Supplementary

The CADScor®System and algorithm

The acquisition system, the CADScor®System, recorded heart sounds using a dedicated microphone attached to the patient chest wall using a double adhesive patch. In addition to heart sounds the equipment recorded ambient room noise using an external microphone. The acoustic recordings were stored as raw files at the device and immediately after recording the automated acoustical analysis began.

The acoustical analysis was initiated by segmentation of the heart sounds into systolic and diastolic periods [1]. Furthermore, the timing of eventual third and fourth heart sounds were used to define onset and end of the mid diastolic period. Next, the ambient noise was suppressed by subtracting the recorded ambient noise from the heart sound signal using an adaptive filtering method. Noisy heart beats were discharged and an automated quality control algorithm validated the recording quality. Four acoustic features (properties), which are mathematical measures that quantify the signal characteristics, were extracted from the diastolic heart sound: a low frequency power ratio (FPR), automutal information (AMI), Principle component analysis of the diastolic frequency spectrum (PCASpec) and the amplitude of the fourth heart sound (S4Amp), before the CAD-score is constructed as a weighted linear combination of the four features (Figure 2) [2]. The four acoustic features from the diastolic heart sounds relate to murmurs and other heart sound characteristics related to CAD [1 2 3 4].

The updated score, CAD-score V3, was calculated using post-processing of the audio recordings obtained with the recording device combined with clinical risk factors. The updated CAD-score V3 algorithm reuses the acoustic features FPR and S4Amp from the CAD-score V2 algorithm and adds sixth new features: a low frequency power ratio from the systolic period (SysFPR), the estimated slope of diastolic frequency spectrum (SpecSlope) [5], a simple measure of heart rate variability (HRV), a principle component analyses based measure of the randomness of the diastolic sound (PCARand) [6], Sample Entropy of the diastolic sound (SampEn) [7 8] and a frequency distribution of the second heart sound (S2freq). These features were combined into an acoustic score using a linear discriminant function (Figure 2). The features SpecSlope, FPR, PCARand and SampEn all quantify the mid diastolic sound where the coronary murmurs are expected to be loudest. The S2freq distribution quantifies changes of the S2 sound which can be interpreted as the myocardial vibration response to the impact of valve closing. Thereby both the S4Amp and the S2freq features aim at quantifying myocardial stiffness. The

systolic feature SysFPR is included to better capture subjects with right coronary artery stenosis where the flow is expected to peak during the systolic period.

Using logistic regression, we then combined the acoustic score with gender, age, and hypertension, defined as systolic blood pressure ≥140 mmHg or receiving antihypertension medicine. This score was then scaled so that 90% of subjects with CAD in the initial Acarix heart sound database had a CAD-score V3 above 20 and such that the minimum CAD-score is zero and maximal CAD-score is 100. All patient with a DF score >85% were classified as having a minimum CAD-score V3 of 21. Hence, a CAD-score value >20 was categorized as abnormal.

References

1 Schmidt SE, Holst-Hansen C, Graff C, *et al*. Segmentation of heart sound recordings by a duration-dependent hidden markov model. *Physiol Meas* 2010;**31**: 513-29.

2 Winther S, Schmidt SE, Holm NR, *et al*. Diagnosing coronary artery disease by sound analysis from coronary stenosis induced turbulent blood flow: Diagnostic performance in patients with stable angina pectoris. *Int J Cardiovasc Imaging* 2016;**32**: 235-45

3 Schmidt S, Holst-Hansen C, Hansen J, *et al*. Acoustic features for the identification of coronary artery disease. *IEEE Trans Biomed Eng* 2015;**62**:2611-19

4 Semmlow J, Rahalkar K. Acoustic detection of coronary artery disease. *Annu Rev Biomed Eng* 2007;**9**: 449-69.

5 Shukla S, Dandapat S, Prasanna SRM. Spectral slope based analysis and classification of stressed speech. *Int J Speech Technol* 2011;**14**: 245-58

6 Giuliani A, Colafranceschi M, Webber CL, *et al*. A complexity score derived from principal components analysis of nonlinear order measures. *Phys A Stat Mech Appl* 2001;**301**: 567-88

7 Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol* 2000;**278**: H2039-49

8 Schmidt SE, Hansen J, Hansen CH, Toft E, Struijk JJ. Comparison of sample entropy and AR-models for heart sound-based detection of coronary artery disease. *Comput Cardiol* 2010;**37**:385-8

Table S1,

Table S1A Acoustic CAD-score V2	
Analysis not performed	12 (0.7%)
Arrhythmia	46 (2.8%)
Too much noise or too weak heart signal	50 (3.0%)
IC4 could not be identified	48 (2.8%)
Device-related problems	29 (1.7%)
Other	5 (0.3%)
Total	**190 (11.4%)**

Table S1B CAD-score V3	
Analysis not performed	12 (0.7%)
Arrhythmia	46 (2.8%)
Too much noise or too weak heart signal	50 (3.0%)
IC4 could not be identified	48 (2.8%)
Device-related problems	29 (1.7%)
Short systolic period	14 (0.8%)
Other	5 (0.3%)
Total	**204 (12.3%)**

Table S1, Tables stating reasons for missing acoustic CAD-score V2 (S1A) and CAD-score V3 (S1B).

Values are n (%)

Table S2,

Table S2A	CAD-score Version 3 Training cohort	CAD-score Version 3 Validation cohort	P-value
AUC	73.9 (CI: 67.0 - 80.8)	71.3 (CI: 65.6 - 77.0)	= 0.29
Sensitivity	82.8 (CI: 70.6 - 91.4)	80.0 (CI: 70.5 - 87.5)	= 0.67
Specificity	53.7 (CI: 49.3 - 58.1)	51.9 (CI: 48.4 - 55.5)	= 0.53
PPV	16.6 (CI: 12.5 - 21.3)	17.0 (CI: 13.6 - 20.8)	= 0.88
NPV	96.6 (CI: 93.8 - 98.3)	95.5 (CI: 93.0 - 97.3)	= 0.48

Table S2B	CAD-score Version 3 Training cohort	CAD-score Version 3 Validation cohort	P-value
AUC	73.5 (CI:66.5-80.5)	69.9 (CI:63.9-75.9)	= 0.23
Sensitivity	84.6 (CI:71.9-93.1)	78.7 (CI:68.7-86.6)	= 0.41
Specificity	53.9 (CI:49.5-58.2)	52.1 (CI:48.5-55.7)	= 0.51
PPV	15.4 (CI:11.4-20.1)	15.9 (CI:12.6-19.7)	= 0.78
NPV	97.3 (CI:94.7-98.8)	95.5 (CI:93.0-97.3)	= 0.23

Table S2, Diagnostic accuracy of CAD-score Version 3 with a cut-off of 20 divided by trainings (n=593) vs. validation (n=1082) cohort according to a reference of S2A) anatomically significant stenosis diagnosed with core lab QCA and S2B) hemodynamically significant stenosis diagnosed with invasive FFR as reference.

Figure legends

Figure S1 Plots for CAD-score Version 3 divided by QCA stenosis degree in patients referred to ICA Abbreviations as in Figure 1