Baseline characteristics of the study population. P values comparing the CAD-score groups (unadjusted < vs ≥ 20 and adjusted < vs ≥ 20); adjusted CAD-score adjusted for age, sex and hypertension.
CAD, coronary artery disease; PCI, percutaneous coronary intervention.

had previously known diabetes (18.6% vs 0%; p=0.0021) (table 1). PCI was performed more frequently in patients with low CAD-score values (23.3% vs 6.8%; p=0.036) (table 2). Individuals with adjusted CAD-score values <20 were significantly younger than those with values ≥20 (42.5 vs 62.0 years; p<0.001) and less often had documented hypertension (20% vs 66.2%; p=0.015) (table 1).

Regarding the patients with attempted CAD-score measurement, these patients were significantly younger (median age 62 years vs 67 years, p=0.013) than those, with not attempt made. Patients without attempted CAD-score measurement were also significantly more frequently diagnosed with having MI (24.9% vs 10.8%, p<0.001) and PCI was performed more often in that part of the population (39.1% vs 24.%, p<0.001). Comparing patients with successful and unsuccessful CAD-score measurement, patients with successful CAD-score recording were younger (median age 58.5 years vs 67 years, p=0.0099). Patients with unsuccessful CAD-score recording had PCI performed more frequently (33.8% vs 17.6%, p=0.027), yet no statistically significant difference in diagnosis of MI was found between the two groups. For a detailed overview of baseline characteristics of all patients, patients with and without CAD-score attempt as well as for those with unsuccessful recording, please see online supplemental tables S1 and S2.

The highest NPV for the diagnosis of MI using unadjusted CAD-score was calculated for CAD-score values <10. At this cut-off, NPV was 94.1% (95% CI 73.0% to 99.7%) with a rather low PPV. Accordingly, specificity was also low while achieving a high sensitivity of 87.5% (95% CI 52.9% to 99.4%). At the cut-off of CAD-score value <10 160.7% of the study population would be ruled out with one false-negative tested patient. With higher CAD-score values as cut-off NPV and sensitivity decreased, whereas specificity increased substantially. With a cut-off CAD-score of <20 NPV was 90.7% (95% CI 78.4% to 96.3%) with a corresponding sensitivity of 50.0% (95% CI 21.5% to 78.5%) ruling out 42.2% of the population with 4 patients tested false negative. At this cut-off specificity was 41.5% (95% CI 32.1% to 51.6%) with a PPV of 6.8% (95% CI 2.7% to 16.2%). At a cut-off of <60 1000.0% of the population would be ruled out (with every patient with MI tested negative), so sensitivity would be 0% (95% CI 0% to 32.4%) and specificity 100.0% (95% CI 96.1% to 100.0%). The AUC for diagnosis of MI was 0.525. For detailed listing of diagnostic parameters for the defined cut-off values, see table 3.

Table 2 Interventions performed in the study population

	All (N=102)	CAD-score <20 (N=43)	CAD-score ≥20 (N=59)	P value	Adjusted CAD-score <20 (N=10)	Adjusted CAD-score ≥20 (N=65)	P value
Angiography no (%)	18 (17.6)	11 (25.6)	7 (11.9)	0.13	2 (20.0)	13 (20.0)	1.00
PCI no (%)	14 (13.7)	10 (23.3)	4 (6.8)	0.036	1 (10.0)	10 (15.4)	1.00
CABG no (%)	2 (2.0)	2 (4.7)	0 (0)	0.34	0 (0)	2 (3.1)	1.00

Interventions performed in the study population. P values comparing the CAD-score groups (unadjusted < vs ≥ 20 and adjusted < vs ≥ 20); adjusted CAD-score adjusted for age, sex and hypertension.
CABG, coronary artery bypass graft; CAD, coronary artery disease; PCI, percutaneous coronary intervention.

