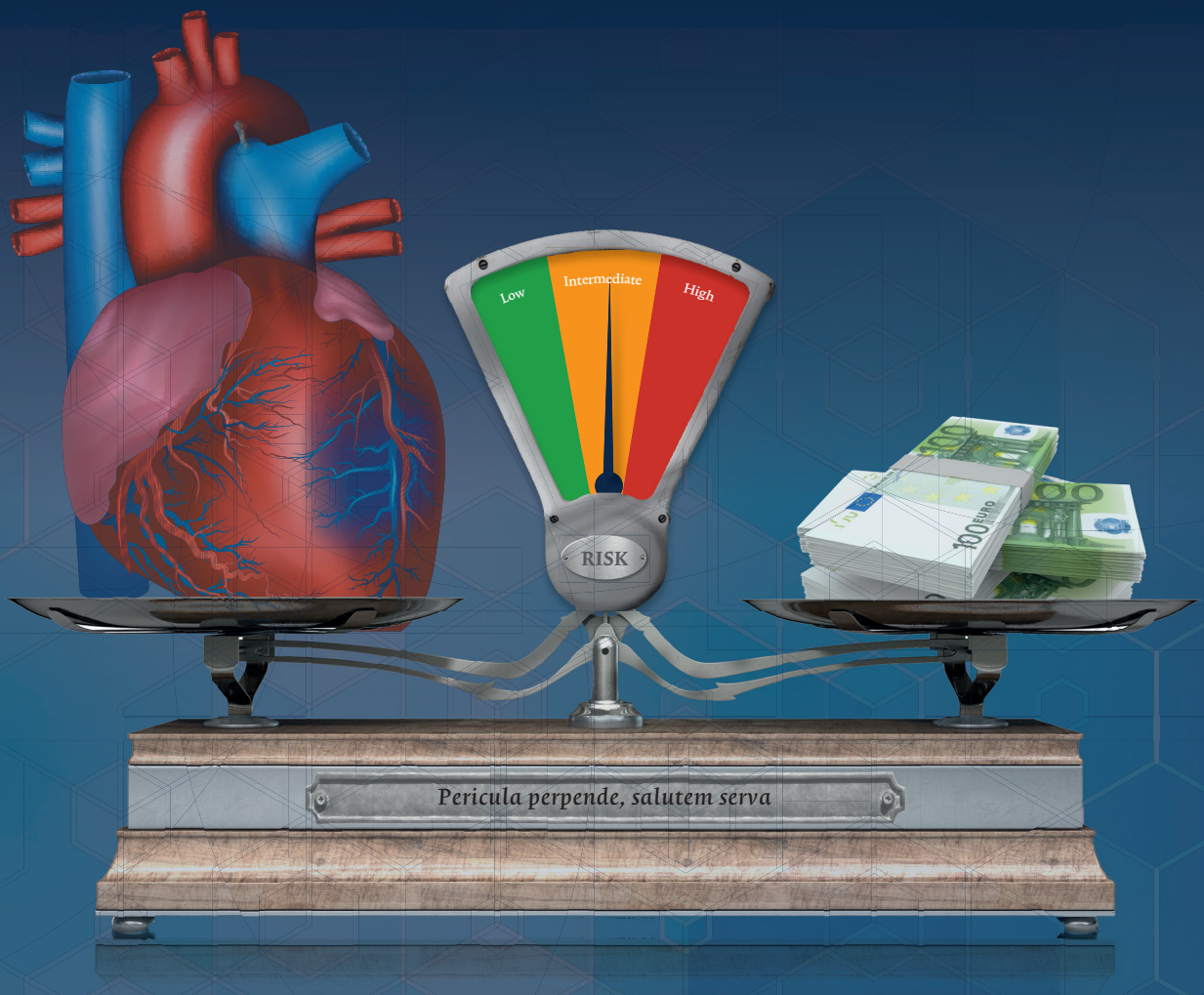
Cyril Camaro

# Innovations and Health-Economic Aspects of (Pre)Hospital Triage in Acute Coronary Syndrome



# Stellingen

behorende bij het proefschrift:

## Innovations and Health-Economic Aspects of (Pre)Hospital Triage in Acute Coronary Syndrome

1. Het prehospitaal direct uitsluiten van laag-risico op een hartinfarct leidt tot een aanzienlijke kostenbesparing (dit proefschrift).

2. Patiënten die een laag-risico hebben op een hartinfarct en thuisblijven laten niet meer overlijdens of ziekenhuisopnamen zien (dit proefschrift).

3. Ambulanceverpleegkundigen onderschatten de afwijkingen op het ECG bij patiënten met pijn op de borst (dit proefschrift).

4. HEART [History-ECG-Age-Risk factors-Troponin]-afgeleide risicoscores zijn zeer effectief in het identificeren van patiënten met een heel laag risico op 30-dagen mortaliteit (dit proefschrift).

5. Bij meer dan 90% van de patiënten wordt de 72-uurs tijdswindow voor invasieve coronair angiografie bij NSTEMI gerealiseerd, zowel in dotter- als in niet-dotterziekenhuizen (dit proefschrift).

