TIGER STUDY

High-Sensitivity Troponin I in Addition to Guideline-Based Care in Emergency Medical Service- an Open Randomized Controlled Trial

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Statistical Analysis Plan (SAP)

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1. Abbreviations

Abbreviations	Definition / Description
EMS	Emergency medical service
MI	Myocardial infarction
LVEF	Left Ventricular Ejection Fraction
MACE	MI, LVEF<50%, Stroke, all cause death, PCI?
CFS	Clinical Frailty Score
FMC	First medical contact
pECG	Prehospital ECG
PCI	Percutaneous Coronary Intervention
POC	Point-of-care
hs-TnI	High sensitive Troponin I
LOS	Length of stay

2. Study Design

This study is an open randomised controlled trial (RCT) designed to evaluate the impact of high-sensitive Troponin (hs-TnI) I testing in emergency medical services (EMS) for the early identification of patients suffering from myocardial infarction (MI). The study, named the TIGER study, is conducted by the Ambulance Service in Greater Stockholm (AISAB), and Supported by grants provided by Region Stockholm (NSV project). The TIGER study is expected to initiate data collection in mid-2025, with data collection continuing through 2026.

The study population consists of adult patients presenting to the EMS with chest pain or clinical suspicion of MI, as assessed by EMS personnel. Participants are randomly assigned to one of two

study arms with a 2:1 ratio: the intervention group, which receives hs-TnI testing in addition to standard guideline-based care, and the control group, which receives standard of care according to existing medical guidelines. The primary endpoint of the study is to assess whether the use of hs-TnI analysis in the prehospital setting improves early identification of patients with MI and supports timely decision-making and treatment.

Data collection is carried out using the electronic case report form (CRF) system RedCAP, complemented by data from the Stockholm Regional Healthcare Data System (VAL), the EMS patient records (FRAPP), and a quality registry Swedeheart. This approach allows for comprehensive data collection, including both prehospital and in-hospital variables. The primary endpoints measure is the time from first medical contact (FMC) to percutaneous coronary intervention (PCI), while secondary endpoints measures include the incidence of Major Adverse Cardiovascular Events (MACE) at 72 hours and 30 days, length of stay (LOS), and diagnostic accuracy metrics such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

An interim analyse will be conducted to ensure protocol adherence and data reliability, with external experts reviewing the study's progress and safety outcomes. The study aims to determine whether incorporating hs-TnI testing in the EMS setting can facilitate earlier identification and management of MI, potentially contributing to improved patient care.

3.1 Endpoints

3.1.1 Research question

What is the impact of adding hs-TnI testing in addition to guideline-based care for identifying patients with MI in the EMS?

3.1.2 Primary endpoint

1. Time from First Medical Contact to Vascular Access (FMC-to-Access Time)

   Description: Time in minutes from the initial contact with emergency medical services (EMS) to vascular access (arterial puncture) for percutaneous coronary intervention (PCI), representing the time to initiation of the invasive procedure. Time Frame: From time of first medical contact by EMS to time of vascular access during index PCI procedure, assessed during index hospitalization (typically within 72 hours)

3.1.3 Secondary endpoints

Secondary analyses will investigate whether adding hs-TnI testing in addition to guideline-based care affects the incidence of MACE within 72 hours and 30 days, as well as hospital admission rates and the LOS, both prehospital and in-hospital. Furthermore, the study aims to assess the diagnostic accuracy of POC hs-TnI testing in the EMS setting, including sensitivity, specificity, PPV, and NPV, in order to determine its clinical relevance in early identification of patients with MI. Subgroup analyses will be conducted to examine potential differences in diagnostic accuracy based on symptom onset time (≤120 minutes vs. 121–179 minutes vs. ≥180 minutes). An additional secondary endpoint is to determine the incidence of patients presenting with other time-critical conditions within 72h and 30 days post FMC, focusing on those in the intervention group with either negative or positive troponin results. Subgroup analyses will explore how potential confounding factors such as comorbidities and time from symptom onset to intervention may influence these endpoints.

