The Karolinska Pilot Study for Cardiac Magnetic Resonance Imaging Prior to Invasive Coronary Angiography in Patients With Suspected Non-ST-Elevation Myocardial Infarction

Study Protocol and Statistical Analysis Plan

NCT Number
NCT06566625

Document date
2026-07-04

Project description

Theory

The main hypothesis of the study is that in >15% of patients, early Cardiac Magnetic Resonance (CMR) can defer Invasive Coronary Angiography (ICA) as there is no sign of acute myocardial infarction (MI). In addition, we hypothesize that there will be a proportion of patients (>15%) where the PCI would benefit from CMR guidance, defined as patients where there is a mismatch in the territory treated/not treated with PCI and CMR findings of myocardial necrosis or oedema. The 15% levels are chosen from previous studies. We hypothesize that around 1/3 of patients (30%) will have a clinical benefit of pre-ICA CMR. We will compare if this proportion of patients where CMR offers a clinical advantage is different in patients with previous MI or revascularization.

Methods

This is a prospective, blinded, observational study of suspected NSTEMI patients admitted to the hospital with a planned ICA. Potential study patients are identified by daily reviews of ward admissions and medical records. Patients fulfilling the inclusion criteria and where there are no exclusion criteria are approached by an investigator. The investigator informs patients about the study both in writing and orally, and patients are given the opportunity to ask questions before providing written informed consent. Patients then undergo CMR, totally taking about 60 minutes, typically within 24 hours after admission. The participants will be selected such that the CMR does not delay ICA. Any clinical indication to do an ICA before CMR indicated by treating clinicials will be respected.

CMR is performed using 1.5T MRI scanner (MAGNETOM Sola; Siemens Healthineers, Erlangen, Germany) and includes cine imaging, T1- and T2 mapping, quantitative rest perfusion mapping, and late gadolinium enhancement (LGE). All images are acquired in short-axis and 3 long axis projections.

The CMR images will be initially reviewed by a study physician to rule out any unexpected extracardiac pathology, such as suspected tumours and pulmonary embolism. Any such incidental findings are reported. Otherwise, investigators are blinded to the CMR findings until completion of the study, meaning that the CMR findings will not guide clinical decision-making in these patients. The justification for this, considering the hypothesized superior diagnostic accuracy of CMR, is that the performance of CMR versus ICA is not known in this setting and that observational data is needed to inform change in clinical guidelines. If patients undergo ICA without an identified infarct related artery and no stent is placed, the CMR can be made available for the clinical care. This approach is chosen because many of these patients undergo a clinically indicated CMR following the MINOCA diagnostic algorithm in this scenario and it is not deemed ethical to undergo a second CMR when this has already been done in the study. Patients will be given the opportunity to take part of CMR findings after completion of the study and discuss possible changes in management with a study physician. The CMR images will be unblinded and stored in the clinical archiving system after the completion of the study so that patients and physicians have access to these results for future clinical management. The study is a single centre study but at two different tertiary sites, Karolinska University Hospital Solna and Huddinge, which in turn admit patients from the Södertälje Sjukhus AB (STSAB) and Visby Lasarett hospitals referred for ICA.

CMR images will be interpreted by 2 independent observers blinded to the clinical findings and ICA, and cases of discrepancy will be adjudicated in consensus with 3 readers. Acute ischemic injury is defined as elevated T1 (>1100 ms) and T2 (>55 ms) with corresponding LGE findings of ischemic pattern. Non-is achemic acute findings are defined as elevated T1 and T2 with a non-ischemic LGE pattern. Chronic myocardial injury is defined as LGE in the absence of elevated T1 and T2. Subsequent clinical management including revascularization decision-making is performed without knowledge of the CMR results.

Patient population

We will include 150 patients, aiming for 100 patients without previous MI and 50 patients with previous MI or revascularization. In-house data from the Karolinska University Hospital Solna- and Huddinge sites show that around a third of patients with NSTEMI or unstable angina have previous MI. Therefore, the inclusion of 150 patients in total with suspected NSTEMI which are unselected regarding previous MI will yield around 50 patients with- and 100 patients without previous MI.

The methodology for sample size calculations in a diagnostic study differs from power analysis in outcome studies. We have used the sample size calculation described by Buderer et al for this study (Buderer, 1996). Assuming a sensitivity of 95% and specificity of 90%, with 95% confidence interval with an acceptable width of 10%, to defer ICA due to non-ischemic or chronic myocardial infarction in a population with 70% prevalence of true acute NSTEMI will require a population size of 116 patients. The population size of 150 patients will enable a comparison of diagnostic accuracy between patients with and without prior infarction or revascularization with a power of 80% and alpha value of 0.05.