6. Voorkomen van zorg is de meest duurzame vorm van zorg (uitgangspunt Green Deal Duurzame Zorg).

7. Niet de arts maar het lichaam geneest de ziekte (Hippocrates).

8. Als je denkt dat alles tegenzit, denk dan opnieuw (anoniem citaat).

C. Camaro, oktober 2026

# Innovations and Health-Economic Aspects of (Pre)Hospital Triage in Acute Coronary Syndrome

Cyril Camaro

The ARTICA study presented in this thesis was funded by the Netherlands Organisation for Health Research and Development (ZonMw; grant no. 852001942) and supported by the Betaalbaar Beter Program (Radboudumc)

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# *Innovations and Health-Economic Aspects of (Pre)Hospital Triage in Acute Coronary Syndrome*

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aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.M. Sanders,
volgens besluit van het college voor promoties
in het openbaar te verdedigen op

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geboren op 18 augustus 1978

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# Chapter 1

## General introduction and outline

## Scope of the problem

Each year, nearly 335.000 patients in the Netherlands seek medical attention for acute chest pain [1]. Given that thoracic pain is frequently regarded as potentially indicative of an acute coronary syndrome (ACS), patients are referred for hospital-based evaluation with low clinical threshold. In most cases ambulance transport to the nearest emergency department (ED) remains the standard of care [2,3]. Current literature suggests that the majority (80-90%) of these patients do not have an actual ACS [4-6], while most of these patients are referred to the (cardiac) ED. At the cardiac ED, patients undergo a thorough evaluation including serial electrocardiograms (ECG's), blood tests including cardiac-specific biomarkers and invasive or non-invasive coronary imaging [7]. Identifying which patients need to be evaluated in the hospital is essential ensuring care is provided in the most appropriate setting (right care in the right place). This can reduce hospital overcrowding and make ambulance use more efficient. Improving the efficiency of healthcare processes can help reduce healthcare costs, which is becoming increasingly important due to the high global burden of cardiovascular disease [8,9].

Reducing healthcare costs is crucial, given that they represent one of the government's largest budgetary expenditures and contribute significantly to the financial burden on most citizens (Figure 1).

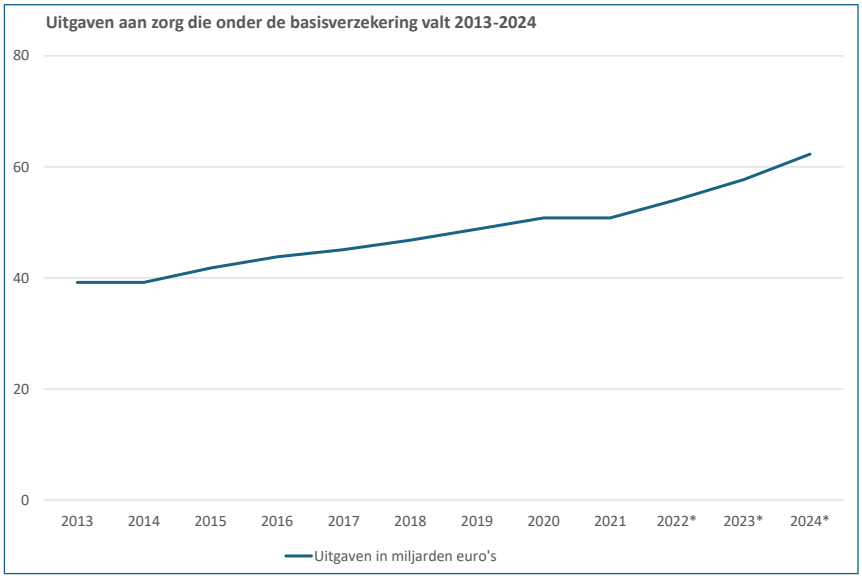



**Figure 1**. Expenditures on healthcare covered by the basic health insurance trend 2013-2024 Source: Uitgaven Zorgverzekeringswet (Zvw) | De Staat van Volksgezondheid en Zorg; www.staatvenz.nl/kerncijfers)

Figure 2 illustrates the increasing expenditures on Dutch Healthcare. The Health Insurance Act (zorgverzekeringswet – ZVW) covers services including hospital care and ambulance services.

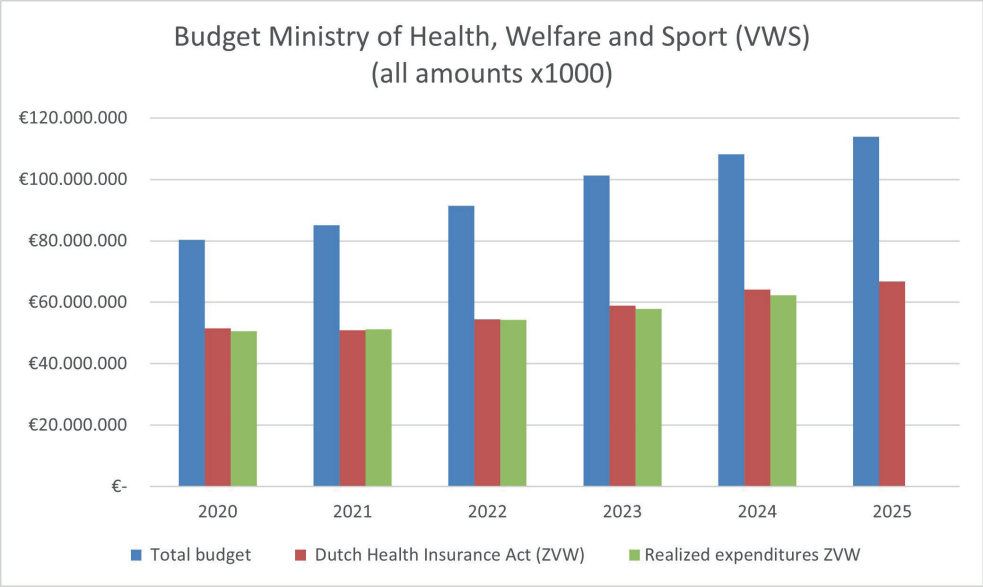



**Figure 2.** Budget VWS and specifically the budget for ZVW
Source: Visuele begroting | Ministerie van Financiën - Rijksoverheid; www.rijksfinanciën.nl; Information on the realized ZVW healthcare expenditures for 2025 were still not available.

