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Cost-effectiveness of adding a non-invasive acoustic rule-out test in the evaluation of patients with symptoms suggestive of coronary artery disease: rationale and design of the prospective, randomised, controlled, parallel-group multicenter FILTER-SCAD trial

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ABSTRACT

Introduction Most patients with symptoms suggestive of chronic coronary syndrome (CCS) have no obstructive coronary artery disease (CAD) and better selection of patients to be referred for diagnostic tests is needed. The CAD-score is a non-invasive acoustic measure that, when added to pretest probability of CAD, has shown good rule-out capabilities. We aimed to test whether implementation of CAD-score in clinical practice reduces the use of diagnostic tests without increasing major adverse cardiac events (MACE) rates in patients with suspected CCS.

Methods and analysis FILTER-SCAD is a randomised, controlled, multicenter trial aiming to include 2000 subjects aged ≥30 years without known CAD referred for outpatient assessment for symptoms suggestive of CCS. Subjects are randomised 1:1 to either the control group: standard diagnostic examination (SDE) according to the current guidelines, or the intervention group: SDE plus a CAD-score. The subjects are followed for 12 months for the primary endpoint of cumulative number of diagnostic tests and a safety endpoint (MACE). Angina symptoms, quality of life and risk factor modification will be assessed with questionnaires at baseline, 3 months and 12 months after randomisation. The study is powered to detect superiority in terms of a reduction of ≥15% in the primary endpoint between the two groups with a power of 80%, and non-inferiority on the secondary endpoint with a power of 90%. The significance level is 0.05. The non-inferiority margin is set to 1.5%. Randomisation began on October 2019. Follow-up is planned to be completed by December 2022.

Ethics and dissemination This study has been approved by the Danish Medical Agency (2019024326), Danish National Committee on Health Research Ethics (H-19012579) and Swedish Ethical Review Authority (Dnr 2019-04252). All patients participating in the study will sign an informed consent. All study results will be attempted to be published as soon as possible.

Trial registration number
NCT04121949; Pre-results.

Strengths and limitations of this study

- ► Multicenter randomised controlled trial of a novel acoustic-based risk stratification coronary artery disease (CAD)-score for CAD.
- ► First randomised controlled trial to investigate the safety of CAD-score and the impact of the CAD-score in clinical practice.
- ► Study design follows newest international guidelines on chronic coronary syndrome.
- ► The study is unblinded as the treatment is based on the value of the CAD-score.

BACKGROUND

Chest discomfort is a common symptom leading to cardiological assessment for chronic coronary syndrome (CCS).[1] According to the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines, the diagnostic work-up should be based on the pretest probability (PTP) of obstructive coronary artery disease (CAD) estimated from sex, age and symptoms,[2 3] as originally suggested by the Diamond-Forrester model.[4 5] However, in clinical practice, PTP models have limited

sensitivity and specificity. In recent large studies, <10% of patients referred with symptoms suggestive of CAD needed revascularisation, and their prognosis was good.[6 7] The addition of risk factors to improve PTP precision has minor impact on prediction abilities.[6 8] This test strategy exposes patients to unnecessary procedure-related risks, medication and radiation, and the costs of diagnostic work-up may be unnecessarily high. Consequently, better methods of identifying patients with low probability of obstructive CAD and no need for diagnostic testing are needed.

The CAD-score is a risk stratification score for CAD obtained by the non-invasive acoustic device, CADScorSystem (Acarix A/S), which has shown good rule-out capabilities in patients with suspected CAD.[9] The device is approved for medical use, and mentioned in a Medtech innovation briefing in the National Institute for Health & Care Excellence (NICE)-guidelines as a rule-out test early in the diagnostic CAD work-up before coronary computed tomographic angiography (CCTA).[10] However, the CAD-score has never been tested as a rule-out tool in a clinical setting. Hence, the FILTER-SCAD trial will examine whether adding CAD-score to the standard diagnostic work-up reduces the number of diagnostic tests and associated healthcare costs without compromising safety in the outpatient assessment of patients with symptoms suggestive of CCS.

