CLINICAL STUDY PROTOCOL

Randomized evaluation of coronary computed tomographic angiography (CCTA) in intermediate-risk patients presenting to the emergency department with chest pain

FAST-CCTA

An Electronic Health Record-based, parallel, open-label,

randomized multicenter trial

Investigational Product:	A strategy using early coronary computed tomographic angiography
Sponsor:	Karolinska Institutet
Sponsor Representative:	Håkan Wallén
Project Manager:	Liselotte Persson
Coordinating Investigator:	Tomas Jernberg
Chair and Co-chair:	Chair: Tomas Jernberg Co-chair: Bertil Lindahl

Protocol version and date

SYNOPSIS

Title of study: Randomized evaluation of coronary computed tomographic angiography (CCTA) in intermediate-risk patients presenting to the emergency department with chest pain - FAST-CCTA	
Name of Sponsor/Company: Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm	
Investigational product: A strategy using early coronary computed tomographic angiography	
Investigator(s) and study center(s): Tomas Jernberg, Danderyds sjukhus, Stockholm Bertil Lindahl, Akademiska Sjukhuset, Uppsala David Erlinge, Skånes Universitetssjuhus, Malmö/Lund Joakim Alfredsson, Universitetssjukhuset, Linköping Ole Fröbert, Universitetssjukhuset Örebro, Örebro Per Svensson, Södersjukhuset, Stockholm. Robin Hofmann, Södersjukhuset, Stockholm Jens Jensen, St Görans sjukhus, Stockholm Ellen Östenfeld, Skånes Universitetssjuhus, Malmö/Lund Henrik Löfmark, Danderyds sjukhus, Stockholm	
Planned study period: 04-SEP-2020 – 04-SEP-2025	
Objectives: To determine whether a diagnostic strategy including early coronary computed tomographic angiography (CCTA) in intermediate-risk patients presenting to the Emergency Department (ED) with chest pain reduces the composite endpoint of death, readmission because of myocardial infarction (MI) or unstable angina requiring revascularization.	
Methodology: Nationwide, multicenter, Electronic Health Record (EHR)-based open-label randomized controlled trial (EHR-RCT)	
Number of subjects (planned): 3500	
Diagnosis: Chest pain, Suspected ACS with intermediate risk	
Inclusion criteria: 1. Age≥18 years. 2. Within 24 hours from presenting to the ED with chest pain or other symptoms suggestive of coronary artery disease (CAD) 3. Acute MI excluded. 4. HEART-score >3 (according to http://www.heartscore.nl/) 5. Written informed consent obtained	
Exclusion criteria:	

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1. Any condition that may influence the patient's ability to comply with study protocol. 2. Known obstructive CAD. 3. Clear alternative diagnosis 4. Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m2 5. Major allergy to iodinated contrast media 6. Circumstances making high quality images unlikely. 7. Not a Swedish resident with a personal ID-number. 8. Pregnancy or breast feeding 9. Further investigation for CAD not indicated, due to limited life expectancy, quality of life or functional status 10. Previous inclusion in the trial
Investigational product: A strategy using early CCTA and usual care
Duration of treatment: Examination in-hospital or at least within 7 days from randomization
Active control, dosage and mode of administration: Usual care
Primary endpoint: The composite of death, readmission because of myocardial infarction (MI) or unstable angina requiring revascularization at 3 years. **Secondary endpoints:** Death or readmission because MI at 3 years Death at 3 years Cardiovascular death at 3 years MI (fatal or non-fatal) at 3 years Readmission because of unstable angina requiring revascularization at 3 years Resource use / Health care costs at 3 years Re-presentation to the ED because of chest pain at 3 years Invasive coronary angiography at 3 years Non-obstructive CAD at first invasive coronary angiography Angina after 1 year (at least grade 1 according to Rose questionnaire). Use (dispensed prescriptions) of prevention medications (antiplatelet therapy, Statins, blood pressure lowering therapy) at 1, 2 and 3 years. Quality of life at 1 year (RAND-36: 8 domains/scales will be compared). **Safety endpoints:** Allergy or anaphylaxis within 24 hours from CCTA or invasive coronary angiography Acute kidney injury within the first 7 days from CCTA or invasive coronary angiography Radiation exposure from CCTA

Statistical methods:
The 3-year risk of death, readmission because of MI or unstable angina requiring revascularization in patients randomized to strategy not including early CCTA is estimated to 8.0 %. The long-term effect of performing a CCTA is estimated to a relative risk reduction of 30%. To be able to reject the null hypothesis with a probability (power) of 0.80, 1,727 patients per group are needed. The type I error probability is 0.05. The number of patients that are of lost-of follow-up is expected to be low (due to virtually complete coverage in the EHR and national registries). Still, to compensate for a possible loss,1750 patients will be randomized to each group.

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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACS	acute coronary syndrome
CACS	coronary artery calcium score
CAD	coronary artery disease
CCTA	coronary computed tomographic angiography
CDS	clinical decision support
CV	curriculum vitae
DLP	dose-length product
DSMB	data safety monitoring board
ECG	electrocardiogram
ED	emergency department
eGFR	estimated glomerular filtration rate
EHR	electronic health records
EHR-RCT	electronic-health-record-based randomized clinical trial
EU	European union
GCP	good clinical practice
GDPR	general data protection regulation
HEART	history, electrocardiogram, age, risk factors, troponin
ICD	International Classification of Diseases
IEC	independent ethics committee
IQR	inter quartile range
ITT	intention to treat
LAD	left anterior descending coronary artery
LCX	left circumflex coronary artery
MI	myocardial infarction
RCA	right coronary artery
RRCT	registry-based randomized clinical trial
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SD	standard deviation
SDV	source data verification
SWEDEHEART	The Swedish Web-system for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies

STUDY ORGANIZATION

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3 SIGNATURE PAGES

SPONSOR

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Signature and date:	_____

PRINCIPAL, CO-PRINCIPAL AND CO-ORDINATING INVESTIGATORS

We, the undersigned, have read and understand the protocol and agree that it contains all necessary information for conducting the study.

We agree to conduct the study according to this protocol and according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable national laws and regulations.