1. Time from First Medical Contact to Initial ECG (FMC-to-ECG Time)

Description: Time in minutes from the first contact with emergency medical services (EMS) personnel—defined as the moment EMS arrives at the patient—to completion of the first 12-lead ECG. Time Frame: From time of initial patient contact by EMS personnel to time of first ECG, assessed during prehospital phase (typically within 1 hour).

2. Time from First Medical Contact to Emergency Department Admission (FMC-to-ED Admission Time)

   Description: Time in minutes from first EMS contact to arrival and registration at the emergency department. Time Frame: From time of first medical contact to ED admission, assessed on the day of presentation (typically within 4 hours).

3. Emergency Department Length of Stay

   Description: Duration in minutes from emergency department registration to transfer or discharge from the ED. Time Frame: From time of ED admission to ED discharge, assessed during index visit (typically within 24 hours).

4. Total Hospital Length of Stay

   Description: Duration in minutes from emergency department admission to hospital discharge (from acute care facility). Time Frame: From ED admission to hospital discharge, assessed during index hospitalization (up to 14 days)

5. Major Adverse Cardiovascular Events (MACE)

   Description: Composite outcome including the occurrence of any of the following within the specified time frames: myocardial infarction, angina pectoris, all-cause mortality, stroke, or heart failure with reduced ejection fraction (HFrEF). Time Frame: Assessed at 72 hours and at 30 days from the time of first medical contact, defined as the arrival of emergency medical services (EMS)

6. Number of Interventions Performed During Acute Care Episode

   Analysis of the total number and types of interventions in each study arm, presented both as absolute numbers and percentages per patient from first medical contact through hospital discharge. From the time of first medical contact—defined as the arrival of EMS personnel at the patient's side—through hospital discharge, assessed during the full acute care episode (up to 14 days). Interventions to be assessed include:

   a. PCI
   b. Pharmacological interventions
      i. Pain relief
      ii. Antithrombotic therapy
      iii. Sedatives
      iv. Heart rate-increasing agents
      v. Antiemetics
   c. ECG (Electrocardiography)
   d. Vital signs:
      i. Temp (°C)
      ii. Respiratory rate (RR/min)
      iii. Systolic blood pressure (BP/mmHg)
      iv. Partial pressure of oxygen in arterial blood (%)
      v. Heart rate (HR/min)

vi. Blood pressure
vii. Oxygen saturation
viii. Respiratory rate (RR/min)

e. Glasgow Coma Scale (GCS)
f. P-Glucose (mmol/l)

7. Level of Care Required During Acute Hospitalization

From the time of hospital admission through hospital discharge, assessed during index hospitalization (up to 14 days). The highest level of care required by each participant during the acute care episode, categorized as:

a) Emergency Department
b) Cardiac Intensive Care Unit
c) Direct PCI
d) Intermediate Care Unit
e) Cardiac Ward
f) General Ward
g) Other Healthcare Facility
h) Other

8. Clinical Utility: Sensitivity, Specificity, Negative Predictive Value (NPV), and Positive Predictive Value (PPV).

Diagnostic performance of prehospital assessment for identifying patients with Myocardial infarction. Includes calculation of sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV), using confirmed diagnosis (ICD-code) at discharge as reference standard. From the time of EMS assessment (first medical contact) to confirmation of final diagnosis at hospital discharge (typically within 7–14 days).

9. Incidence of Other Time-Critical Medical Conditions

Number of participants diagnosed with other time-critical medical conditions within 30 days of first medical contact. These may include but are not limited to stroke, sepsis, aortic dissection, pulmonary embolism, or major trauma. Assessed up to 30 days from the time of first medical contact by emergency medical services (EMS).

4. Statistical Analyses

All statistical analyses will be conducted using R version 4.3.3 or later.

4.1 Study Population

The study includes adult patients aged ≥18 years who received EMS transport in Stockholm, subsequently diagnosed with MI at hospital discharge. Patients transported as Level 1 trauma cases are excluded due to significant differing management protocols.