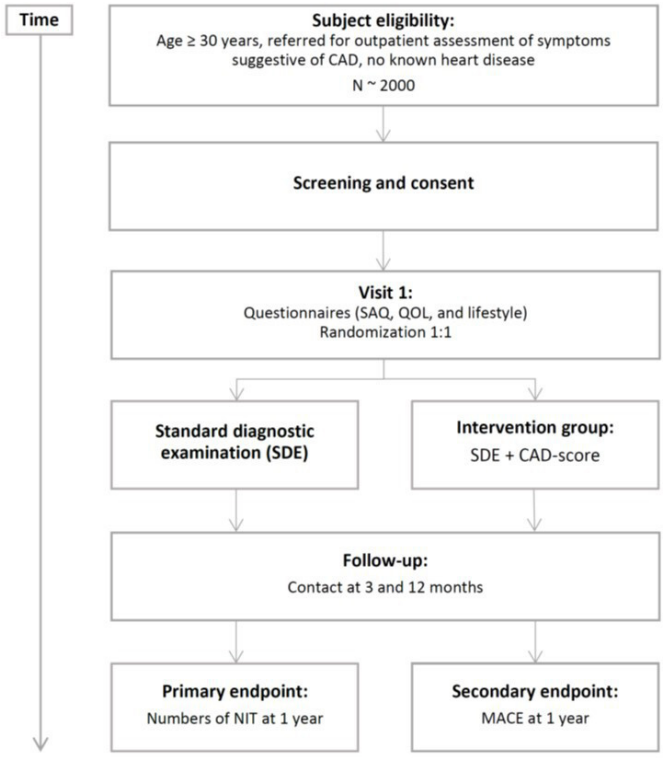

Figure 1 Study design. CAD, coronary artery disease; MACE, major adverse cardiac events; NIT, non-invasive test; QoL, quality of life; SAQ, Seattle Angina Questionnaire; SDE, Standard diagnostic examination.

OBJECTIVES

The primary objective of the FILTER-SCAD trial is to compare an initial diagnostic strategy based on a PTP according to guidelines plus CAD-score with a standard PTP-guided strategy when selecting patients with suspected CCS for diagnostic testing. The key secondary objective is to assess whether this strategy is non-inferior in terms of major adverse cardiac events (MACE). We hypothesised that an initial rule-out strategy guided by a PTP plus a CAD-score will reduce overall number of diagnostic procedures without compromising the safety when compared with a PTP-guided strategy alone over a follow-up period of 1 year.

METHODS

Trial design

Figure 1 shows an overview of the study design. The FILTER-SCAD trial is an investigator-initiated, prospective, randomised, controlled, parallel-group, multicenter trial planned to include 2000 subjects aged ≥30 years without known CAD referred for outpatient evaluation of symptoms suggestive of CCS at 5–6 sites; 4–5 sites in Denmark and 1 site in Sweden. The protocol is available as online supplemental file 1.

Study population

Study subjects are men and women aged ≥30 years without known CAD referred for evaluation of symptoms suggestive of suspected CAD in planned 5–6 cardiology outpatient clinics in Denmark and Sweden. Inclusion and exclusion criteria are listed in box 1.

Randomisation and blinding

Randomisation is done in a randomisation module in the electronic case report form (eCRF) and will be unblinded as the physician must act on the given CAD-score and PTP. Eligible subjects are allocated in a 1:1 manner to control or intervention group using permuted block randomisation stratified by study site and PTP-value (very low vs low-intermediate) by a computer-generated allocation table.

The study was designed based on the 2013 ESC guidelines on the management of stable CAD.[11] However, the ESC guidelines were updated in 2019 downgrading the PTP for obstructive CAD considerably,[2] and the FILTER-SCAD trial protocol was adjusted to be in accordance with these state-of-the-art recommendations. First subject was randomised on 22 October 2019. The first 78 subjects in the FILTER-SCAD trial were randomised according to the first protocol based on the 2013 ESC guidelines. The remaining subjects will be enrolled in consistency with the updated protocol.

Standard diagnostic examination

Subjects randomised to the control group will undergo a standard diagnostic examination (SDE) according to the ESC 2019 guidelines including clinical examination, PTP assessment based on age, sex and type of angina, risk

Box 1 Inclusion and exclusion criteria

Inclusion criteria

- Signed informed consent form.
- Male or female, aged ≥30 years.
- Patients able and willing to comply with the clinical investigational plan.
- Symptoms suggestive of stable coronary artery disease (CAD).
- No history of CAD (prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft).

Exclusion criteria

Related to pretest likelihood of obstructive CAD:

- Prior non-invasive testing for stable CAD or invasive coronary angiography within 6 months of randomisation.