Principal Investigator	**Tomas Jernberg, Professor** **Department of Cardiology, Danderyd Hospital** **182 88, Stockholm**
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Co-ordinating Investigator	**Tomas Jernberg, Professor** **Department of Cardiology, Danderyd Hospital** **182 88, Stockholm**
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4 BACKGROUND INFORMATION

Patients with chest pain or other symptoms consistent with acute coronary syndrome (ACS) but without ST-segment elevations on the ECG constitute about 10% of all patients at the emergency department (ED). Early assessment of these patients has lately been improved. After the introduction of high-sensitive biomarkers (troponins) and fast rule-out algorithms about half of the patients can now be identified as low-risk patients and discharged directly from the ED[1]. Of the other half about 10 % will ultimately be diagnosed with acute myocardial infarction (MI) and undergo invasive coronary angiography and revascularization as appropriate. However, about 45 % of all patients will be considered as having at least intermediate risk but not be diagnosed with MI. In this group early assessment is still challenging, and the process needs to be improved.

A large proportion of the intermediate risk patients undergo further non-invasive testing with exercise-ECG, stress echocardiography or stress nuclear imaging, but these methods still have limited sensitivity (80-90%) and specificity (75-85%) and cannot detect non-obstructive coronary artery disease (CAD) which is associated with a worse long-term prognosis.
The diagnostic accuracy of coronary computed tomographic angiography (CCTA) has been extensively validated and there has been a continuous improvement regarding image quality and radiation exposure[2, 3]. Recent studies suggest a better diagnostic performance of CCTA compared with functional testing and better selection of patients who should undergo coronary angiography. CCTA is now recommended as a first-line investigation in patients with suspected stable CAD[4]. An important advantage of CCTA is that it can identify patients with non-obstructive atherosclerosis who may benefit from prevention strategies. Recently, the SCOT-HEART investigators showed that the use of CCTA reduced the long-term risk of coronary death or MI in patients with suspected stable CAD[5].

Although recommended in patients with stable CAD, the use of CCTA in patients with symptoms suggestive of ACS remains to be defined. There have been several studies evaluating CCTA in chest pain patients. However, these studies have included mainly low-risk patients and followed patients for a short period resulting in no differences in clinical outcome[6-8]. There is one Scottish study that plans to examine the long-term effect of CCTA in chest pain patients without acute MI but with elevated troponins, but that study has not yet started (Clinical Trials: NCT03952351). Today, there is no consensus how chest pain patients without MI but with an intermediate risk should be managed.

Recently a new type of cost-effective trials (Registry-based Randomized Clinical Trials (R-RCTs)) has been developed by us and others[9-11]. These trials take advantage of the clinical quality registries in Sweden and, thus, collect most of clinical data through already existing registries. However, for many diseases, the clinical quality registries

are poorly developed and there is a need to develop pragmatic trials in which patients are identified in and data are collected from the EHR, a so called EHR-RCT.

5 STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVES

To determine whether a diagnostic strategy including early CCTA in intermediate-risk patients presenting to the ED with chest pain reduces the composite endpoint of death, readmission because of MI or unstable angina requiring revascularization.

5.2 SECONDARY OBJECTIVES

To determine whether a diagnostic strategy including early CCTA in intermediate-risk patients presenting to the ED with chest pain reduces:

- Death or readmission because of MI
- Death
- Cardiovascular death
- MI (fatal or non-fatal)
- Readmission because of unstable angina requiring revascularization
- Resource use and health care costs
- Re-presentation to the Emergency department because of chest pain
- Proportion undergoing invasive coronary angiography
- Proportion with non-obstructive CAD at invasive coronary angiography
- Angina symptoms after 1 year (measured with the Rose questionnaire).

To determine how a diagnostic strategy including early CCTA in intermediate-risk patients presenting to the ED with chest pain influences the use of prevention medications (antiplatelet therapy, statins, blood pressure-lowering therapy).

To determine whether a diagnostic strategy including early CCTA in intermediate-risk patients presenting to the ED with chest pain improves health related quality of life after 1 year (measured with RAND-36) in a subgroup.

To determine whether an initial diagnostic strategy including early CCTA in intermediate-risk patients presenting to the ED with chest pain and no MI influences the proportion of patients with allergy, anaphylaxis or acute kidney injury.

To describe the distribution of radiation exposure, measured as dose-length product (mgy cm) in patients undergoing CCTA.

6 ENDPOINTS

6.1 PRIMARY ENDPOINT

Composite of death, readmission because of MI or unstable angina requiring revascularization at 3 years.

6.2 SECONDARY ENDPOINTS

- Death or readmission because MI at 3 years
- Death at 3 years
- Cardiovascular death at 3 years
- MI (fatal or non-fatal) at 3 years
- Readmission because of unstable angina requiring revascularization at 3 years
- Resource use / Health care costs at 3 years
- Re-presentation to the ED because of chest pain at 3 years
- Invasive coronary angiography at 3 years
- Non-obstructive CAD at first invasive coronary angiography
- Angina after 1 year (at least grade 1 according to Rose questionnaire12).
- Use (dispensed prescriptions) of prevention medications (antiplatelet therapy, Statins, blood pressure lowering therapy) at 1, 2 and 3 years.
- Quality of life at 1 year (RAND-36: 8 domains/scales will be compared13).

Safety endpoints:

- Allergy or anaphylaxis within 24 hours from CCTA or invasive coronary angiography
- Acute kidney injury within the first 7 days from CCTA or invasive coronary angiography
- Other non-cardiac findings on CCTA.
- Radiation exposure from CCTA

7 STUDY DESIGN

7.1 STUDY OUTLINE

This will be an EHR-based, randomized, open, parallel trial, with blinded endpoint adjudication (figure).

Patients

Patients presenting to the ED with chest pain or other symptoms suggestive of ACS, without acute MI but with an intermediate risk (HEART-score >3) will after written informed consent be randomized to either a strategy with an initial CCTA or not.