Chest pain is a challenging clinical presentation, and given its high prevalence, optimizing the efficiency of its assessment is essential in view of the continually rising healthcare costs.

## Pre-hospital triage: the importance of risk assessment

The availability of clinical decision rules, along with new high-sensitivity (hs) POC troponin analyzers, presents new opportunities for the early identification of patients with *low* probability of developing ACS. In this context, the clinical decision rules that were validated in the pre-hospital setting include the (modified) HEART (history–ECG–age–risk–troponin) score [10] and the PREHEART score [5] which have been evaluated in observational studies. These clinical risk scores can stratify patients into low-, intermediate-, and high-risk categories for non-ST segment elevation ACS (NSTE ACS). It is known that low-risk patients have a very low observed rate of major adverse cardiac events (MACE) [11,12]. Avoiding ED referral for low-risk patients may lead to a significant reduction in healthcare expenditures and contribute to relieving ED overcrowding [13,14]. However, there are no published randomized

trials that evaluate both healthcare costs and major adverse cardiac events (MACE) using such a clinical risk score.

## NSTE ACS: the importance of timing

For patients with established NSTE ACS, two major aspects have remained subjects of debate for decades: the optimal timing of antithrombotic therapy —particularly pretreatment with $P2Y_{12}$ receptor blockers —and the timing of invasive coronary angiography (CAG).

Antithrombotic treatment is the cornerstone in NSTE ACS patients regardless of invasive management. The choice, combination, timing of initiation and treatment duration, all depend on patient characteristics, including the ischemic and bleeding risk, as well as on procedural aspects. Activation of platelet aggregation and the coagulation cascade plays a key role in the initial phase and evolution of NSTE ACS. Therefore, platelet inhibition and anticoagulation are important, especially in those patients undergoing revascularization. Several studies address this topic, but there is still inconclusive evidence regarding the optimal timing of $P2Y_{12}$ inhibition [15-20].

Following the discussion on the timing of antithrombotic therapy, the optimal timing of invasive coronary evaluation also remains a subject of debate. Guidelines recommend an early invasive strategy which has been downgraded from a class I to a class IIa recommendation [2]. An early invasive strategy does not reduce mortality compared with a delayed approach in the overall NSTE ACS population, but it may offer a mortality advantage in those at high-risk [21,22]. An overview of the risk criteria is provided in Table 1. Furthermore, although patients who experience an out-of-hospital cardiac arrest (OHCA) due to NSTE ACS are considered very high-risk, even in this population a strategy of immediate angiography did not improve clinical outcomes when compared with delayed angiography [23]. Whether an early or delayed invasive strategy has benefits in terms of health care resource use and costs is currently unknown.

**Table 1.** Risk criteria mandating invasive strategy in non-ST segment elevation acute coronary syndrome (NSTE ACS). Adapted from the European Society of Cardiology (ESC) guidelines[2].

| **Very-high-risk criteria** |
|---|
| Hemodynamic instability or cardiogenic shock |
| Recurrent or ongoing chest pain refractory to medical treatment |
| Life-threatening arrhythmias or cardiac arrest |
| Mechanical complications of MI |
| Acute heart failure |
| Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation |
| **High-risk criteria** |
| Rise or fall in cardiac troponin compatible with MI |
| Dynamic ST-or T-wave changes (symptomatic or silent) |
| GRACE score >140 |
| **Intermediate-risk criteria** |
| Diabetes mellitus |
| Renal insufficiency (eGFR < 60 mL/min/1.73m$^2$) |
| LVEF <40% or congestive heart failure |
| Early post-infarction angina |
| Prior PCI |
| Prior CABG |
| GRACE risk score >109 and < 140 |
| **Low-risk criteria** |
| Any characteristics not mentioned above |

CABG = coronary artery bypass graft ; eGFR = estimated glomerular filtration rate;

GRACE = Global Registry of Acute Coronary Events ; LVEF = left ventricular ejection

fraction; PCI= percutaneous coronary intervention; MI = myocardial infarction

## Outline of the Thesis

This thesis consists of two parts. Part one – Healthcare costs and pre-hospital assessment in patients at risk for NSTE ACS: the ARTICA randomized trial. In **Chapters 2 - 8**, the ARTICA (Acute Rule-out of Non–ST-Segment Elevation Acute Coronary Syndrome in the (Pre)Hospital Setting by HEART Score Assessment and a Single Point-of-Care Troponin) trial evaluated the efficiency and cost-effectiveness of an ambulance-based triage strategy in which low-risk patients with suspected NSTE ACS are identified already in the ambulance, allowing for the avoidance of transport to the hospital. The second part (Timing of (invasive) treatment in patients with NSTE ACS) of this thesis consists of **Chapters 9 - 11**. In patients diagnosed with NSTE ACS, two key strategies aimed at improving the care for this patient population are examined: antithrombotic therapy and the timing of invasive coronary angiography (CAG). For this purpose, a large nationwide cohort was analyzed using data from the Netherlands Heart Registry (NHR) and claims data from all individuals insured in the Netherlands (VEKTIS database). Finally, healthcare costs were analyzed for out-of-hospital resuscitated patients with a non–ST-segment elevation myocardial infarction (NSTEMI) who underwent early invasive coronary evaluation, using data from the COACT (coronary angiography after cardiac arrest) trial [23].