Related to feasibility of performing a CAD-score measurement:

- Implanted donor heart, mechanical heart, mechanical heart pump.
- Pacemaker or cardioverter defibrillator.
- Implanted electronic equipment in the area above and around the heart.
- Significant operation scars, abnormal body shape, fragile or compromised skin in the fourth left intercostal space recording area.
- Receiving same day treatment with nitroglycerine on the day of randomisation.

Related to women of childbearing potential:

- Pregnancy.

The exclusion criteria 'Diamond-Forrester score >85%' was removed after updating the study according to the 2019 European Society of Cardiology guidelines on chronic coronary syndrome.

factor assessment and echocardiography.[2] The echocardiography will be done during the clinical investigation for CAD, but not necessarily on the day of randomisation. The SDE will be followed by non-invasive tests (NIT) if indicated (figure 2) according to the current European guidelines on CCS[2]; patients with very low PTP ≤5% should not receive further diagnostic testing, in patients with PTP 6%–15% NIT may be considered based on the overall clinical likelihood and patients with PTP >15% should be offered NIT as standard first choice of diagnostic test. Invasive coronary angiography (ICA) may be offered to selected patients with very high clinical likelihood, but no patients should receive ICA based on their PTP alone.

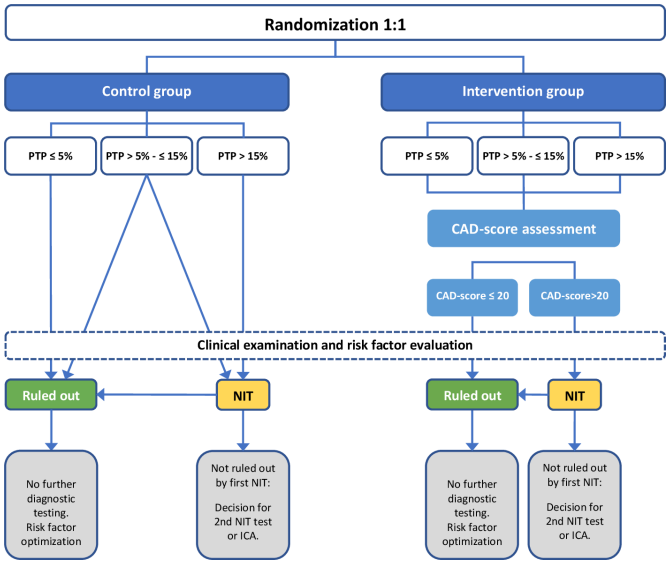

Figure 2 Flow chart. CAD, coronary artery disease; ICA, invasive coronary angiography; NIT, non-invasive tests; PTP, pretest probability.

Intervention (CAD-score)

Patients randomised to the intervention group will receive a CAD-score measurement in addition to the SDE. The CAD-score is measured using the acoustic device CADScorSystem (Acarix A/S).

The CAD-score is a risk stratification score scaled from 0 to 99 for obstructive CAD measured from an advanced analysis of sounds originating from blood flow turbulence in the coronary arteries and myocardial motion combined with the patients age, sex and blood pressure.[9 12] The measurements are done by a non-invasive acoustic device, CADScorSystem (Acarix A/S), which has shown good rule-out capabilities (cut-off: CAD-score ≤20) in patients with suspected CAD.[9] In a population with a prevalence of obstructive CAD on 9.4% (n=2245) the sensitivity, specificity, negative predictive value and positive predictive value were 88.7%, 41.5%, 97.2% and 13.7%, respectively.[12]

During a 3 min period with the patient lying in supine position, a transcutaneous recording of heart sounds is done by a microphone attached by a patch at the left fourth intercostal space (IC4).[13] Four times during the recording, the patient is asked to hold his/her breath for 8 s. From eight acoustic features, a fully automatic algorithm (software V.3.2) estimates an acoustic score which combined with the risk factors sex, age and hypertension by logistic regression results in the CAD-score.[9 13] The CAD-score measurements are done by specially trained study staff. If the measurement fails, up to four measurements are attempted.

Success of the new strategy depends critically on the physician's knowledge of strength and weakness of the CAD-score measure. At study start, each site will be trained in the CAD-score background literature and method. The training will be repeated after 3–6 months after enrollment of the first patient. Moreover, every physician is provided written information about the study and the CAD-score. The training of the physicians is intended to make physicians comfortable with the CAD-score and its strengths and weaknesses.