To allow quick inclusion the study module (in which randomization can be performed) will be directly accessible from and seamlessly integrated into the EHR

systems. All necessary structured baseline data about the patients will be automatically collected from the patient´s original health records and transferred to a study database. Other necessary data will be entered manually into the study module and then transferred to the study database. Patients with chest pain and Heart score >3 will be high-lighted as potential study patients for the clinician. Regarding care after randomization, patients will be followed both in the EHR-system, manual registration and by using national registries.

Intervention

Patients randomized to strategy including early CCTA will receive standard care according to responsible physician and perform a CCTA as soon as possible (in most cases within 24 hours, but at least within 7 days). Local scanning protocols will be used on ≥64-slice multi-detector CT scanners able to perform ECG-gated coronary angiography. The coronary angiography will be classified as normal (or near normal) or as having atherosclerosis (CAD). The report will also classify each segment regarding degree of stenosis (no stenosis, 0-49%, ≥50%, or not possible to estimate because of calcification or technical reason).

The result will be presented to the responsible physician who will plan further care of the patients. The responsible physician will be encouraged to initiate secondary prevention measures if CCTA shows signs of CAD.

Controls

Patients randomized to a strategy not including early CCTA will receive further care (including examinations) according to responsible physician but not include early CCTA. These patients will often undergo a non-invasive functional test, such as Exercise-ECG, stress echocardiography or nuclear imaging according to local routines, but not always.

All patients

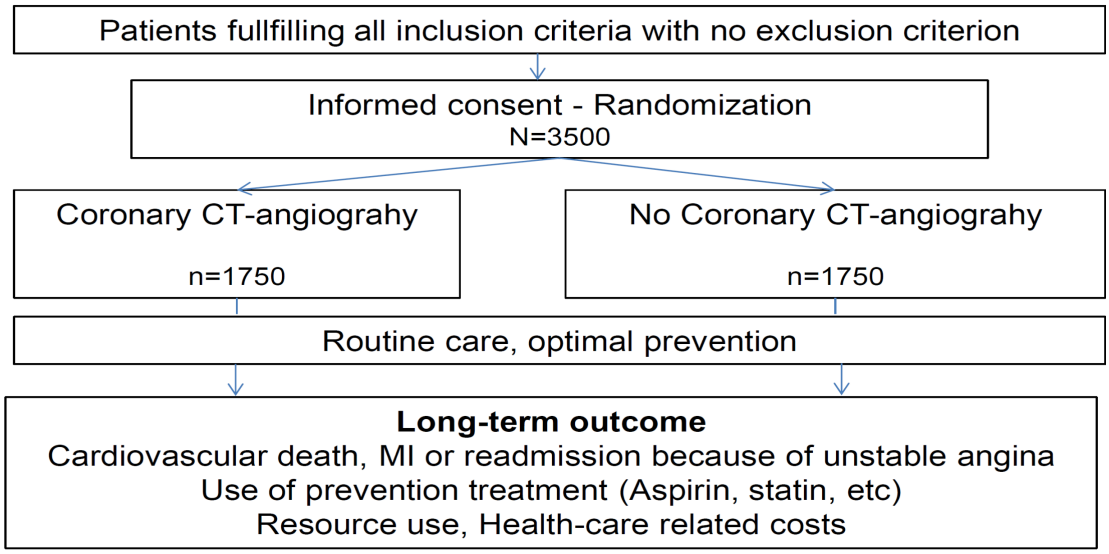
All patients should receive optimal prevention according to current guidelines.

Outcome

The primary endpoint is composite of death, readmission because of MI or unstable angina requiring revascularization at 3 years.

7.2 SCHEDULE OF EVENTS

Flowchart of planned EHR-RCT



8 SELECTION AND WITHDRAWAL OF SUBJECTS

8.1 SUBJECT INCLUSION CRITERIA

1. Age≥18 years.
2. Within 24 hours from presenting to the ED with chest pain or other symptoms suggestive of coronary artery disease (CAD)
3. Acute MI excluded.
4. HEART-score >3 (according to http://www.heartscore.nl/)
5. Written informed consent obtained

8.2 SUBJECT EXCLUSION CRITERIA

1. Any condition that may influence the patient's ability to comply with study protocol.
2. Known obstructive CAD.
3. Clear alternative diagnosis
4. Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m^2
5. Major allergy to iodinated contrast media
6. Circumstances making high quality images unlikely.
7. Not a Swedish resident with a personal ID-number.
8. Pregnancy or breast feeding
9. Further investigation for CAD not indicated, due to limited life expectancy, quality of life or functional status
10. Previous inclusion in the trial

8.3 WITHDRAWAL OF SUBJECTS

In accordance with the principles of the current revision of the Declaration of Helsinki (amended October 2000, with additional footnotes added 2002 and 2004) and any other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason, without prejudice to his or her future medical care by the physician or at the institution, and is not obliged to give his or her reasons for doing so.
The Investigator may withdraw the subject at any time in the interests of the subject's health and well-being.

If the patient is withdrawn, the patient will be censored at that time point. Also, mortality data will be obtained for all patients according to intention to treat since this is public data.

8.4 SUBJECT LOG AND SCREENING OF SUBJECTS

There will be no screening log.

9 DIAGNOSTIC STRATEGY OF SUBJECTS

9.1 ADMINISTRATION OF DIAGNOSTIC STRATEGY

Patients randomized to strategy including early CCTA will receive standard care according to responsible physician and referred to a CCTA as soon as possible, preferably within 24 hours, but not later than within 7 days. Local scanning protocols can be used on ≥64-slice multi-detector CT scanners able to perform ECG-gated coronary angiography.

The coronary angiography will be classified as normal (or near normal) or as having atherosclerosis (CAD). The report will also classify each vessel (left main, prox LAD, mid or distal LAD, LCX and RCA regarding degree of stenosis (no stenosis, 0-49%, ≥50%, or not possible to estimate because of calcification or technical reason).

The result will be presented to the responsible physician as soon as possible and who will plan further care of the patients.

Patients randomized to a strategy not including early CCTA will receive further care (including examinations) according to responsible physician but not include early CCTA. These patients will often undergo a non-invasive functional test, such as Exercise-ECG, stress echocardiography or nuclear imaging according to local routines, but not always.

