Study Protocol

Chronic coronary syndrome in Swedish primary care (COSPRI)

A cluster-randomized study on a single-visit package investigation versus routine sequential investigation for chronic coronary artery disease conducted in Swedish primary health care.

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Document revision history

Issue	Summary of change
	According to approved amendment 2024-01599-02: Change of principal investigator Health economic analyses after one and five years Some clarifications in the text and Figure 1
01	New document March 10, 2023
01.1	Updated document January 31 2025
01.2	Updated document Januari 21 2026

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1. **Background**

In primary health care patients with chest symptoms are common. In many cases the cause is benign but chronic coronary artery disease (CAD) must often be considered [1, 2]. In the clinical work, evaluation of symptoms and risk factors are fundamental for a plausible working diagnosis and to judge if any further investigation is needed. The probability of CAD for a person of a certain age, sex and character of chest symptoms, scored from 0-3, i.e. pretest probability (PTP) for CAD, is substantially lower now than it was a decade ago in western countries [3, 4]. Consequently, recent European guidelines recommend that further investigation to rule out CAD may be omitted if the risk for CAD is judged to be low (PTP<15 %) and there are no further cardiovascular risk factors [4]. If further investigation is needed in the low-risk group, coronary computed tomography angiography (CTA) is preferable [4]. When the risk for CAD is judged to be intermediate (PTP> 15 %) an imaging investigation is advocated instead of the well-established exercise stress bicycle test. A much-used imaging test is myocardial perfusion scan in which an exercise stress bicycle test is performed, with the addition of an intravenous injection of a small amount of radioactive tracer, whereafter the myocardial blood flow is demonstrated by imaging. Sensitivity for myocardial perfusion scan to detect significant CAD is 87 % (95 % CI 83–90) in comparison with exercise stress bicycle test where it is only 58 % (95 % CI 46–69). Specificity is 70 % (95 % CI 63–76) and 62 (95 % CI 54–69), respectively [5]. However, the exercise stress bicycle test can reveal indirect signs of myocardial ischemia, is reasonable in price, easy to perform and available in many clinics and hospitals. It is since long the first-line method for referral from the primary care setting in Sweden. If the result from the exercise stress bicycle test is inconclusive, the work-up should be continued, e.g. with myocardial perfusion scan. An echocardiogram is often performed as well to evaluate the condition of the myocardium, heart valves and left ventricular ejection fraction. This stepwise or sequential clinical work-up strategy is well known and reasonable in general practice where patients in general have a low prevalence of serious diseases compared to organ specialist clinics. Since June 2021 in Region Östergötland, Sweden, (471 912 inhabitants, 2022) coronary CTA is recommended if further investigation is deemed necessary in patients with a low risk

of CAD (PTP< 15 %) in primary care. For patients with intermediate risk of CAD (PTP> 15 %) exercise stress bicycle test is still the first-line choice. Echocardiography may also be considered.

There may be advantages if the imaging investigation, myocardial perfusion scan and echocardiogram is performed on a single visit. In addition, a CT scan of the heart to determine coronary artery calcification (CAC) score is easy to perform on the same visit and adds only a small amount of radiation. The CAC-score has been shown to be an independent predictor of future cardiovascular events and is useful for reclassification of cardiovascular risk based on traditional risk factors like age, cholesterol levels and smoking habits [6]. CAC score may be used for reclassification of cardiovascular risk based on traditional risk factors like age, cholesterol, blood pressure and smoking [7].

Furthermore, a clear and coherent answer to the referring GP on all three investigations, myocardial perfusion scan, echocardiogram and CT scan of the heart may provide a completer and more illustrative basis for clinical decision-making. For the individual patient it is probably an advantage to get a thorough investigation done at one single visit and possibly a faster and more valid statement from the investigations by the GP.

On the other hand, if many advanced investigations are done unnecessarily, expenses and exposure to radiation will increase unjustifiably. Possibly there is also a risk of medicalization and to create worries for future cardiovascular events communicating the CAC-score to people that has not asked for the information.

In order to get a faster and more complete basis for the evaluation of CAD in primary care patients with an intermediate (PTP> 15 %) risk we created a package investigation comprised of myocardial perfusion scan, echocardiogram and CT scan of the heart on a single visit. The results from myocardial perfusion scan will be written according to national Swedish guidelines and communicated to the referring GP together with results from echocardiogram and CAC-scoring as a coherent answer. Moreover, registration of heart sounds followed by risk calculation by a technical device Cadscore® will be performed but only for scientific analyzes and not given as a clinical answer [8].