***PART ONE : Healthcare costs and pre-hospital assessment in patients at risk for NSTE ACS: the ARTICA randomized trial***

**Chapter 2** provides an overview of the design of the ARTICA study.

**Chapters 3** and **4** present the 30-day and the final 12-month results of the ARTICA study, respectively.

**Chapter 5** examined the agreement between ambulance paramedics and physicians in the assessment of the HEAR score (without Troponin).

**Chapter 6** provides a comment to concerns regarding the use of non-high-sensitivity point-of-care troponin devices in the ARTICA study.

**Chapter 7** is the result of a collaboration with the department of Cardiology Catharina Hospital Eindhoven, the Netherlands. This chapter provides an individual patient data meta-analysis including multiple studies utilizing the HEART score algorithm.

The first part ends with **Chapter 8**, which presents nationwide recommendations for pre-hospital triage of patients with suspected ACS.

***PART TWO : Timing of (invasive) treatment in patients with NSTE ACS***

**Chapter 9** provides a review of contemporary antithrombotic management in patients with NSTE ACS.

**Chapter 10** describes a retrospective cohort study of all NSTEMI patients undergoing PCI between 2018 and 2021. This study evaluated the timing of invasive coronary angiography and PCI in the Netherlands, stratified by hospital type (PCI-centers versus non-PCI centers).

Part two concludes with **Chapter 11**, which investigates hospital costs in OHCA patients with NSTEMI enrolled in the COACT trial.

**Chapter 12** summarizes the main findings and conclusions of the studies presented in this thesis. This chapter places the findings of the preceding research chapters into a broader perspective. It discusses their impact on the scientific field and on society, acknowledges the studies' limitations, and outlines opportunities for future research.

The **appendices** provide a summary of this thesis in Dutch, research data management, PhD portfolio, curriculum vitae and acknowledgements.

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# Part One

*Healthcare costs and pre-hospital assessment in patients at risk for NSTE ACS:*

***the ARTICA randomized trial***

# Chapter 2

## Acute rule out of non ST-segment elevation acute coronary syndrome in the (pre)hospital setting by HEART score assessment and a single point of care troponin: Rationale and design of the ARTICA trial.

Goaris W.A. Aarts, Cyril Camaro, Robert-Jan M. van Geuns, Gilbert E. Cramer, Roland R.J. van Kimmenade, Peter Damman, Pierre M. van Grunsven, Eddy M.M. Adang, Paul Giesen, Martijn H. Rutten, Eva Ouwendijk, Marc E.R. Gomes, Niels van Royen

*British Medical Journal Open, 2020*

## Abstract

*Background:* Because of the lack of pre-hospital protocols to rule out a non-ST elevation acute coronary syndrome (NSTE-ACS), patients with chest pain are often transferred to the emergency department (ED) for thorough evaluation. However, in low-risk patients, an ACS is rarely found, resulting in unnecessary health-care consumption. Using the HEART score, low-risk patients are easily identified. When a point-of-care (POC) troponin measurement is included in the HEART score, an ACS can adequately be ruled out in low-risk patients in the pre-hospital setting. However, it remains unclear whether a pre-hospital rule-out strategy using the HEART score and a POC troponin measurement in suspected NSTE-ACS patients is cost-effective.

*Methods:* The ARTICA trial is a randomized trial in which the primary objective is to investigate the cost-effectiveness after 30 days of an early rule-out strategy for low-risk patients suspected of a NSTE-ACS, using a modified HEART score including a POC troponin T measurement. Patients are included by ambulance paramedics and 1:1 randomized for 1) presentation at the ED (control group) or 2) POC troponin T measurement (intervention group) and transfer of the care to the general practitioner in case of a low troponin T value. In total, 866 patients will be included. Follow-up will be performed after 30 days, 6 months and 12 months.

*Conclusion:* The ARTICA trial is the first randomized trial on cost-effectiveness of an early rule-out strategy for low-risk patients suspected of an acute coronary syndrome, using a POC troponin measurement outside the hospital setting.

## Keywords

Acute coronary syndrome, pre-hospital, ambulance, point-of-care troponin, modified HEART score, cost-effectiveness