Regardless of diagnostic strategy, the responsible physician is encouraged to initiate secondary prevention measures if the investigations indicate signs of CAD, including medication with aspirin and statins.

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9.2 RANDOMIZATION AND BLINDING

In the randomization part of the study module, inclusion and exclusion criteria will be checked and patient information and informed consent form can be retrieved and printed. The randomization will be performed in the module using 1:1 ratio and stratified according to center. Randomization can be performed at any time within 24 hours from randomization.

The assigned diagnostic strategy will be open for the clinician and patient following randomization. The study module will improve identification of potential study patients by indicating for the clinician that the patient may be eligible for the study.

9.3 CONCOMITANT MANAGEMENT INCLUDING OTHER STUDIES

Optimal secondary prevention with regard to lifestyle and pharmacological treatment with target levels according to present guidelines will be recommended for all patients. Cardiovascular pharmacological treatments will be registered in the study module and later also obtained from the Swedish Prescribed Drug Register. Enrolled patients can participate in any other study that does not directly alter the effect of a diagnostic strategy with early CCTA.

9.4 COMPLIANCE WITH THE DIAGNOSTIC STRATEGY

The inclusion in the study and the randomization to diagnostic strategy will be documented in the patient´s health records. Any cross-overs from non-CCTA- to CCTA-strategy will be captured in SWEDEHEART which is a quality registry registering all CCTA performed in Sweden.

9.5 CONTINUATION OF DIAGNOSTIC STRATEGY

If indicated according to responsible physician the patient can perform a (new) CCTA at any time during the study. After discontinuation of the study, the patient may undergo any diagnostic work-up at the discretion of the responsible physician.

10 ASSESSMENT OF EFFICACY

10.1 CLINICAL EFFICACY ASSESSMENTS AND ADJUDICATION

Primary endpoint is the composite of death, readmission because of MI or unstable angina requiring revascularization at 3 years. Information about deaths will be obtained from the population registry at Statistics Sweden. All readmissions with an ICD code of I20-I25 and all revascularization procedures will be captured by the EHR, the patient registry, and the SWEDEHEART registry and then centrally adjudicated by

two independent blinded cardiologist and by a third one if disagreement. The events will be adjudicated as myocardial infarction or not in patients admitted with a diagnosis of I20-I25 and as unstable angina or not in patients without acute MI undergoing revascularization. Adjudication will be performed according to a CEC charter and be based on current recommendations.

Secondary endpoints

- Death or readmission because MI at 3 years
- Death at 3 years
- Cardiovascular death at 3 years
- MI (fatal or non-fatal) at 3 years
- Readmission because of unstable angina requiring revascularization at 3 years
- Resource use / Health care costs at 3 years
- Re-presentation to the ED because of chest pain at 3 years
- Invasive coronary angiography at 3 years
- Non-obstructive CAD at first invasive coronary angiography
- Angina after 1 year (at least grade 1 according to Rose questionnaire12).
- Use (dispensed prescriptions) of prevention medications (antiplatelet therapy, Statins, blood pressure lowering therapy) at 1, 2 and 3 years.
- Quality of life at 1 year (RAND-36: 8 domains/scales will be compared13).

Cardiovascular death, defined as ICD codes I00-I99, will be obtained from the cause-of-death registry. Fatal MI will be obtained from the EHR, the patient registry and adjudicated as described above. Fatal MI outside hospital will be obtained from the cause-of-death registry and defined as ICD-codes I21-I23.

Resource use (and subsequent health care costs) will be measured as the number of days hospitalized, prescribed and dispensed drugs and use of coronary angiographies, PCI and by-pass surgery. These data will be obtained from the EHR, the patient registry, the prescribed drug registry and Swedeheart. Re-presentation to the ED because of chest pain at 3 years will be obtained from the electronic health records.

Invasive coronary angiography at 3 years and non-obstructive CAD at first invasive coronary angiography will be obtained from Swedeheart/SCAAR registry. Questionnaires regarding angina after 1 year (at least grade 1 according to Rose questionnaire) and quality of life at 1 year (RAND-36: 8 domains/scales will be compared) will be sent to the patients at one year.

10.2 CLINICAL SAFETY ASSESSMENTS

Safety endpoints will be:

- Allergy, anaphylaxis or acute kidney injury in association with CCTA.

- Radiation exposure, measured as dose-length product (mgy cm) in patients undergoing CCTA.

Allergic reactions and radiation exposure will be obtained from Swedeheart, whereas acute kidney injury will be defined as an increase of S-creatinine by 26.5 µmol/l within 48 hours or by 50% within 7 days.

10.3 LABORATORY ASSESSMENTS

Biochemical data measured in the clinical routine that will be collected by the study module: Hb, CRP, creatinine, and P-Glucose on admission, maximum troponin, Cholesterol, LDL- and HDL-cholesterol, triglycerides and HbA1c.

11 SAFETY ASSESMENT AND DATA SAFETY MONITORING BOARD

There will be no data safety monitoring board (DSMB). When all patients have been included the median follow-up will be only 1 year. Thus, all patients will have been included before it is realistic to see any significant differences between the patient groups.

12 STATISTICS AND DATA MANAGEMENT

12.1 DATA MANAGEMENT

A platform for clinical decision support, the “CDS-platform”, developed by Cambio Healthcare system, will be used. This platform is open, and thus can be integrated into any EHR, enabling a nationwide solution. On this platform there will be a study-module and a randomization module.

Patients presenting to the emergency department is triaged by a nurse and a doctor at the emergency department of the participating hospitals. If the patient present with chest pain and data regarding symptoms, ECG, age, risk factors and troponin-level (either transferred automatically from the EHR or registered directly in the study module) indicate a HEART-score (https://www.heartscore.nl) >3, a dialogue box will indicate that the patients may be eligible for the study. The clinician will be able to respond either (1) OK or (2) Do not show this message again. If the response is OK, the message will be repeated every 6 hours when the records are opened, up to 24 hours from presentation.

When randomizing the patient, the investigator will go to randomization-module and be asked to klick yes/no on inclusion and exclusion-criteria where criteria based on already retrieved data will already have a pre-selected yes or no (possible to change). If all inclusion criteria and no exclusion criterion are fulfilled the patient will be randomized. The randomization will be performed in the module using permuted

block randomization with 1:1 ratio. The study module will link to a document with all relevant study information which can be added to the EHR after the investigator's approval.