In this study we aim to compare the standard routine sequential investigation for detecting CAD with a single-visit package investigation.

2. Objectives and research questions

The objective of the study is to compare the effects of a coherent ischemia investigation on a single visit with the current clinical sequential routine for patients in primary care with a medium probability (PTP> 15%) of chronic CAD regarding:

Research questions:

Is there a significant difference between study groups

- Regarding waiting time for invasive coronary angiography or for the participants to be given results from completed non-invasive myocardial investigation?
- Regarding the outcome, connected to the main symptom i.e. chest pain/discomfort or dyspnoea?
- The costs per patient?
- The frequency of given advice on lifestyle changes?
- Health related quality of life, self-reported physical activity, physical fitness, dietary habits, mental symptoms and heart related anxiety on the day of inclusion, after 1, 3 and 5 years?
- The prescription of and adherence to drugs for CAD prevention 2 years before the day of inclusion, 2 and 5 years thereafter?
- The incidence of cardiac events after 2 and 5 years?

3. Outcome measures

3.1 Primary outcome measure

The waiting time, counted in days, begins on the date when the results of the package investigation (package investigation group), exercise bicycle stress test (standard investigation group) are

approved and immediately available for the physician at the PHCs. It extends until the day for performance of invasive coronary angiography or until the communication of results, from the completed non-invasive myocardial ischemia investigation to the trial participant (patient), as reported in medical records. It is important to note that waiting time for the initial investigation will not be included in this measurement (Figure 1).

3.2 Secondary outcome measure

Time points for assessment of secondary outcome measures are described in Figure 1.

- Presence of pathological q-waves on resting ECG.
- Reversible ischemia, ST-depression provoked by exercise.
- Signs of reversible ischemia on any test
- Radiation per patient measured in millisievert (mSv).
- Sick leave (days).
- Physical activity will be measured by two categorical questions asking for level of physical activity [9].
- Dietary habits will be measured by five categorical questions about consumption of fruit, vegetables, snacks and soft drinks during the last week [10].
- Heart focused anxiety will be measured by the Cardiac Anxiety Questionnaire – CAQ An 18-item scale [12].
- Generalized anxiety will be measured by the Brief Measure for Assessing Generalized Anxiety Disorder - GAD-7 A seven item scale [13].
- Depression symptoms will be measured by the Patient Health Questionnaire - PHQ-9 Maximum score 27 [14].
- Sleep quality will be measured by The Pittsburgh Sleep Quality Index – PSQI A 19-item scale which assesses sleep quality and disturbances over a 1-month time interval [15].
- Physical fitness will be measured by The International Fitness Scale – IFIS A 5-item scale [16].

- Questions on being a professional worker or not, working hours per week, smoking habits and passive smoking, by a questionnaire constructed for the study, the COSPRI questionnaire.
- Dental health will be explored by a 5-item questionnaire constructed for the study.
- Alcohol consumption will be measured by the Alcohol Use Disorders Identification Test - AUDIT. Score range: 0-40. (WHO-publications 2001) [18].
- Coffee consumption will be measured with questions about how often and how many cups of coffee are consumed.
- Major adverse cardiovascular events (MACE). Data from register SWEDEHEART, National Patient Register and National Cause of Death Register [19-21].
- Adherence to prescribed cardioprotective drugs. Data from the National Prescribed Drug Register [22].

Health-related quality of life will serve as the outcome in the health economic analysis and will be measured by EQ-5D-5L and RAND-36 Swedish versions to estimate quality-adjusted life-years (QALYs) [11, 17]. The incremental costs for package- vs. standard investigation will be divided by incremental QALYs for the same comparison to get the incremental cost-effectiveness ratio (ICER), i.e., cost per QALY, of package investigation vs. standard investigation.

4. Project description

4.1 Design

A cluster randomized study in Region Östergötland (471 912 inhabitants, 2022) in southeast Sweden. All currently existing 47 (January 2023) primary health care centers in the region are invited to participate. There are three hospitals in the Region Östergötland, one university hospital with a Physiology clinic and Cardiac clinic, a non-university hospital with Physiology clinic and a Cardiac clinic and a smaller hospital with an internal medicine clinic serving the nearby primary health care centers

with cardiac consultations. In addition, there is a privately run cardiac specialist clinic in one of the cities serving some primary health care centers with cardiac consultations. Almost all inhabitants in the region are registered at one of the 47 primary health care centers.