## Background and rationale



Acute chest pain poses a daily challenge for general practitioners and ambulance paramedics. Since ischemic heart disease is the single most common cause of death worldwide, early risk stratification is crucial.[1] The diagnostic foundation when an ACS is suspected is a combination of a 12-lead electrocardiogram (ECG), clinical evaluation and cardiac troponin measurements.[2] In patients presenting with an acute ST-segment elevation myocardial infarction (STEMI), the diagnosis is relatively straightforward after obtaining an ECG. However, in more than one-third of the non-ST elevation acute coronary syndrome (NSTE-ACS) patients, the ECG is normal.[2] Hence, the vast majority of suspected ACS patients is in need of further evaluation and transferred to the emergency department (ED). Chest pain is therefore one of the most chief complaints in the ED, accounting for 5-10% of all ED visits.[3-5] The number of patients visiting the ED with chest pain is increasing, causing overcrowding and even temporary closing of EDs, which is associated with worse patient outcomes.[5-7] In addition to the increasing number of patients, health care costs are also increasing, leading to a growing demand for efficiency.[8,9] Only 10-20% of the chest pain patients have an ACS and in patients at low risk for ACS, a NSTE-ACS is rarely found.[10-12] Still, these ED visits often include echocardiography, additional non-invasive ischemia detection and prolonged in-hospital stay. [10,13-15] These empirical strategies are costly, while low-risk patients are not likely to benefit from additional testing.[10,15,16] A simple tool for risk stratification of chest pain patients is the HEART (History, ECG, Age, Risk factors, Troponin) score [figure 1], which is widely validated for use in the ED. [17-18] In the HEART score, patients can be given 0 to 10 points and patients with 0 to 3 points are at low risk for having an ACS. A recent meta-analysis showed that one-third of the patients presenting with chest pain have a HEART score of 0 to 3, with a risk of 1.9% of developing short-term (30 days to 6 weeks) major adverse cardiac events (MACE).[19] The risk of MACE is even lower, 0.8%, when a modified low-risk HEART score is used, in which patients with a HEART score of 0 to 3 are only classified as low-risk patients if the troponin value is below the 99$^{th}$ percentile.[19] Implementation of the HEART Pathway, a protocol in which early discharge from the ED without further testing is recommended in low-risk patients, resulted in significant cost savings without any MACE in the discharged patients.[16,20] The HEART score has proven to have a high degree of reproducibility and an excellent inter-operator agreement in both nurses and doctors.[21] The FAMOUS triage study group has demonstrated that HEART score assessment by ambulance paramedics is feasible and safe.[22] Moreover, ambulance paramedics can adequately assess a complete HEART score, using a point-of-care (POC) troponin T measurement.[23] Thus, pre-hospital triage of patients suspected of a NSTE-ACS is possible. The cost-effectiveness of this pre-hospital strategy has not been investigated yet. Therefore, it remains unclear whether identification of low-risk patients presenting with chest pain in the pre-hospital setting and accordingly not transferring them to the ED will lead to a reduction in health care costs. The aim of the ARTICA trial is to assess the cost-effectiveness of rule-out of a NSTE-ACS in low-risk patients in the pre-hospital setting.

## HEART score for chest pain patients

| | | |
|---|---|---|
| **H**istory | Highly suspicious | 2 |
| | Moderately suspicious | 1 |
| | Slightly suspicious | 0 |
| **E**CG | Significant ST-deviation | 2 |
| | Non-specific repolarisation disturbance / LBBB / PM | 1 |
| | Normal | 0 |
| **A**ge | ≥ 65 years | 2 |
| (Leeftijd) | 45-65 years | 1 |
| | < 45 years | 0 |
| **R**isk factors (Risicofactoren) | ≥3 risk factors or history of athersosclerotic diseae | 2 |
| | 1 or 2 risk factors | 1 |
| | No risk factors known | 0 |
| **T**roponin | ≥ 3x normal limit | 2 |
| | 1-3x normal limit | 1 |
| | < normal limit | 0 |
| | | **Total** |

**Risk factors for atherosclerotic disease**:

| | |
|---|---|
| Hypercholesterolemia | Cigarette smoking |
| Hypertension | Positive family history |
| Diabetes Mellitus | Obesity (BMI > 30) |

**Figure 1.** The original HEART score, with permission of the authors
ECG = electrocardiogram, LBBB = Left bundle branch block, PM = pacemaker , BMI = body mass index

## Methods and analysis

*Objectives*

The primary objective of the ARTICA trial is to investigate the cost-effectiveness, assessed by health care costs after 30 days, of a pre-hospital rule-out strategy for low-risk patients suspected of a NSTE-ACS, using a modified HEART score and a POC troponin T measurement, compared with standard transfer to the ED. The secondary objective is to determine safety of this pre-hospital rule-out strategy, defined as the incidence of MACE.

*Design and population*

The ARTICA trial is a randomized, investigator-initiated, multi-center study. Patients with possible ACS are screened for eligibility by trained ambulance paramedics [figure 2]. The patients are screened using the Castor Electronic Data Capture (Castor EDC) platform, in which the ambulance paramedics register every aspect of the HEAR(T) score and the in- and exclusion criteria in order to check for eligibility. The paramedics are able to send the ECG to a cardiologist digitally, in case of doubt. After being informed by the ambulance professional and having provided written consent, the patients will be subjected to a digital 1:1 randomization in Castor EDC. The standard care arm will be transferred to the ED for further evaluation, as is current practice in The Netherlands. The intervention arm will undergo a POC troponin T measurement. If the POC troponin T is negative (<40 ng/L), the care for the patient will be transferred to the general practitioner. The general practitioner will further evaluate the symptoms with focus on other non-cardiac causes of the chest pain. In order to ensure the safety of this trial, a Data Safety and Monitoring Board (DSMB) has been assigned. Furthermore, the study will be independently monitored by the Radboudumc technology center for clinical studies according to Good Clinical Practice (GCP).