Table 3 Diagnostic performance of unadjusted CAD-score for diagnosis of myocardial infarction

Cut-off	Sensitivity	Specificity	PPV	NPV	Ruled out %
<10	87.5 (52.9, 99.4)	17.0 (10.8, 25.9)	8.2 (4.0, 16.0)	94.1 (73.0, 99.7)	16.7 (10.7, 25.1)
< 20	50.0 (21.5, 78.5)	41.5 (32.1, 51.6)	6.8 (2.7, 16.2)	90.7 (78.4, 96.3)	42.2 (33.0, 51.9)
<30	37.5 (13.7, 69.4)	72.3 (62.6, 80.4)	10.3 (3.6, 26.4)	93.2 (84.9, 97.0)	71.6 (62.2, 79.4)
<40	12.5 (0.6, 47.1)	94.7 (88.1, 97.7)	16.7 (0.9, 56.4)	92.7 (85.7, 96.4)	94.1 (87.8, 97.3)
<50	0 (0, 32.4)	97.9 (92.6, 99.4)	0 (0, 65.8)	92.0 (85.0, 95.9)	98.0 (93.1, 99.5)

Diagnostic performance for diagnosis of myocardial infarction for unadjusted CAD-score.
The key result of the table is shown in green.
CAD, coronary artery disease; NPV, negative predictive value; PPV, positive predictive value.

For the recommended and CE marked adjusted CAD-score at the lowest defined cut-off <10 NPV was 100.0% (95% CI 34.2% to 100.0%) with a low PPV and corresponding low specificity. Sensitivity was 100.0% (95% CI 67.6% to 100.0%). At this cut-off, 2.7% of all patients would have been correctly ruled out. Applying CAD-score values <20 as cut-off, NPV was 90.0% (95% CI 59.6% to 99.5%), ruling out 13.3% (95% CI 7.4% to 22.8%) of the patients tested with one patient tested false negative. This cut-off resulted in a PPV of 10.8% (95% CI 5.3% to 20.6%), sensitivity of 87.5% (95% CI 52.9% to 99.4%) and specificity of 13.4% (95% CI 7.2% to 23.6%). At a cut-off of <60 sensitivity was 0% (95% CI 0% to 32.4%) and specificity 100.0% (95% CI 94.6% to 100.0%), ruling out 100.0% of the study population, including all patients diagnosed MI. For diagnosis of MI, AUC for adjusted CAD-score was 0.586. See table 4 for detailed listing of diagnostic parameters for different cut-off values using adjusted CAD-score.

DISCUSSION

In this study, we found that a new algorithm, using acoustic heart sound analysis and patient characteristics (age, sex, hypertension) can potentially exclude MI with a rather high NPV, yet this method does not seem feasible in an emergency setting due to a high number of record failures. Further, rule-out performance is inferior to serial high-sensitivity cardiac troponin (hs-cTn) measurements, as the current standard of care. Although this method is being explored in other ED, this is the first attempt to collect a prospective pilot series in an ED setting.

With 102 individuals with available CAD-score values for analyses the population of this study is rather small compared with previous works, evaluating diagnostic performance of CADScorSystem or other microphone-based systems.[4 13 14 16 17] Of the total 548 patients, who were included in the BACC study during the inclusion period, a rather large proportion was not evaluated for CAD-score calculation, mostly due to limited personnel capacity, as no trained staff was present in the ED. Main reasons for not attempting a CAD-score measurement in the remaining patients were inability to lay down (eg, due to pain or dyspnoea) or patients already planned for or undergoing invasive diagnostic. Successful measurement was accomplished in 61.1%, respectively, 44.9% of all screened patients. Reasons for measurement failure were in most cases cardiac arrhythmia or excessive internal noise from the patient. Examining only patients without cardiac arrhythmia is not feasible in an ED, and thus not easily avoided in that clinical setting. These factors result in an inherent selection bias, with presumably excluding a larger proportion of highly symptomatic patients, patients in need of urgent diagnostic as well as patients with cardiac arrhythmia, possibly influencing prevalence of MI in our study population. This is supported by the higher prevalence of MI in those patients, where no measurement attempt was made (24.9% vs 10.8%), as well as the significantly higher frequency of performed

Table 4 Diagnostic performance of adjusted CAD-score for diagnosis of myocardial infarction