4.2 Randomization

The management of each primary health care center must accept randomization to either coherent ischemia investigation on a single visit “package investigation” or current clinical sequential routine “standard investigation” for applicable patients. When enough primary health care centers have accepted to participate the centers will be stratified based on the number of listed inhabitants on each of the primary health care centers and randomized 1:1 to package or standard investigation. Randomization will be performed by a statistician at Forum Östergötland, a support function for clinical translational research at Linköping University and Region Östergötland. The goal is to include at least 20 primary health care centers in total.

4.3 Masking/blinding

No masking or blinding of participating physicians or study participants.

4.4 Registration

The study is registered at clinicaltrials.gov.

5. Subjects

5.1 Selection and recruitment

Patients who seek primary care for symptoms judged to be compatible with a medium probability (PTP> 15) for symptomatic CAD, without exclusion criteria, at any of the participating primary health care centers will be informed about the possibility to participate in the study.

5.2 Number of research participants

The sample size calculation is based on a comparison of the two mean waiting time (days) values, based on historical data, in a cluster randomized design where the clusters are the PHCs. We have used 18 clusters for the calculation, and we estimate the within cluster correlation to be 0.1. Since the size of the clusters differ in size, we included a coefficient of variation of 0.46, based on the actual sizes of the PHCs. We have assumed the mean number of waiting time to be 37 days in the standard investigation group and 22 days in the package group with a standard deviation of 39 and 16, respectively. This assumption is based on, historical data on waiting times and a regional dialogue between representatives from Primary health care, Clinical Physiology- and Cardiology Departments prior the start of the study. With these assumptions, we estimate, with a power of 80% and a significance level set to 5%, that we need 416 participants, 208 per group. We expect that there will be some dropouts, so we increase the number of participants to 250 in each group.

5.3 Inclusion criteria

- Patients who seek primary care for symptoms judged to be compatible with a medium probability (PTP> 15) for symptomatic CAD at any of the participating primary health care centers.

5.4 Exclusion criteria

- Suspicion of acute coronary syndrome when care is sought.
- Previously diagnosed acute myocardial infarction.
- Revascularization with PCI/CABG.
- Proven reversible ischemia according to myocardial scintigraphy.
- Left Bundle Branch Block (LBBB).
- Ventricular pacemaker.
- Age below 18 years

- People whose meaning due to illness, mental disorder, weakened state of health or any other similar condition cannot be obtained, to be included in a research project.
- Insufficient understanding of spoken and written Swedish language.

Results will be reported according to CONSORT 2010 - extension to cluster randomized trials.

6. Interventions

Participants in the package investigation group will be subject to investigation by:

1.Resting ECG,

2.Evaluation of risk according to PTP-table.

3.Echocardiography.

4.Exercise stress bicycle test (secondarily drug provocation) with injection of isotope for myocardial scintigraphy.

5.Scanning for myocardial perfusion

6.CAC-scoring with CT.

7. Sound registration with Cadscore® and added risk calculation. Recording of cardiac diastolic sounds enabling the calculation of a risk score.

Participants in the standard investigation group will be subject to investigation by:

1.Resting ECG

2.Evaluation of risk according to PTP-table.

3. Echocardiography.

4.Exercise stress bicycle test.

If judged to be needed according to clinical indication sequentially completed by:

Exercise stress bicycle test (secondarily drug provocation) with injection of isotope for myocardial scintigraphy and/or coronary CTA. In addition, cardiac examinations done with other modalities chosen on clinical grounds will be examined in the study.

7. Measurements/variables

	STUDY PERIOD						
	Enrolment	Allocation	POST ALLOCATION				Close-out
	PHC enrolment		1 year follow up	2 years follow up	3 years follow up	5 years follow up	
Time point, (months relative to randomization)	-4- -0	0	12	24	36	60	60
ENROLMENT							
PHC consent (for trial)	X						
Patient's consent for study participation		X					
ALLOCATION							
PHC randomisation	X						
INTERVENTION							
Intervention and comparator arm:							
Resting ECG		X					
Riskevaluation based on PTP		X					
Echocardiograpy		X					
Exercise bicycle stress test		X					
Intervention arm:							
SPECT		X					
CT scan for CAC scoring		X					
CadScore		X					
ASSESSMENT							
MACE				X		X	X