Further diagnostic pathway

All treating physicians are trained in the study protocol including the CAD-score. The physician is provided with a decision sheet with PTP, CAD-score and the recommended further diagnostic pathway (NIT or no further assessment; figure 1). Based on the available information, the physician decides whether to follow the recommended diagnostic pathway or not. A crossover could

be justified by the presence of cardiac risk factors with a higher perceived clinical likelihood.

Diagnostic tests for both intervention and control group

Patients with intermediary–high PTP in the control group or high CAD-score >20 in the intervention group are referred for further standard diagnostic testing including NIT and ICA, and this is done as standard procedure of each site. All decisions regarding diagnostic testing, including choice of testing modality, and medical/surgical treatment of the patient is done at the discretion of the treating physician, and is not a part of the study protocol.

Study periods

A run-in period with an expected duration of 3 months at each site is intended to serve as a training period where the study staff and attending cardiologists will be made familiar with performing and interpreting the CAD-score measurement by obtaining CAD-score of around 50–100 subjects at each participating site.

The planned duration of the study is 24 months; 12 months for the inclusion period, defined as first patient first visit to last patient first visit, for the main study starting after the run-in period, and approximately 12 months for the follow-up period. However, due to the COVID-19 pandemic and associated study delay, the enrollment period is extended to 15 months. Hence, the follow-up is planned to be completed by December 2022.

End of study will be when the following have occurred: (1) at least 2000 patients have been randomised and (2) 12±1 month (1 year) have elapsed since the last patient was randomised.

The study population will be followed for 1 year after randomisation.

Endpoints

Primary endpoint

The primary endpoint defined as the cumulative number of NIT and invasive procedures 1 year after randomisation. NITs include exercise ECG, CCTA, rubidium positron emission tomography (PET) CT, myocardial perfusion imaging, cardiac MRI and stress echocardiography. Invasive procedures include ICA only.

If the analysis shows a significant difference in the primary endpoint, a cost-effectiveness analysis will be conducted alongside the trial. The potential cost-effectiveness analysis will be based on information from the trial, as well as data from health registers. The register linkage will provide information at individual level on healthcare utilisation, including general practice, medication, etc; as well as labour market consequences and other societal costs. The cost-effectiveness analysis will apply two different effectiveness measures: procedures avoided, cf. the primary endpoint and quality-adjusted life-years based on the reporting of EuroQol-5D in the trial.[14]

Secondary endpoints

The key secondary endpoint is the safety endpoint MACE; a combined endpoint of all-cause mortality, non-fatal myocardial infarction (MI), hospitalisation for unstable angina pectoris (UAP), heart failure (HF), ischaemic stroke and major complication from cardiovascular procedures or diagnostic testing at 1 year after end of randomisation. An independent clinical event committee will adjudicate MACE endpoints blinded to the allocated intervention. Definitions of all-cause mortality, MI, UAP, HF and ischaemic stroke follow the ACC/AHA description of key data elements and definitions for cardiovascular endpoint events in clinical trials.[15] Major complication from cardiovascular procedures or diagnostic testing is defined as major bleeding, renal failure, stroke or anaphylaxis that occurred within 72 hours in accordance with the PROMISE Trial's definition.[7] Other individual secondary endpoints are (1) clinical endpoints: all-cause mortality, MI, hospitalisation for UAP, HF and ischaemic stroke, medication, time to CAD diagnosis, repeat referrals and bleeding requiring hospitalisation assessed 1 year after randomisation, (2) procedure-related endpoints: numbers of first NITs, numbers of ICA, number of downstream tests (NITs and ICAs done after the first NIT), contrast dose, radiation dose and adverse events related to the CAD-score measurement at 1 year after randomisation and (3) questionnaire endpoints: change in chest pain assessed by the Seattle Angina Questionnaire,[16] quality of life assessed by the EuroQol-5D,[17] and lifestyle assessed by the HeartDiet Questionnaire.[18] Questionnaires are collected at baseline, 3 months and 12 months after randomisation.

All endpoints are listed in online supplemental table 1.

Data handling

Data are collected in the eCRF Research Electronic Data Capture 10.3.3[19 20] by trained study staff. Blood samples, ECG and echocardiography data at baseline are standard test for ambulatory patients and will be collected from medical records and entered in the eCRF. Data on diagnosis, medications, diagnostic testing, repeat referrals, safety endpoints and bleeding requiring hospitalisation will be collected. All diagnostic test will be classified as positive, negative or inconclusive. This will be done at each individual site according to local criteria/guidelines.