Most other baseline data and data about in-hospital course will be collected directly from the EHR to the study module and then mirrored to a study database. All data that are entered or stored in a structured way can be automatically retrieved to the two modules. Information that is not structured will be entered directly to the study modules. The study module will deliver a suggested text-note which the investigator can use in the EHR. Before sending data to the study database, all data will be displayed for the Investigator who will be able to add missing data, correct data and give approval of transfer of data.

Background variables that will be registered include demographics (age and sex), risk factors (family history, BMI, previous or current smoking, hypertension, hyperlipidemia, diabetes mellitus and chronic kidney disease), past medical history (prior MI, angina, stroke, peripheral artery disease, heart failure and atrial fibrillation) medical treatment before admission (Aspirin, P2Y12-receptor blockers, beta-blockers, ACE-inhibitors or angiotensin receptor blockers, calcium blockers, diuretics, statins or other lipid lowering therapy). At presentation, data regarding symptoms (chest pain, dyspnea or other) and whether typical or not, ECG findings (rhythm, ST-T changes), all troponin measurements, but also heart rate, blood pressure, and pulmonary rales. To be able to calculate duration of hospital stay and use of resources, type of wards, time for presentation, admission and discharge will be registered.

Results from examinations will be collected. For echocardiography data regarding ejection fraction and significant valve disorders will be collected. For functional tests, data to judge the performance of the test and signs of permanent or reversible ischemia will be registered. These examinations will be performed at different departments. All structured data will be automatically extracted to the study module. The Investigator will be asked to check (and complete) that all necessary data from the report of the examination have been registered.

For patients undergoing CCTA, variables will be registered in the EHR and the registry of coronary angiography and PCI (SCAAR) registry (a nationwide registry and a part of SWEDEHEART), including a detailed description of angiographic findings including segment (RCA:1, 2, 3, 4, 18 and 19 LM:5, LAD; 6-10, 20, CX: 11-16, IM: 17 if larger than 2 mm and with visible stenosis), degree of stenosis, coronary artery calcium score (CACS), radiation exposure expressed as dose-length-product (DLP) and any allergy or anaphylaxis after examination. Invasive coronary angiography or angioplasty will also be registered in SCAAR in a similar fashion. For patients undergoing coronary artery by-pass grafting variables are registered in the EHR and Swedish heart surgery registry. The SCAAR and the Swedish heart surgery registry register all procedures in Sweden (100% completeness) and data from these

registries will be transferred to the study database. S-creatinine values within 1 week from examinations will be extracted to identify any acute kidney injury.

For follow-up purposes, national registries with 100% complete data will be used. Information about death and cause of death will be obtained from the Swedish population registry and the cause of death registry. Cardiovascular death will be defined as ICD codes I00-I99. Information regarding length of stay, re-attendances and readmissions because MI will be obtained from the in-patient registry of the National board of health and welfare. To collect data regarding “unstable angina requiring revascularization” the SCAAR registry and the Swedish heart surgery registry will be used.

Information about future medications will be obtained from the national prescribed drug register, including all dispensed prescriptions in all individuals in Sweden. Patients will contacted by e-mail, sms, telephone or ordinary mail after 1 year. The patient will receive a link and login by BankID to respond to questionnaires (Rose Angina questionnaire and RAND-361,2). Patient without BankID or for other reason not able to respond to a web-based questionnaire will do it on paper.

12.2 STATISTICAL ANALYSIS

For the primary endpoint and the secondary endpoints death, cardiovascular death, death or readmission because MI, MI (fatal or non-fatal), readmission because of unstable angina requiring revascularization, re-presentation to the Emergency department because of chest pain and invasive coronary angiography, time-to-event will be presented with the use of Kaplan–Meier plots, and differences between the diagnostic strategies will be assessed with the use of the log-rank test and Cox regression with hazard ratios presented with 95% confidence intervals. Data on any patient who will be lost to follow-up (emigration or withdrawal of consent) or die will be censored at the date of emigration, withdrawal of consent or death.

Regarding primary end point, prespecified stratified analyses with interaction tests will be performed to detect any heterogeneity in the effect of the two diagnostic strategies. The pre-specified sub-groups are: Age ≥65 / <65 years; Males /Females; Troponin T level <5, 5-14, >14; and Heart-score ≥5 /<5.

Comparison regarding proportion having non-obstructive CAD at invasive coronary angiography, angina after one year and use of prevention medications at 1, 2 and 3 years will be compared with chi-square test. For Health-related quality of life at 1 year we will use RAND-36 and compare outcome in the 8 domains/scales by Mann-Whitney U-test. The safety endpoints will be reported as proportions (95% confidence interval) and as mean (SD) and median(IQR) values, and comparison will be made by chi-square test (or Fisher's exact test if low numbers).

12.2.1 ANALYSIS POPULATION

All analyses will be performed on an intention-to-treat (ITT) basis. Randomization numbers assigned unintentionally, such as by clicking the wrong box or randomly assigning the wrong patient record will be recorded in the clean file documentation and removed from the analysis database. A supplementary per-protocol analysis will be conducted in which patients will be excluded if they have not been managed according to randomization.

Attempts will be made for randomization numbers with incorrect patient identifiers to identify if there is an intentionally randomised patient linked to the number. A randomization number, for which it is not possible to clearly identify a patient for follow-up of mortality, will be recorded and removed from the analysis database, even if a patient might have been randomised. No patients will be removed from the ITT population due to violated inclusion or exclusion criteria or deviations from the treatment algorithm.

12.3 DETERMINATION OF SAMPLE SIZE

By applying inclusion and exclusion criteria on chest pain population from previous studies[1, 12], the 3-year risk of cardiovascular death, readmission because of MI or unstable angina requiring revascularization in patients randomized to strategy not including early CCTA is estimated to 8.0 %. The long-term effect of performing a CCTA is estimated to a relative risk reduction of 30% (40% in previously performed SCOT-HEART[5]). To be able to reject the null hypothesis with a probability (power) of 0.80, 1,727 patients per group are needed. The type I error probability is 0.05. The number of patients that are of lost-of follow-up is expected to be low (due to virtually complete coverage in the EHR and national registries). Still, to compensate for a possible loss,1750 patients will be randomized to each group.