Pathological q-waves on resting ECG		X					
Signs of reversible ischemia on any test		X					
Waiting time (days)			X				
Previuos medical history			X				
Clinical conclusion of cardiac investigations			X				
Laboratory tests			X				
Cardiovascular prevention: lipid-lowering, platelet-inhibiting or oral anticoagulating drugs and counseling			X				
Cardiopulmonary examinations related to ongoing investigation			X			X	X
Adherence to prescribed cardiovascular drugs				X		X	X
Number of contacts with primary care, hospital out-patient clinics and in-hospital care			X			X	X
Radiation exposure			X			X	X
Family history of cardiovascular diseases		X	X		X	X	X
Smoking habits		X	X		X	X	X
Alcohol consumption: AUDIT		X	X		X	X	X
Coffee consumption		X	X		X	X	X
Physical activity		X	X		X	X	X
Physical fitness: IFIS		X	X		X	X	X
Dietary habits		X	X		X	X	X
Heart focused anxiety, CAQ		X	X		X	X	X

Generalized anxiety: GAD-7		X	X		X	X	X
Depression symptoms: PHQ-9		X	X		X	X	X
Sleep quality: PSQI		X	X		X	X	X
Dental health		X	X		X	X	X
Health related quality of life: EQ-5D-5L, RAND-36		X	X		X	X	X

Figure 1

Schedule of enrolment, intervention and assessment in the Chronic cOronary Syndrome in Swedish PRImary care (COSPRI) study. PHC = Primary Healthcare Center; ECG = electrocardiogram; PTP = Pre-test Probability; SPECT = Single photon emission computed tomography; CT = Computed Tomography; CAC = Coronary Artery Calcification; CadScore = is an acoustic risk score; MACE = Major Adverse Cardiovascular Events; AUDIT = Alcohol Use Disorders Identification Test; IFIS = International Fitness Scale; CAQ = Cardiac Anxiety Questionnaire; GAD-7 = Generalized Anxiety Disorder; PHQ-9 = Patient Health Questionnaire; PSQI = Pittsburgh Sleep Quality Index; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level Version.

8. Statistical methods

Reference to statistical analyzes plan (SAP)

9. Data collection

One year after the day of inclusion all participants' computerized medical records will be reviewed and data entered a pre specified digital form RedCAP©. These data are about at what date an answer of the CAD investigation is communicated to the research participant on the result of the CAD-investigation, current diseases like hypertension, previous stroke or TIA, type 2 diabetes, laboratory results, creatinine, cholesterol, HBA1C and NT-proBNP and sick leave during study time. Notes about cardio preventive lifestyle counseling found in the medical records are also entered in RedCAP©.

Coronary CTA results if any, for all research participants and whether myocardial perfusion scan is performed is noted for the standard investigation group. Moreover, any X-ray or MRI investigations of the upper part of the body excluding head or upper extremities and the results noted as normal, difficult to assess or clearly pathological is entered in RedCAP©. Number of visits, telephone calls and video consultations by the participant to the primary care health center or cardiology clinic are also entered as well as any in-hospital care and for what diagnosis.

Data will be retrieved from the National Patient Register, the Cause of Death Register run by the National Board of Health and Welfare and SWEDEHEART run by Uppsala Clinical Research Center (UCR) to construct a major cardiovascular event MACE. Further, data will be retrieved from the National Prescribed Drug Register run by the National Board of Health and Welfare to follow prescription of and purchased cardioprotective drugs and from Statistics Sweden about days on sick leave.

10. Informed consent

Detailed information about the study will be sent to the research participants together with appointment for package investigation or stress bicycle test and echocardiography (standard investigation) from one of the two Physiology clinics. At the Physiology clinic the research participants are asked to give written informed consent to participate in the study meaning questionnaires on the day of inclusion, after 1, 3 and 5 years, review of medical records and retrieval of data from Swedish National registries. The research participants must be given full and adequate oral and written information about the study, its purpose, possible risks and benefits. Research participants must also be informed that they are free to discontinue their participation in studies at any time without having to give a reason. The research person must be given the opportunity to ask questions and be allowed time to consider the information provided. A copy of the research participant information and the signed consent is provided to the research participant. The research participant's signed and dated informed consent must be obtained before performing any study-specific activity in the study.