Monitoring will be carried out by an external monitor and will include 100% monitoring of all potential serious adverse events related to the CAD-score measurement, informed consent forms and power of attorneys, and 20% monitoring of inclusion and exclusion criteria.

Statistical methods

The study is powered to detect superiority in terms of an absolute reduction of ≥15% in the cumulative number of diagnostic tests (primary endpoint) between the intervention and control groups with a power of 80% and a significance level of 0.05 with a sample size of 521 subjects in each randomisation group. The study is powered for

non-inferiority on the secondary safety endpoint (MACE) with a power of 90% and a significance level of 0.05 with a sample size of 1914 subjects (957 in each randomisation group). The non-inferiority margin is set to 1.5%.

The final sample size was chosen to be 2000 patients (1000 in each randomisation group), allowing for a 4% loss to follow-up and drop-out. The power calculation remains unchanged after updating the study protocol to reflect the latest 2019 ESC guidelines on CCS.

The main analysis will be intention-to-treat analysis. Analysis of the cumulative numbers of diagnostic test will be done with Poisson-based test and visualised by Nelson-Aalen nonparametric estimator. The secondary safety endpoint MACE will be analysed using a continuity-corrected modification of the Wilson's score method.

Prespecified subgroup analysis will be performed investigating the following subgroups: PTP (≤5% vs 5%–15% vs >15%), PTP (≤5% vs >5%), PTP (≤5% vs 5%–15%), age (<65 years vs ≥65 years), sex (male vs female), hypertension (yes vs no), dyslipidaemia (yes vs no), diabetes mellitus (yes vs no), smoking (yes vs no), family history of CAD (yes vs no) and BMI (<30 kg/m^2 vs ≥30 kg/m^2). An interim analysis for futility will be done after enrollment of at least 20% of the expected 2000 patients. We expect approximately 25% of the population to have low PTP or CAD-score ≤20. The study is considered futile if >90% of the overall population undergo further NIT or ICA after the initial SDE.

All statistical tests will be made using statistical software R and will have a two-sided significance level of 0.05.

Patient and public involvement

Patients and the public were not involved in the phase of the study, as the study addresses the physician's decision-making in the diagnostic strategy for ischaemic heart disease. However, the results will be relevant for both patients and the general public, and the result will be attempted to be published through patient organisations and public media. The study results will be distributed directly to the study participants.

Ethics and dissemination

The FILTER-SCAD trial is conducted in compliance with the principles of the Declaration of Helsinki of the World Medical Association, and laws of Denmark and Sweden. The study has been approved by the Danish Medical Agency (2019024326), Danish National Committee on Health Research Ethics (H-19012579) and Swedish Ethical Review Authority (Dnr 2019-04252). All patient participating in the study will sign an informed consent form. All study results will be attempted published as soon as possible.

DISCUSSION

The FILTER-SCAD trial will investigate whether adding a CAD-score to the SDE is a feasible way to reduce the use of excess diagnostic testing without compromising safety in the assessment of patients with symptoms suggestive of CCS.

CAD-score probabilities

The diagnostic performance of the CAD-score has been thoroughly examined.[9 12 13]

In a retrospective pooled study of 2245 patients undergoing CCTA, the diagnostic sensitivity and specificity for obstructive CAD of the CAD-score were 88.7% and 41.5%, respectively, with ≥50% stenosis on ICA as gold standard.[12] In this population with a 9.4% prevalence of obstructive CAD verified on ICA, the negative predictive value was 97.2% at a CAD-score cut-off ≤20, which stresses the potential of the CAD-score as a rule-out test for obstructive CAD.[12] In addition, the CAD-score's capability of reclassifying patients was simulated in the study; by adding a CAD-score to the patients with intermediate PTP of obstructive CAD, one-third of the patients were downgraded to the low likelihood of CAD group, and might accordingly have been ruled-out at that step without any further excess NIT, potentially reducing the accompanying risks and costs.[12] This reclassification only slightly insignificantly increased the CAD-prevalence in the low-risk group from 3.1% to 4.0%.[12] The previous CAD-score studies are based on the former ECS 2013 PTP. However, the non-invasive sound-based CAD-score tool, remains effective as a rule-out test also following implementation of the adjusted PTP in the recent 2019 ESC guidelines on CCS; 4 of 10 patients evaluated by the latest PTP were reclassified to low likelihood of obstructive CAD after adding a CAD-score.[21] The FILTER-SCAD trial will, to our knowledge, be the first study to test the CAD-score's ability in a clinical setting as a rule-out tool in patients with suspected CCS, testing both the efficacy and the safety in a randomised prospective study. Thereby, this study may enhance and simplify the diagnostic pathway for patients referred with suspected CCS, possibly allowing a reduction in excess use for NIT and ICA.