Cut-off	Sensitivity	Specificity	PPV	NPV	Ruled out %
<10	100.0 (67.6, 100.0)	3.0 (0.8, 10.2)	11.0 (5.7, 20.2)	100.0 (34.2, 100.0)	2.7 (0.7, 9.2)
< 20	87.5 (52.9, 99.4)	13.4 (7.2, 23.6)	10.8 (5.3, 20.6)	90.0 (59.6, 99.5)	13.3 (7.4, 22.8)
<30	87.5 (52.9, 99.4)	34.3 (24.1, 46.3)	13.7 (6.8, 25.7)	95.8 (79.8, 99.8)	32.0 (22.5, 43.2)
<40	62.5 (30.6, 86.3)	52.2 (40.5, 63.7)	13.5 (5.9, 28.0)	92.1 (79.2, 97.3)	50.7 (39.6, 61.7)
<50	37.5 (13.7, 69.4)	79.1 (67.9, 87.1)	17.6 (6.2, 41.0)	91.4 (81.4, 96.3)	77.3 (66.7, 85.3)

Diagnostic performance for diagnosis of myocardial infarction for adjusted CAD-score (adjusted for gender, age, hypertension).
The key result of the table is shown in green.
CAD, coronary artery disease; NPV, negative predictive value; PPV, positive predictive value.

angiography in those patients (39.1% vs 24%). Another difference between this study and previous studies evaluating CADScorSystem is the inclusion of patients with different clinical likelihood for CAD and MI as previously published studies only included patients after initial risk assessment and with low to intermediate pretest probability.[4 5 16 17]

In general, comparability of results between our work and those of Schmidt *et al* and Winther *et al* is limited due to different clinical settings and different patient populations. Winther *et al* and Schmidt *et al* evaluated diagnostic performance for detecting stable CAD in patients presenting with symptoms suggestive of stable CAD, which is what the CAD-score algorithm is developed for, whereas we investigated performance in diagnosis of MI in patients presenting with acute symptoms.[4 5 16 17] Therefore, our work is of exploratory nature, since the algorithm was not developed to detect MI. Regarding baseline characteristics of the present study population, most patients were older men with a distinct cardiovascular risk profile, which is rather representative compared with other studies of diagnostic approached in suspected MI.[30–32] However, in other studies evaluating the diagnostic performance of CADScorSystem in detecting stable CAD, the populations have had a slightly more equal gender distribution. As male gender is contributing to a higher CAD-score, it is expected that the rule-out capacity is lower in the present study compared with previous studies.[4 16 17]

The diagnostic performance of CADScorSystem for rule-out of MI in this emergency setting showed a formally high NPV around 90%. Compared with the standard diagnostic method of serial measurement of hs-cTn the evaluated method in this work performs inferior to current 0 hour/1 hour algorithms, recommended by the ESC These algorithms result in an almost 100% NPV, but time-to-decision would be longer, as at least one, and in most cases two separate blood samples are needed, resulting in a minimum time of around 1 hour (collecting blood samples, transport to laboratory, performing hs-cTn measurement, interpreting results).[21 30–35] Rule-in capacity of CADScorSystem was very limited in our analyses. The AUC of (un)adjusted CAD-score was low, ranging from 0.525 to 0.586, respectively. The AUC for detection of significant CAD in Winther *et al*'s work was higher assumingly due to a different investigated endpoint of CAD and a preselected study population.[17] For the unadjusted CAD-score both sensitivity and specificity were equal or below 50.0% at a cut-off value of <20. Adjusted for age, sex and hypertension, according to CAD-score algorithm version 3.1 the diagnostic performance increased to a sensitivity of 87.5% and an NPV of 90.0% at the same cut-off.[4 17] Interestingly, these results are comparable to the results of Winther *et al*, evaluating the diagnostic performance in detecting significant CAD in stable coronary syndromes.[17] Of notice, they used a slightly different cut-off of ≤20 to distinguish normal from abnormal, whereas we displayed the entire spectrum off potential cut-off ranging from <10 to < 90 and the resulting predictive values. Only two patients, both without MI, in our study had a CAD-score of exactly 20. Having used the 'usual ≤20 cut-off' both these patients would have been correctly ruled out if anything, thus increasing NPV and specificity. Using a lower cut-off of <10 would even increase the safety of ruling-out MI, but significantly reduce the number of patients ruled out. Like in our study, the corresponding specificity is quite low, but this relationship and trade-off is well known for almost all diagnostic methods in cardiology. One example is troponin measurement for emergency rule-out of MI where a rapid triage can be performed with almost 100% NPV, again at the expense of a low specificity. Obviously, using serial measurements of troponins for the diagnosis of MI (rule-in), the PPV increases to clinically useful figures as indicated by the current ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.[25 30 31 36]