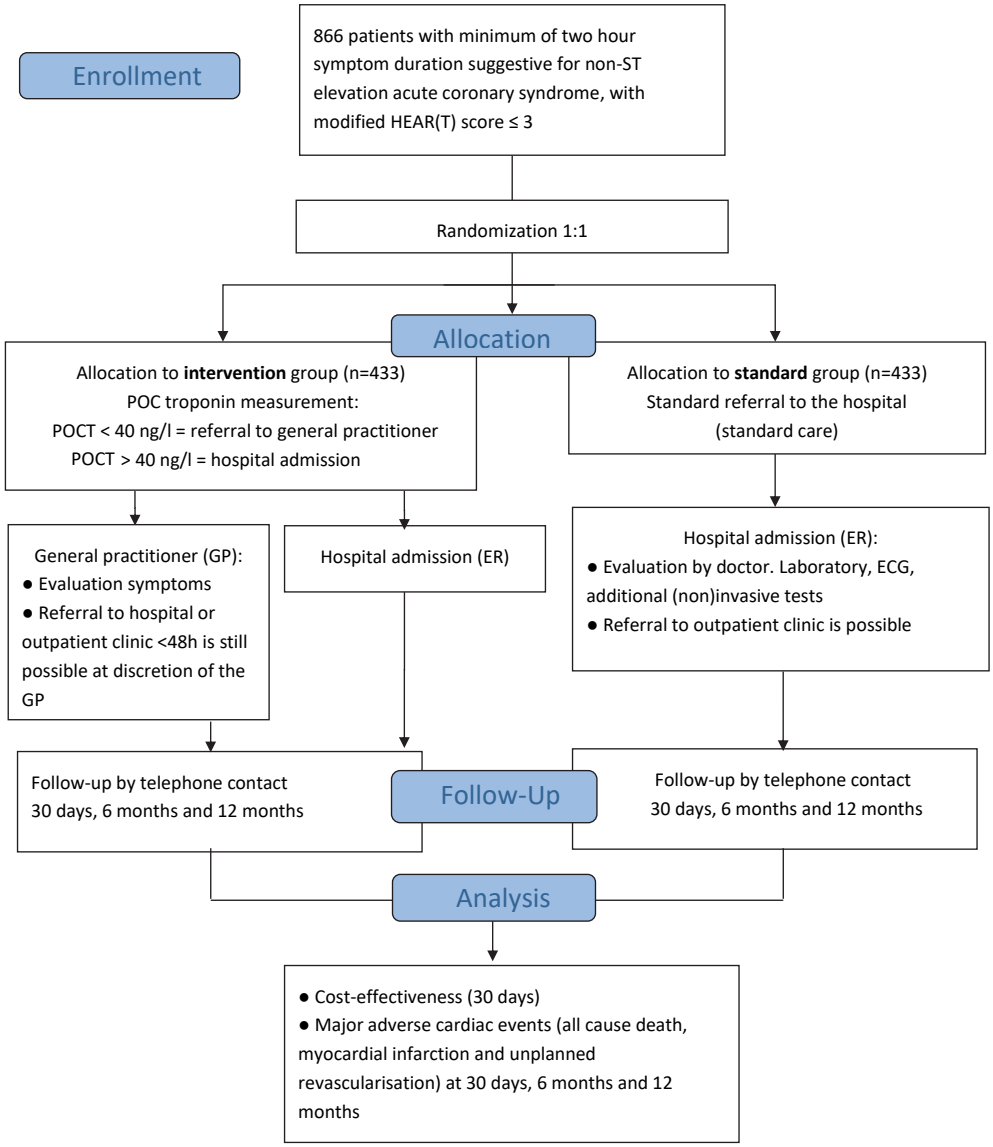



**Figure 2.** The ARTICA trial flow chart.

ED = emergency department; GP = general practitioner; HEAR score = History, ECG, Age, Risk factors score; POC = point of care; POCT = point-of-care troponin

*In- and exclusion criteria (table 1)*

Patients are eligible if they are 18 years or older, are suspected of a NSTE-ACS, have symptom duration of at least two hours and have a modified HEAR(T) score of ≤3. Patients are not eligible if they are suspected of another diagnosis requiring evaluation at the ED or if they are unable to be fully informed about the trial, e.g. in case of a language barrier or cognitive impairment.

**Table 1**. In- and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| • Age ≥ 18 years<br>• Suspected NSTE ACS<br>• Symptom duration of at least 2 hours<br>• Modified HEAR(T) score ≤3 and<br>• Provided written informed consent | • ST-segment elevation<br>• Suspected non-cardiac cause for the symptoms requiring evaluation at the emergency department<br>• Comatose state, defined as a GCS score <8<br>• Known cognitive impairment<br>• Pregnancy<br>• Cardiogenic shock, defined as: systolic blood pressure <90mmHg, heart rate >100 and peripheral oxygen saturation <90%<br>• Syncope<br>• Signs of heart failure<br>• Heart rhythm disorders and second-degree or third-degree atrioventricular block<br>• Known end-stage renal disease (dialysis and/or MDRD < 30 ml/min)<br>• Suspected aortic dissection or pulmonary embolism<br>• Confirmed AMI, PCI or CABG <30 days prior to inclusion<br>• Communication issues with the patient and/or language barrier<br>• Decision of a present general practitioner to evaluate the patient at emergency department<br>• Decision of the consultant cardiologist to evaluate patient at the emergency department<br>• Any significant medical or mental condition, which in the Investigator's opinion may interfere with optimal participation in the study |

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; GCS = Glasgow Coma Scale; MDRD = Modification of Diet in Renal Disease formula; NSTE ACS, = non–ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention

*Modified HEART score (figure 3)*

In the ARTICA trial a modified HEART score is used. This modification is based on the inclusion of a POC troponin T measurement. Furthermore, when patients are screened for eligibility, only the H, E, A and R components of the HEART score are evaluated. The HEAR score is turned into a HEART score either by POC troponin T measurement in the ambulance, or by high-sensitive troponin T measurement in the ED as part of standard care.