Safety

We are aware of the risk of incorrectly ruling out patient with CAD with a (false negative) low CAD-score. As for all other diagnostic tests, there will always be a risk of false negative test; sensitivity of exercise stress echocardiography, exercise stress single photon emission computed tomography (SPECT) and CCTA are 80%–85%, 73%–92% and 95%–99%, respectively, and false-negative test will occur.[11] However, these tests are more comprehensive and expensive than a simple CAD-score measurement. Also, current ESC guidelines recommend no further investigation with NIT in patients with PTP ≤5%. Thus, guidelines accept ruling out a proportion of patient with unacknowledged obstructive CAD to avoid large numbers of false positive tests and unnecessary exposure of patients to diagnostic test and accompanying risk. Moreover, the prognosis of patients referred with symptoms suggestive of CCS appears good,[7 22 23] especially among the patients classified with low PTP,[6] but also in both suspected CCS

and confirmed CAD.[24] The good prognosis is independent of treatment with percutaneous coronary intervention or optimal medical therapy including antianginal medication.[25]

In the FILTER-SCAD study, risks are mitigated in several ways; the participants are contacted by the study nurse after 3 months and 1 year, where angina symptoms are assessed. In case of worsening of symptoms, the nurse can contact the treating physician who can decide to schedule a follow-up visit. Also, the patients are instructed to contact the study nurse or their general practitioner if their symptoms continues or worsens. Finally, the treating physician may choose to disregard the recommended action according to the protocol and cross the patient over to NIT despite a CAD-score ≤20 if, for example, cardiovascular risk factors deemed to increase the patient's likelihood for CAD, the treating physician require further investigation, or choose to schedule a follow-up visit.

Notably, the CADScorSystem is CE-marked and approved for clinical use in patients ≥40 years of age, and is stated as a rule-out test early in the diagnostic CAD work up in the NICE-guidelines Medtech innovation briefing.[10] Thus, the FILTER-SCAD trial aims to test the implementation of an already approved clinical rule-out device in a clinical setting and its impact as an add-on device in the current diagnostic work-up, and not to test the diagnostic accuracy of the device.

Endpoints

The low diagnostic yield of the current work-up for patients with suspected CCS has questioned the value of the currently recommended diagnostic test strategy.[26–28] Many patients may be exposed to unnecessary procedure-related risks, medication, and radiation without achieving any benefits, and the costs of diagnostic work-up may be unnecessarily high. This study aims to investigate if a CAD-score added as a rule-out test in patients with suspected CCS will reduce unnecessary testing and thus increase the cost-effectiveness of the diagnostic workup. Hence, comparison of the cumulative number of NIT and ICA in two groups with and without CAD-score as rule-out test is relevant. Moreover, not compromising safety for patients by adding a CAD-score as a rule-out test is essential. Therefore, a key secondary composite safety endpoint MACE of numbers of all-cause death, myocardial infarction, unstable angina pectoris, heart failure, ischaemic stroke, and major complication from cardiovascular procedures or diagnostic within 72 is relevant and will enlighten the accuracy of excluding obstructive disease in patient groups with and without CAD-score measurements.

Another important secondary endpoint is angina symptom control, quality of life and patients' satisfaction with the diagnostic work-up. These are assessed with validated questionnaires.[16 17] Other secondary endpoints in the study include medication, time to diagnosis, contrast and radiation dose and adverse events related to the CAD-score measurement.

CONCLUSION

The FILTER-SCAD trial study will investigate the cost-effectivity and safety in a clinical setting of adding an advanced acoustic tool, the CAD-score, as a rule-out test in the diagnostic work-up of patients with symptoms suggestive of CCS.

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Contributors EIBP, SG and KWH designed and initiated the study. LHB, KWH, EIBP and SG obtained funding. LHB wrote the manuscript. LHB, KWH, TB-S, JB-S, HE, DE, SAH-P, MH, JDH, MTJ, MK, SR, SS, SG and EIBP revised and approved the final version of the article.

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Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Author note The CADScorSystem and analysis relating hereto will be offered freely by Acarix A/S.

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