This present pilot study was planned as a proof of concept assessing the applicability of an already developed algorithm for stable CAD in patients with suspected MI in an emergency setting. This analysis has some limitations. First, the sample size was rather small and not powered to assess diagnostic performance. The small sample size resulted in a rather low prevalence of MI (8 of 102 patients, corresponding to 7.8%). One possible explanation could be that MI patients are more likely to have persistent symptoms, which possibly led to inability of tolerating the measurement procedure, as well as a higher likelihood for early invasive approach, making those patients unavailable for CAD-score measurement. The main reason for the small sample size were shortages of CADScorSystem trained staff, as reflected in the difference between patients included in the BACC study and those screened for CAD-score measurement. Also, the number of patients with calculated CAD-score was diminished mainly due to many recording failures, mostly because of patients related factors like inability to rest, acute illness or even unavailability due to ongoing emergency testing and procedures. Additionally, most patients received only a single attempt to calculate a CAD-score, aside from the standard procedure of up to four retries. This is explained by the emergency setting itself, where it was often not feasible to repeatedly perform measurements due to low capacity of examination rooms with appropriate and silent environment as well as need for urgent diagnostic in standard patient care. Device related factors also contributed to the lower-than-expected inclusion rate, which creates a selection bias. The most important factors here being irregular heart rate resulting from atrial fibrillation or extrasystole. The study was indeed exploratory as the comparator in the algorithm behind the CE marked device was the present of a ≥50% stenotic coronary artery in stable CAD patients, whereas we used MI as the final diagnosis. Nevertheless, we found the device able to rule out MI with an NPV similar to that found when ruling out

significant CAD in stable patients.[17] Finally, the specificity in this study has been rather low, using a rule-out cut-off of <20. One confounding factor could possibly be a significant proportion of included patients with previous documented CAD or even PCI with stent implantation (24.5%), formerly an exclusion criterion in non-MI patients, which consequently led to a decrease in rule-out capacity and thus specificity of the device. Comparing to other works using troponin measurement to rule out MI it is noteworthy that a high NPV inadvertently comes with the price of a low PPV and specificity.[24 33–36]

In an explorative analysis assessing the use of a transcutaneous ultrasensitive microphone for heart sound analysis in patients with suspected MI, the resulting NPV for rule-out of MI was analogous to the findings in rule-out of stable CAD in elective patients yet inferior to the standard diagnostic assessment for patients with suspected MI with serial hs-cTn measurements. Major limitations of the present analyses were a low specificity, as well as a high number of recording failures and a rather small percentage of measurement retries, as feasibility for performing those is limited in the chosen setting. In conclusion, the tested device deems not feasible for wide application for diagnosis of MI in an emergency setting.

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Funding The BACC study was supported by German Center of Cardiovascular Research (DZHK). This study received funding (unrestricted grant) from Abott Diagnostics (USA) and Acarix Europe (DK). We also acknowledge financial support from the Open Access Publication Fund of UKE - Universitätsklinikum Hamburg-Eppendorf- and DFG – German Research Foundation. Neither was involved in the study design, data collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication. JTN is recipient of a fellowship by the Deutsche Forschungsgemeinschaft (NE 2165/1-1).

Competing interests JL is grant-recipient of a not project related grant by the Ernst und Bertha Grimmke Stiftung SB has received honoraria from Abbott Diagnostics, Siemens, Thermo Fisher and Roche Diagnostics and is a consultant for Thermo Fisher. DW reports personal fees from Bayer, Boehringer-Ingelheim, Berlin Chemie, Astra Zeneca, Biotronik and Novartis. PMC received honoraria/reports personal fees from Abbott, Acarix, AstraZeneca, Aventis, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli-Lilly, Evolva, Fibrex, Janssen, Merck, Myogen, Medtronic, Mitsubishi Pharma, The Medicines Company, Nycomed, Organon, Pfizer, Pharmacia, Regado, Sanofi, Searle and Servier.

Patient consent for publication Not applicable.

Ethics approval The BACC study was approved by the local ethics committee Hamburg (PV4306) on 25 July 2013.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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