ARTICA RANDOMIZED TRIAL

## Modified HEART Score

| | | |
|---|---|---|
| **H**istory | Highly suspicious | 2 |
| | Moderately suspicious | 1 |
| | Slightly suspiciuos | 0 |
| **E**CG | Significant ST-segment depression | 2 |
| | Non specific repolarization disturbance | 1 |
| | LBBB or PM | 1 |
| | Normal | 0 |
| **A**ge | ≤65 years | 2 |
| | 45-65 years | 1 |
| | >45 years | 0 |
| **R**isk factors | ≥3 risk factors OR history of atherosclerotic disease | 2 |
| | 1 or 2 risk factors | 1 |
| | No risk factors | 0 |
| **T**roponin T point of care | >60 ng/L | 2 |
| | 40-60 ng/L | 1 |
| | <40 ng/L | 0 |

Risk factors:

- Smoking
- Hypertension
- Diabetes mellitus
- Obesity (BM( > 30 kg/m$^2$)
- Hyperchol
- Positive family history

**Figure 3**. Modified HEART score in the ARTICA trial.

BMI = body mass index; LBBB = left bundle branch block; PM = pacemaker.

*Point-of-care troponin T*

For the POC troponin T measurement, the Roche Cobas h232 is used. The detection limit is 40-2000 ng/L. According to Roche, the measurement should be performed in a temperature of 18-32 °C and a relative humidity of 10-80%.[24] Blood is obtained in a heparinized tube by venipuncture or venous line. Using a Roche Cardiac pipette, 150 µL of blood is applied to the POC troponin T testing strip, after inserting the testing strip in the Cobas h232 POC system. After 14 minutes, the results are available.

*Follow-up*

Follow-up will be performed by phone after thirty days, six months and twelve months. All potential events, including hospital admissions, will be verified by review of medical record. Since the primary aim in this study is to assess the cost effectiveness of the pre-hospital rule-out strategy, all health care resources utilized by the patients will be collected in both arms.

*Patient involvement*

During the development of the study protocol, a participant of "Harteraad", a patient advisory council for patients with cardiovascular disease, was involved.

*Study endpoints and cost effectiveness analysis*

The primary outcome is health care costs at 30 days. This economic evaluation investigates the cost-effectiveness of full implementation of a pre-hospital rule-out strategy compared to the standard transfer to the hospital to rule out ACS. This will be done from a societal perspective. The empirical cost effectiveness analysis (CEA) timeframe will adhere to the follow-up scheme of the secondary endpoint, being thirty days, six months and twelve months. Cost and quality adjusted life years (QALYs) will be measured on a per patient basis over the relevant time path in which the (most important) differences between both arms manifest themselves. The design of the economic evaluation follows the principles of a cost-utility analysis and adheres to the most recent Dutch guidelines for performing economic evaluations in health care.[25] For reporting, the CHEERS checklist will be used where relevant.[26] Cost-effectiveness will be expressed in terms of costs per QALY gained. Quality of the health status of the patients is measured with a validated health-related quality of life (HRQoL) instrument, the EuroQol-5D (EQ-5D-5L). This HRQoL instrument will be completed by the patients and is available in a validated Dutch translation.[27] The EQ-5D is a generic HRQoL instrument comprising five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. To assess productivity losses associated with chest pain, the Institute for Medical Technology Assessment Productivity Cost Questionnaire (iMTA PCQ) will be used.[28] Uncertainty will be dealt with by one-way sensitivity analysis (deterministic) and by parametric statistics ultimately presenting cost-effectiveness acceptability curves. To ensure the quality of the economic evaluations, the Radboudumc Technology Center Health Economics will be involved. Secondary endpoints will determine the safety of the early

rule-out strategy at 30 days, six months and twelve months, by determining the incidence of MACE. MACE is defined as acute coronary syndrome (ACS), unplanned revascularization and all cause death. Subgroup analyses will be performed according to gender, assessment of the HEART score by paramedics or cardiologists, diabetic status and female-specific risk factors.

*Sample size calculation*

The cost of hospital treatment is determined by the Dutch *Diagnose Behandel Combinatie (DBC)* hospital reimbursement system and the *DBC* information system, similar to the international diagnosis related groupings system (DRG).[29] When discharged from the ED after a negative evaluation for ACS, 50% will undergo further outpatient evaluation. This percentage and the percentages of further diagnostic testing (echocardiography and treadmill: 30%, non-invasive ischemia detection: 10% and coronary angiography: 5%) are all based on the 2017 DBC administration in the Radboudumc. In the pre-hospital rule out group, cost prices for diagnostics by the cardiologist (e.g. non-invasive ischemia detection and coronary angiography) are included, even when the probability of undergoing these tests is low. Based on the aforementioned percentages, the cost difference between both groups is estimated to be € 507. For the primary outcome we assume a small effect size (0,2) and equal standard deviations in both arms of the trial. Group sample sizes of 392 and 392 achieve 80% power to detect the difference of € 507 between both groups with a significance level (alpha) of 0,05 using a two-sided two-sample t-test. To compensate for any loss of follow-up, the sample size is enlarged by 10% to a total of 866 patients. The estimated inclusion rate will be one patient per day.

## Discussion

The majority of patients suspected of a non ST-segment elevation acute coronary syndrome (NSTE-ACS) is currently presented at emergency departments (ED) to rule out an ACS. EDs are increasingly overcrowded and ambulance services are confronted with more patient transfers. However, in low-risk patients an ACS is rarely found.[1,2]

*Cost-effectiveness*

Health care costs are increasing because of multiple factors, such as increases in health care service price and intensity, population growth and aging.[8] Low-risk patients suspected of a NSTE-ACS often require an overnight stay in the hospital to undergo additional stress testing and imaging, but are not likely to benefit from additional testing.[10] Even in pre-hospital-adjudicated low-risk patients, acute healthcare utilization and costs are high, with limited added value.[15] In the year 2018 in the Netherlands, over one-fourth of the patients who were evaluated for chest pain and eventually discharged with benign non-cardiac chest pain were admitted to the hospital for at least one day. The average price for these admissions was

€ 1.355 in 2018 and is € 1.410 in 2019, while it was € 1.220 in 2012.[30] The price for visiting the general practitioner (GP) for 5-20 minutes is € 9,97 during working hours and € 117,50 after working hours. However, it remains unclear how often the GPs will order additional tests or refer the patients to the ED or outpatient clinic, after a NSTE-ACS has been ruled out in the ambulance. Furthermore, the health care resource consumption in these patients represents the degree of reassurance in patients and in health care professionals (e.g. the general practitioner).