13 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigators will permit study-related monitoring, audits, review and regulatory inspections, providing access to source data/hospital records. Sponsor verifies that each patient has consented in writing to direct access to the original source data/hospital records by the use of written patient information and signed Informed Consent.

During the monitoring, the data recorded in the CRFs by the Investigator will be controlled for consistency with the source data/hospital records by the study monitor (source data verification). Any discrepancies of data will be documented and explained in the monitoring reports.

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 SOURCE DATA

The following minimum amount of information should be recorded in the hospital records:

- Clinical study number.
- Subject identification.
- Date when patient information was given and when signed Informed Consent was obtained.
- Diagnosis.
- Fulfillment of inclusion criteria and no exclusion criteria

14.2 MONITORING

In accordance with the principles of Good Clinical Practice (GCP), monitoring of the study will be arranged by the Sponsor. During the study, the Monitors will have regular contacts with the study site(s) to ensure that the study is conducted and documented properly in compliance with the protocol, GCP and applicable regulatory requirements.

The monitoring activities are more general described in detail in a “Monitoring plan” (see appendix). Source Data Verification (SDV) will be done in 2 % of the enrolled subjects. Central monitoring activities will be used to monitor the informed consent (IC) procedure. In order to monitor the IC-process, the site will log all completed informed consents on on-going basis and send an up-dated log to monitor end of each month. The Monitor will check the log against the database for a random subset for each site (10%). If inconsistencies are noted between the log and database, the site will be contacted by the monitor for clarification and to agree on any action required. During the study period, monitors will have regular contact with the participating centers to ensure that the trial is conducted in compliance with the protocol and applicable regulatory requirements. The monitors will also provide information and support to the investigator.

The study centers may also be subject to quality assurance audit by the Sponsor as well as inspection by other authority. The Investigator and other responsible personnel must be available during the monitoring visits, audits and inspections and should devote sufficient time to these processes.

The Investigator should provide a curriculum vitae (CV) or equivalent documentation of suitability to be responsible for the study. All Investigators and other responsible personnel should be listed together with their function in the study on the signature list.

15 ETHICS

15.1 INDEPENDENT ETHICS COMMITTEE

It is the responsibility of the Sponsor to obtain approval of the study protocol/protocol amendments, the patient information and the Informed Consent from the IEC before enrolment of any subject into the study.

The written approval from the IEC should be dated and have an attached list of those persons (with names and positions) present at the IEC meeting.

If a study stops prematurely at a study centre for any reason, the IEC must be informed. At the end of the study, the Sponsor should notify the IEC. The Sponsor should file all correspondence with the IEC.

15.2 ETHICAL CONDUCT OF THE STUDY

The study will be conducted in accordance with the protocol, applicable regulatory requirements, GCP and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions.

An application to the Swedish Ethical Review Authority has been submitted and all data linkages will be approved by the National board of health and welfare. All patients will be informed, both in written form and orally, about the study. An informed consent will be signed before being enrolled in the study. The patient may at any time during the study withdraw from the study without having to give an explanation and without affecting the patient´s future healthcare. Originals of signed consent forms will stay in the hospital, the patient will get a copy.

15.3 RISK - BENEFITS

A general problem with clinical studies is that patients often feel dependent on the treating physician and/or personnel. It is therefore of uttermost importance to stress the voluntariness of participating in the study when asking for consent.

The studied population usually undergo a functional test today. Half of the patients that participate in this study will be randomized to CCTA to start with. Although we believe CCTA is superior regarding long-term outcome, we don´t know that. There are potential side-effects that may out-weigh the positive effects, making the old way of assessing these patients more favorable. When performing CCTA you may accidently see other finding around the heart. This may be of benefit but it may also lead to unnecessary anxiety. The only way to find out what is best for future patients is by performing a study.

When dealing with personal data and linking data from different sources there is a theoretical risk that unauthorized persons gets hold of data. However, by following

all laws, regulations and guidelines how data should be handled the risk must be very small.

Overall, this study does not raise more ethical issues than other studies randomizing patients into different diagnostic strategies. The potential negative effects will be outweighed by the positive effects for future patients.

15.4 PATIENT INFORMATION AND INFORMED CONSENT

It is the responsibility of the Investigator to provide each subject with full and adequate verbal and written information about the objectives, procedures and possible risks and benefits of the study. All subjects should be given the opportunity to ask questions about the study and should be given sufficient time to decide whether or not to participate in the study. The written patient information must not be changed without prior discussion with the Sponsor.

The subjects will be notified of their voluntary participation and of their freedom to withdraw from the study at any time and without giving any particular reason. Subjects must also be informed that withdrawing from the study will not affect their future medical care, treatment or benefits to which the subject is otherwise entitled.

The Investigator is responsible for obtaining written Informed Consent from all subjects (or their legally acceptable representatives and/or witnesses, where applicable) prior to enrolment in the study.

The subjects will consent to:
- Participating in the study.
- Personnel concerned at the regulatory authorities to gain full access to hospital records, to control the data collected in the study.
- Recording, collection and processing of data and storing of data in a database.
- Possible transfer of information from the study to countries outside the European Union (EU).
- Possible storing of study samples in a biobank.

It should be clearly stated that the data will not identify any subject taking part in the study, in accordance with the The General Data Protection Regulation (GDPR).

A copy of the patient information and the Informed Consent form should be given to the subject. The Investigator (or the designated representative) who gave the verbal and written information to the subject shall sign the Informed Consent form. The Investigator should file the signed Informed Consent forms in the Investigator's File for possible future audits and inspections.

16 DATA HANDLING AND RECORD KEEPING

16.1 CASE REPORT FORMS (E-CRF)

All data entered via the randomization module and the study module will be stored in a study database at the sponsor. See appendix for variables that will be stored in the study database

16.2 RECORD KEEPING

To enable audits and evaluations by the Sponsor and inspections by regulatory authorities, the Investigator shall keep electronic health records (essential data regarding index hospitalization) and signed informed consent for 10 years.