11. Adverse events

Serious adverse event (SAE) is defined as, clinically diagnosed myocardial infarction, deaths by any cause or hospitalization for heart failure. Adverse event (AE) hospitalization for increased chest pain, indirectly diagnosed myocardial infarction, e.g. by pathologic q-wave. All members af the study staff at the participating Physiology clinics or privately-run cardiologist consultant are encouraged to report any SAE or AE of which they become aware to the steering committee.

Towards the end of time period for inclusion of study participants we are planning for an adjudication committee of independent researchers tasked with determining the prevalence of MACE in both study groups i.e. package investigation or standard investigation, respectively.

12. Data monitoring and research management

Forum Östergötland, a support function for clinical translational research at Linköping university will do a startup check of the study. They will go through and see that all documentation such as permits, agreements and routines around storage and archiving is properly in place at sites taking part in the study and that good clinical practice (GCP) is followed.

When the first 20 participants are included in the study, we will thoroughly analyze inclusion procedure at the Physiology clinics in Linköping and Norrköping and at the privately run cardiac specialist clinic, collection of data from questionnaires answered by participants and data manually collected by review of medical records and noted in the RedCAP©-CRF.

Data retrieved from SWEDEHEART, National Patient Register, National Prescribed Drug Register, National Cause of Death Register and Statistics Sweden will not be monitored by Forum Östergötland.

13. Data management plan

Research persons participating in the study are coded with specific research person numbers. All research persons are registered on a research person identification list (code list) which links the research person's name and social security number with a research personal number. Region Östergötland is responsible for personal data.

Pseudonymized record review (CRF) and survey data will be collected, entered in RedCAP© and stored on a server at Linköping university. Only authorized persons can log in to RedCAP© and the login is through two-step verification. Code list is stored on separate digital medium at the head of research, Region Östergötland. Once the data collection is complete, the data is downloaded from the RedCAP© server and stored in a secure platform at Linköping university. All image material is saved according to clinical routine and data for research purposes is saved in pseudonymised condition. Images are saved digitally. Individuals cannot be identified based on the image material. In Cadscore®, information about age, gender and symptoms is entered. Audio recording is performed which results in summation of probability of disease on a scale of 0-100. The audio recording itself is not saved. Image and supplementary functional data, blood pressure, pulse, pain response, grading of effort from myocardial perfusion scan, cycle work tests and echocardiography are saved in Region Östergötland's clinical databases and during analysis they are exported via pseudonymization equipment to the research database at the Centre for Medical Imaging Science and Visualization (CMIV). Code key is saved on a separate digital medium at the head of research, Region Östergötland.

14. Design and testing of the database

Control of the data set (RedCAP© form and variables) and that the content corresponds to the needs of the study must be done by the responsible researcher before the start of the study. The data must also be tested for export so that the collected research data corresponds to the study protocol/research plan. Variable list is extracted from the RedCAP© system and saved.

All testing of the study database must be carried out before the start of the study.

15. Updating the database

Changes and amendments should be avoided. Inevitable changes and amendments must be planed together with Forum Östergötland.

16. Closure of database

When the study is finished and the data is monitored, the database is closed. After monitoring and after all questions have been resolved or, in cases where the question has not been resolved, commented on, the data can be exported from the system to the responsible researcher. This file then becomes a "clean file".

This file must be archived together with other study material. Copies from this file are then used for data analysis.

17. Management of source data

Source data refers to:

- Informed consents
- Data from patient records
- Data registered directly in RedCAP©.
- Images, supplementary functional data and Cadscore® data.

The source data must be available during the ongoing study and archived according to the archiving plan.

18. Archiving

Research data will be archived for at least 10 years and cleared out according to current routine in the Region Östergötland.

19. Time frame

Activity	Date (yyyy—mm-dd)
First study participant	2023-05-01
Inclusion of last study participant	2027-12-31
Retrieval of imaging data	2029-05-01
Retrieval of last questionnaire data	2033-04-30
Retrieval of last data from Swedish national registries	2033-04-30

20. Policy for publications

Policy for authorship is based on four criteria recommended by International Committee of Medical Journal Editors (ICMJE): 1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND 2. Drafting the work or revising it critically for important intellectual content; AND 3. Final approval of the version to be published; AND 4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who do not meet all four criteria for authorship may be acknowledged e.g. for acquisition of funding, administrative support, statistical advising or collection of data.

21. References

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