4.2 Patient Characteristics

Descriptive statistics will summarize patient characteristics, including age, sex, clinical frailty score (CFS), and comorbidities (such as diabetes, hypertension, previous heart failure, and chronic kidney injury). Continuous variables will be presented as means with standard deviations (SD) or medians

with interquartile ranges (IQR), while categorical variables will be reported as numbers and percentages.

4.3 Potential Confounders

To address potential confounding factors, analyses will be adjusted for age, sex, CFS, comorbidity profile, and time from symptom onset to intervention ensuring robust results. Subgroup analyses will be conducted to examine potential differences in diagnostic accuracy based on symptom onset time (≤120 minutes vs. 121–179 minutes vs. ≥180 minutes). An additional secondary endpoint is to determine the incidence of patients presenting with other time-critical conditions within 72h and 30 days post FMC, focusing on those in the intervention group with either negative or positive troponin results. Subgroup analyses will explore how potential confounding factors such as comorbidities and time from symptom onset to intervention may influence these endpoints.

4.4 Data Cleaning

Missing data will be systematically evaluated. Under the assumption that data are Missing at Random (MAR), multiple imputation by chained equations (MICE) will be employed to handle incomplete data. The imputation model will be adapted to each variable based on its data type, distributional characteristics, and the extent and pattern of missingness. An appropriate number of imputed datasets will be generated to ensure stability of the estimates. Imputation diagnostics will be performed to assess the convergence of the algorithm and the plausibility of imputed values.

Statistical analyses will be conducted on each imputed dataset, and results will be combined using Rubin's rules to obtain valid inference. Duplicate records will be identified and removed using unique patient identifiers and healthcare episode dates. The validity and consistency of key data entries, particularly clinical and temporal variables, will be verified through range checks and outlier detection procedures.

4.5 Descriptive Analysis

Patient demographics, clinical characteristics, medical interventions, EMS priority in and out, and clinical outcomes will be summarized descriptively. Categorical data will be presented as numbers and percentages (%), while continuous data will be summarized with appropriate measures such as mean, standard deviation (SD), median, and interquartile range (IQR).

4.6 Inferential Analysis

To address the primary endpoint, the primary analysis will focus on evaluating whether the addition of hs-TnI testing to guideline-based care in the EMS setting influences the time from FMC-to-balloon. RR will be calculated using modified Poisson regression with robust variance estimation to provide clinically interpretable risk associations. Additionally, time-to-event data for the primary endpoint will be analyzed using Kaplan-Meier survival curves and Cox proportional hazards regression to estimate the hazard ratio (HR) for time from FMC to PCI.

For secondary endpoints, similar RR analyses will be conducted to evaluate whether the addition of hs-TnI testing influences the incidence of MACE within 72 hours and 30 days, as well as hospital admission rates and LOS, both prehospital and in-hospital. LOS will be analysed separately for each study arm using linear regression models to evaluate the association between hs-TnI testing and LOS duration, with subgroup analyses to account for potential confounders. Additionally, hospital admission rates will be assessed, categorizing the type of admission as Emergency Department,

Cardiac Intensive Care Unit, Direct PCI, Intermediate Care Unit, Cardiac Ward, General Ward, Other Healthcare Facility, or Other.

Additional endpoints include linear regression to analyse associations between FMC-to-pECG timing and LVEF, and Cox regression models to assess FMC-to-pECG timing and mortality. The impact of updated pECG guidelines on clinical and procedural outcomes will be evaluated through RR analyses before and after implementation.

Diagnostic accuracy of POC hs-TnI testing within the EMS setting will be evaluated through measures such as sensitivity, specificity, PPV, and NPV. Subgroup analyses will assess the diagnostic accuracy based on symptom onset time (≤120 minutes vs. 121–179 minutes vs. ≥180 minutes) to identify variations in diagnostic performance related to the timing of symptom presentation.