Inclusion criteria:
≥18 years of age
Suspected NSTEMI (signs and symptoms suggest of ACS with initial ECG showing no ST-elevation) Planned ICA where CMR can be performed without delaying ICA
Able to provide written informed consent
Patients with previous MI are included in the study.

Exclusion criteria:
Contraindications for CMR examination with gadolinium contrast (claustrophobia, eGFR <30ml/min/1.73m2, contrast allergy, and non-MRI compatible implants)
Arrythmias
Previous CABG
Hemodynamic instability
Myocardial infarction <6 months prior to inclusion

Data collection
The data used in the study comes from CMR, echocardiography, and ICA image data, medical records, and registry extracts. Chart review of medical records includes comprehensive clinical and laboratory data including previous medical history and medication, age, sex, presenting symptoms and vital parameters, time from admission to CMR and subsequent ICA.
Patients sign a consent form prior to inclusion detailing the nature of collected data.
Later stages of the study will include a health economic analysis using registry data from SWEDEHEART and Socialstyrelsen's (National Board of Health and Welfare) registries.

Outcome Measures
The primary outcome measure is the percentage of patients where an early CMR examination would have added a clinical benefit through safely ruling out the need for an ICA (no ischemic diagnosis) or designating a different infarct related artery compared to ICA. The outcome encompasses both "false-positive" ICAs, where there is stenosis on ICA but no ischemia on CMR, and "false-negative" ICAs, where there is no significant stenosis, but CMR shows MI. Sensitivity and specificity will be calculated for the CMR first approach (see Data analysis below).

The final outcome measure of this project is a finalized study plan for a RCT testing the CMR first approach to guide clinical decision making.

Health-economic analysis
The results will be extrapolated to the general NSTEMI population and compared with extracts from registry data in a health-economic analysis to evaluate the implications of changing clinical management to a CMR-first approach. These potential health-economic savings will be used for justification of the RCT.
A cost-effectiveness analysis can include information about costs of CMR and ICA including, but not limited to, procedure costs (personnel costs, equipment costs, facility costs), procedure complication costs (additional medical interventions, hospital stays, follow-up care), patient productivity loss, and the cost of misdiagnosis and subsequent (revascularization) treatment for misdiagnosed conditions in suspected NSTEMI patients. The objective of such an analysis would be to determine the economic implications of an early CMR approach in the standard clinical procedure for investigating suspected NSTEMI patients.

Planning of the multicentre randomized controlled trial
The outcomes from the pilot study KaPSICA-CMR will be used to design a multicentre study where the CMR results will guide clinical decision of performing or deferring ICA and providing the vessel territory where there is acute myocardial ischemic injury. The answers to the following main questions that are needed for the planning of the RCT will come from KAPSICA-CMR: 1) if patients with prior infarction and revascularization can be included in a CMR first approach, 2) if Troponin T levels are relevant to choose patients where the CMR first approach have the highest clinical value, 3) if a non-contrast CMR is sufficient to defer ICA and 4) if coronary MRA adds diagnostic value and should be included in the CMR protocol.

Time plan and execution
The study started in **2024** when ethical approval, trial registration and necessary permits were acquired at Karolinska University Hospital. Patient inclusion started in July 2024 and is ongoing through **2026.** As of june 2026, 119 patients have been included in the study.

Late 2026. Predicted completion of patient inclusion. CMR data analysis.

2027. One-year follow up from registries of medications, cardiovascular interventions and diagnosis from national registries. Adjudication committee revising all patients for final diagnosis.

2028. Health-economic analysis. Design and application for ethical permission for a multicentre randomized clinical trial based on the results of KaPSICA-CMR.

Data analysis and statistics
CMR data analysis and patient size justification are provided above. Sensitivity and specificity for detecting MI in suspected NSTEMI with CMR will be assessed with the diagnosis from the clinical adjudication committee as reference standard. A stepwise approach will be used to calculate sensitivity and specificity separately for 1) a standalone native (non-contrast) CMR examination, after which 2) contrast-enhanced CMR (LGE) is added to the assessment for an additional analysis, and finally 3) adding CMR angiography. Interobserver agreement will be calculated and presented as an intraclass correlation coefficient. Continuous data will be presented as mean and standard deviation (SD) or, if not normally distributed, as median and interquartile range (IQR). ANOVA (or Kruskall-Wallis if not normally distributed) will be used to compare continuous data between groups as appropriate. $\chi 2$ test will be used for comparisons of discrete data and McNemar test for comparisons of proportions of patients. Statistical tests are 2 tailed, with results $P < 0.05$ regarded as significant.

Buderer, N. M. F. (1996). Statistical Methodology: I. Incorporating the Prevalence of Disease into the Sample Size Calculation for Sensitivity and Specificity. *Academic Emergency Medicine*, *3*(9), 895–900. https://doi.org/10.1111/j.1553-2712.1996.tb03538.x