17 INSURANCE

The Swedish “Patientförsäkring” (patient insurance) is valid and covers all study-associated complications in regards to all the participating hospitals and patients.

18 PUBLICATION POLICY

The pre-defined treatment comparisons of the trial will be submitted to a peer-reviewed journal within a year of study completion. Also, the study outline will be published before study completion in a peer-reviewed journal so that everyone can read the pre-defined treatment comparisons before the results have come in. The Principal Investigator will co-ordinate dissemination of data for this study.

Author order for the first publication: The coordinating investigator will be first author, co-PI second author and PI last author. In the subsequent secondary papers from this study, authorship will be determined according to the degree of engagement in the study.

This list is subject to change considering the degree of input to the completion of the study.

19 SUPPLEMENTS

19.1 CHANGES OF THE STUDY PROTOCOL

No change in the study procedures shall be effected without the mutual agreement of the Investigator and the Sponsor (except where necessary to eliminate an immediate hazard to subjects). All changes of the final study protocol must be documented by signed protocol amendments. If substantial changes to the design of the study are made, The Swedish Ethical Review Authority should be notified for review and approval.

19.2 APPLICATION TO REGULATORY AUTHORITIES

Since this study compare two different diagnostic strategies no application be sent to the MPA.

19.3 STAFF INFORMATION

It is the responsibility of the Investigator to ensure that all personnel involved in the study are fully informed of all relevant aspects of the study, including detailed knowledge in procedures to be followed.

19.4 CRITERIA FOR TERMINATION OF THE STUDY

The Sponsor reserves the right to discontinue the study prior to inclusion of the intended number of subjects but intends to exercise this right only for valid scientific or administrative reasons.

The study could be prematurely discontinued in the following cases (examples):

- New findings about the investigational product(s) that changes the benefit/risk ratio.
- Study protocol is difficult to cope with.
- Recruitment of eligible subjects is far too low.
- Unacceptable low Investigator, Sponsor or subject compliance.
- Critical change in personnel, administrative or scientific standards at the Sponsor or at the study centres.
- No significant result will be obtained as anticipated.

19.5 STUDY TIMETABLE

- 2020 Q3: Registration in Clinical trials.gov
- 2020 Q4: First patient included.
- 2021 Q2: All centers activated Q4 2021.
- At 18 months (End of Q1 2022): 1750 patients included.
- 3500 patients included in Q1 2023

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21 SIGNED AGREEMENT OF THE STUDY PROTOCOL

Protocol number: 0.1

Title of the study: Randomized evaluation of coronary computed tomographic angiography (CCTA) in intermediate-risk patients presenting to the emergency department with chest pain

We, the undersigned, have read and understand the protocol specified above and agree on the contents. The study protocol and the Clinical Study Agreement will serve as a basis for co-operation in this study.

I agree to conduct the study according to this protocol and according to the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and the applicable national laws and regulations.

INVESTIGATOR

Investigator	**Name, title** **Adress**
Signature and date:	
	_____

SUB-INVESTIGATOR

Sub-Investigator	**Name, title** **Adress**
Signature and date:	
	_____

22 APPENDICES

22.1 DECLARATION OF HELSINKI

22.2 DATA THAT WILL BE ENTERED INTO STUDY DATA BASE

Intagningslogistik	
STUDY_NR	Studie nummer
SITE_NR	Site nummer
PRESENTATION_DATE	Date of presentation
ADMISSION_DATE	Date of admission to Hospital
PRESENTING_SYMPTOM	Cause of presentation
TYPICAL_SYMPTOMS	Typical symptoms: No, in between, ja
ECG_STT_PRESENTATION	ST-T changes: No, ospec, ST-deviation
ECG_RHYTHM	ECG rhythm: Sinus, AF/AFl, other
HEART_RATE	Heart frequency
SYSTOLIC_BLOOD_PRESSURE	Systolic blood ressure
PULMONARY_RALES	pulmonary rale
IC	Informed consent
Demografi	
AGE	Age
SEX	Sex
Risk factors	
SMOKING_STATUS	Smoking
HYPERTENSION	Hypertension
DIABETES	Diabetes
HYPERCHOLESTEROLEMIA	Hypercholesterolemia
FAMILY_HISTORY	Family history
BMI	Body mass index
Previous cardiovascular disease	
PREVIOUS_MI	Previous MI (Exclusion criterion)
PREVIOUS_AP	Previous Angina
PREVIOUS_STROKE	Previous stroke or TIA
PREVIOUS_PAD	Previous periphery artery disease
PREVIOUS_HF	Previous heart failure
PREVIOUS_AF	Previous atrial fibrillation or fludder
Treatment on admission	
ACE_INHIBITORS_REG	ACE-inhibitor
ANGIOTENSIN_II_BLOCK_REG	Angiotensin blocker
ORAL_ANTICOAGULANTS_REG	Anticoagulation
OTHER_ANTIPLATELET_REG	Other antiplatelet treatment
ASPIRIN_REG	Aspirin
BETA_BLOCKERS_REG	Beta-blocker
CALCIUM_ANTAGONIST_REG	Ca-blocker
DIURETICS_REG	Diuretics
STATINS_REG	Statins
Lab	
TROPONIN_1_DATE	Date of first troponin
TROPONIN_1_TIME	Time of first troponin
TROPONIN_1_RESULT	Result of first troponin
TROPONIN_2_DATE	Date of second troponin