An additional secondary endpoint includes evaluating the incidence of patients presenting with time-critical conditions other than MI within 72 hours and 30 days post-FMC. These analyses will focus on the intervention group, comparing those with negative versus positive troponin results to determine if hs-TnI testing may inadvertently influence diagnostic pathways for other critical conditions.

4.7 Stratified and Interaction Analyses

Stratified analyses will be performed based on demographic and clinical factors (e.g., age, sex, CFS, comorbidities) to identify potential differential effects. Interaction analyses will examine whether the effect of EMS interventions, including hs-TnI testing, varies according to these patient characteristics.

For the diagnostic performance of point-of-care (POC) hs-TnI testing within the EMS setting, stratified analyses will also include symptom onset time (≤120 minutes vs. 121–179 minutes vs. ≥180 minutes) to assess potential differences in diagnostic accuracy (sensitivity, specificity, PPV, and NPV) related to the timing of biomarker elevation.

3.3 Endpoints and variable definitions

3.3.1 Time variables

FMC (EMS arrival at patientadress (registered in EMS medical record)

Ballon (Arterial access as timestamped in the Swedeheart register)

pECG transmission time (registered in EMS medical record)

3.3.2 MACE

MACE is defined as a composite endpoint including:

a) *All-cause mortality,*
b) *MI,*
c) *Stroke*
d) *New-onset heart failure, characterized by left ventricular ejection fraction (LVEF) <50% in patients without a prior history of heart failure,*
e) *Revascularization procedures, including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)*

3.3.3 CFS

CFS is a validated tool used to assess frailty in patients ≥65 y.o. based on their overall health, functional status, and level of dependence in daily activities. It is a 9-point scale, ranging from 1 (non-frail) to 9 (Terminally ill), where higher scores indicate greater levels of frailty.

a) CFS 1–3: Patients are considered non-frail, ranging from very fit to managing minor medical problems independently.
b) CFS 4–5: Patients are pre-frail or mildly frail, requiring some assistance in daily activities.
c) CFS 6–8: Patients are moderately to severely frail, dependent on others for most activities.
d) CFS 9: Terminally ill patients, typically with a life expectancy of less than six months.

3.3.4 Comorbidities profile:

a) Previous history of diabetes defined as ICD-10: E10.X-E11.X
b) Previous history of atrial fibrillation/flutter defined as ICD-10: I48.X
c) Previous history of heart failure defined as ICD-10: I50.X
d) Previous history of kidney injury defined as ICD-10: N17.X-N18.X
e) Previous history of acute coronary syndrome defined as
    a) I21.X Myocardial infarction
    b) I22.X STEMI and NSTEMI
    c) I24.X Other acute ischemic heart diseases
    d) I252 Old myocardial infarction
        a) I220 Anterior STEMI

3.3.5 Triage levels

Priority levels 1–3, where Level 1 indicates the highest urgency and Level 3 corresponds to non-urgent cases requiring transport only.

Priority out:
Priority level at dispatch is determined by the operator at the Emergency Medical Communication Center (EMCC).

Priority in:
Priority level upon arrival at the hospital is determined by the EMS personnel based on a clinical assessment supported by the RETTS triage system and reflects the urgency of care required at the hospital.

4.8 Sensitivity Analyses

Robustness of the findings will be assessed through sensitivity analyses comparing complete-case and imputed datasets, exploring alternative thresholds for intervention timings, and evaluating the effects of excluding incomplete intervention records.

5. Results Presentation

Results will be presented clearly using risk ratios (RR) and 95% confidence intervals (CI), alongside graphical presentations such as Kaplan-Meier curves and comprehensive descriptive tables.

6. Ethical Considerations

Ethical approval has been obtained, and patient data will be pseudonymized to comply with the General Data Protection Regulation (GDPR), ensuring confidentiality and secure data handling.

7. Timeline

The estimated timeline for the study includes a recruitment and data collection period of two years, with an interim analysis planned after the inclusion of 150 patients. Following data collection, two

months will be allocated for descriptive analyses, four months for inferential analyses, and three months for manuscript preparation and submission. The timeline does not account for the time required for data extraction.

References:

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