TROPONIN_2_TIME	Time of second troponin
TROPONIN_2_RESULT	Result of second troponin
TROPONIN_3_DATE	Date of third troponin
TROPONIN_3_TIME	Time of third troponin
TROPONIN_3_RESULT	Result of third troponin
CREATININE_1_DATE	Date of first creatinine
CREATININE _1_TIME	Time of first creatinine
CREATININE _1_RESULT	Result of first creatinine
CREATININE_2_DATE	Date of second creatinine
CREATININE _2_TIME	Time of second creatinine
CREATININE _2_RESULT	Result of second creatinine
CREATININE_3_DATE	Date of third creatinine
CREATININE _3_TIME	Time of third creatinine
CREATININE _3_RESULT	Result of third creatinine
CREATININE_4_DATE	Date of fourth creatinine
CREATININE _4_TIME	Time of fourth creatinine
CREATININE _4_RESULT	Result of fourth creatinine
CHOLESTEROL_TOTAL_DATE	Date of Cholesterol
CHOLESTEROL_TOTAL_RESULT	Result of Cholesterol
CHOLESTEROL_HDL_DATE	HDL-cholesterol
CHOLESTEROL_HDL_RESULT	HDL-cholesterol
TRIGLYCERIDES_DATE	Date of Triglycerides
TRIGLYCERIDES_RESULT	Result of Triglycerides
HB_DATE	Date of hemoglobin
HB_RESULT	Result of hemoglobin
CRP_DATE	Date of CRP
CRP_RESULT	Result of CRP
PGLUCOSE_DATE	Date of p-glucose
PGLUCOSE_RESULT	Result of p-glucose
Echocardiography	
ECHO_DATE	Date of echocardiography
ECHO_EF	Ejection fraction
ECHO_VITIUM	Vitium (Y/N)
Stress-Echo	
STRESSECHO_DATE	Date of stress-echocardiography
STRESSECHO_CONCLUSIVE	Conclusive stress-echo
STRESSECHO_ISCHEMIA	Ischemia at stress-echo (permanent/stress-induced)
SPECT	
SPECT_DATE	Date of SPECT
SPECT_CONCLUSIVE	Conclusive SPECT
SPECT_ISCHEMIA	Ischemia at SPECT (permanent/stress-induced)
Exercise test	
ET_DATE	Date of exercise test
ET_CONCLUSIVE	Conclusive ET
ET_ISCHEMIA	Ischemia at exercise test(permanent/stress-induced)
Stress-MR	
STRESSMR_DATE	Date of stress-MR
STRESSMR_CONCLUSIVE	Conclusive stress-MR
STRESSMR_ISCHEMIA	Ischemia at stress-MR (permanent/stress-induced)
CCTA	
CCTA_DATE	Date of CCTA
CCTA_ALLERGY	Allergy or anaphylaxis during CCCTA
CCTA_RAD	Radiation during CCTA
CCTA_CACS	coronary artery calcium score

Protocol version and date

NCA	Normal coronary arteries
SEGMENT_1	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_2	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_3	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_4	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_5	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_6	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_7	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_8	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_9	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_10	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_11	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_12	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_13	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_14	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_15	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_16	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_17	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_18	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_19	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
SEGMENT_20	No stenosis, 1-49, ≥50%, calcium bloom, tech failure
Invasive angiography	
INVANG_DATE	Date of invasive angiography
INVANG_ALLERGY	Allergy or anaphylaxis during invasive angiography
INVANG_RAD	Radiation during invasive angiography
INVANG_SIGN_STENOSIS	Significant stenosis at inv. angiography
PCI	
PCI_DATE	Date of PCI
CABG	
CABG_DATE	Date of CABG
Treatment at discharge	
ACE_INHIBITORS_DIS	ACE-inhibitors
ANGIOTENSIN_II_BLOCK_DIS	Angiotensin receptor blocker
ORAL_ANTICOAGULANTS_DIS	Anticoagulation
OTHER_ANTIPLATELET_DIS	Other antiplatelet therpy
ASPIRIN_DIS	Aspirin
BETA_BLOCKERS_DIS	Beta.blocker
CALCIUM_ANTAGONIST_DIS	Ca-blocker
DIURETICS_DIS	Diuretics
STATINS_DIS	Statins
At discharge	
DISCHARGE_DATE	Date of discharge from emergency department/hospital
Treatment after discharge	
ACE_INHIBITORS_DDD	ACE-inhibitors ddd 3 years
ANGIOTENSIN_II_BLOCK_DDD	Angiotensin receptor blocker ddd 3 years
ORAL_ANTICOAGULANTS_DDD	Anticoagulation ddd 3 years
OTHER_ANTIPLATELET_DDD	Other antiplatelet therpy ddd 3 years
ASPIRIN_DDD	Aspirin ddd 3 years
BETA_BLOCKERS_DDD	Beta.blocker ddd 3 years
CALCIUM_ANTAGONIST_DDD	Ca-blocker ddd 3 years
DIURETICS_DDD	Diuretics ddd 3 years
STATINS_DDD	Statins ddd 3 years

Endpoints

DECEASED	Death
CARDIOVASC_DEATH	Cardiovascular death
MI_DEATH	MI death
DECEASED_DATE	Date of death
EMIGRATION_DATE	Date of emigration
MI_ADMI_DATE_1	Date of readmission because of first MI
UAP_REVASC	Date of first UAP requiring revascularization
REPRESENTATION_CP_ED_DATE	Date of representation to ED because of chest pain
READMISSION_DATE_1	Date of first readmission
REDISCHARGE_DATE_1	Date of first redischarge
READMISSION_DATE_2	Date of second readmission
REDISCHARGE_DATE_2	Date of second redischarge
READMISSION_DATE_3	Date of third readmission
REDISCHARGE_DATE_3	Date of third redischarge
READMISSION_DATE_4	Date of fourth readmission
REDISCHARGE_DATE_4	Date of fourth redischarge
READMISSION_DATE_5	Date of fifth readmission
REDISCHARGE_DATE_5	Date of fifth redischarge
READMISSION_DATE_6	Date of sixth readmission
REDISCHARGE_DATE_6	Date of sixth redischarge
READMISSION_DATE_7	Date of seventh readmission
REDISCHARGE_DATE_7	Date of seventh redischarge
ROSE_ANY_ANGINA	Any angina according to Rose
ROSE_TYP_ANGINA	Typical angina according to Rose
RAND_1	RAND-36 domain 1
RAND_2	RAND-36 domain 2
RAND_3	RAND-36 domain 3
RAND_4	RAND-36 domain 4
RAND_5	RAND-36 domain 5
RAND_6	RAND-36 domain 6
RAND_7	RAND-36 domain 7
RAND_8	RAND-36 domain 8