*The pre-hospital HEART score*

Recent studies have shown the safety of identifying low-risk chest pain patients in a pre-hospital environment.[22,23] The FAMOUS triage study group has demonstrated that identifying low-risk chest pain patients by ambulance staff using a modified HEART score is feasible and safe when using a high-sensitive troponin T measurement in the hospital laboratory.[22] They have also shown that using a point of care (POC) troponin T measurement to turn the HEAR score into the HEART score in the pre-hospital setting has important additional predictive value.[31] Furthermore, they have shown that in patients suspected of NSTE-ACS, HEART score assessment using a POC troponin T measurement by ambulance paramedics is accurate in identifying low-risk patients.[23]

*POC troponin T*

The POC troponin T measured with the Roche Cobas h232 yields very good analytical concordance with high sensitive troponin T.[32] This POC-test can be used as a bedside test with a fast turn-around time (<15 minutes) and was also used by the FAMOUS triage study group. The POC troponin T test has already shown to have a high predictive value for mortality in high-risk patient.[33]

*The general practitioner*

In the Netherlands, the GP is a gatekeeper to hospital- and specialist care. GPs offer out-of-hour services by GP cooperatives across the whole country.[34] Therefore, implementation of a rule-out strategy for NSTE-ACS in the ambulance is possible, without leaving the patients to fend for themselves when they are not transferred to the ED.

## Conclusion

The ARTICA trial is the first randomized trial on cost-effectiveness of an early rule-out strategy for low-risk patients suspected of an acute coronary syndrome, using a point-of-care troponin measurement outside the hospital setting. The results of this study are expected to have a major impact on the healthcare organization of chest pain patients.

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# Chapter 3

## Rule-out of non-ST-segment elevation acute coronary syndrome by a single, pre-hospital troponin measurement: a randomised trial

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## ABSTRACT

### Background and Aims:

Patients with suspected non-ST-segment elevation acute coronary syndrome (NSTE-ACS) are routinely transferred to the emergency department (ED). A clinical risk score with point-of-care (POC) troponin measurement might enable ambulance paramedics to identify low-risk patients in whom ED evaluation is unnecessary. The aim was to assess safety and healthcare costs of a pre-hospital rule-out strategy using a POC troponin measurement in low-risk suspected NSTE-ACS patients.

### Methods:

This investigator-initiated, randomised clinical trial was conducted in five ambulance regions in the Netherlands. Suspected NSTE-ACS patients with HEAR (History, ECG, Age, Risk factors) score ≤3 were randomised to pre-hospital rule-out with POC troponin measurement or direct transfer to the ED. The sample size calculation was based on the primary outcome of 30-day healthcare costs. Secondary outcome was safety, defined as 30-day major adverse cardiac events (MACE), consisting of ACS, unplanned revascularisation or all-cause death.

### Results:

A total of 863 participants were randomised. Healthcare costs were significantly lower in the pre-hospital strategy (€1349±€2051 vs €1960±€1808) with a mean difference of €611 (95% confidence interval [CI] 353 to 869; P<0.001). In the total population, MACE were comparable between groups (3.9% [17/434] in pre-hospital strategy vs 3.7% [16/429] in ED strategy; P=0.89). In the ruled-out ACS population, MACE were very low (0.5% [2/419] vs. 1.0% [4/417]), with a risk difference of -0.5% (95% CI -1.6% to 0.7%; P=0.41) in favour of the pre-hospital strategy.

### Conclusions:

Pre-hospital rule-out of ACS with a POC troponin measurement in low-risk patients significantly reduces healthcare costs while incidence of MACE was low in both strategies.



**Keywords:** Point-of-care troponin, Risk stratification, Acute coronary syndrome, HEART score, Prehospital triage

### Trial registration:

Clinicaltrials.gov identifier NCT05466591 and International Clinical Trials Registry Platform id NTR 7346

## Introduction

Emergency department (ED) overcrowding is a growing phenomenon, which is associated with increased length of stay, worse patient outcomes and high costs.(1) According to current guidelines, patients with suspected non-ST-segment elevation acute coronary syndrome (NSTE-ACS) are routinely transported to the ED.[1,2] Of all ED visits, about 10% consists of patients with chest pain suspected of NSTE-ACS[3], and this number is increasing.[4] At the same time, 80-90% of these patients do not have an actual ACS.[5-7] Especially in low-risk patients, ACS is rarely found.[8,9] ED visits for chest pain often include costly additional testing and prolonged in-hospital stay, from which low-risk patients are not likely to benefit.[4,10-12] Therefore, the current management of chest pain in the ED contributes to ED overcrowding.[13] Pre-hospital risk stratification of chest pain patients has been shown to help to reduce ED overcrowding and reduce costs.[12] The HEART (History, Electrocardiogram [ECG], Age, Risk factors and Troponin) score is a simple and well validated tool for risk stratification of chest pain patients in the ED, with a very strong overall inter-operator reliability, regardless of the level of education of healthcare professionals.[9,14] When a point-of-care (POC) troponin measurement is incorporated in the HEART score, ambulance paramedics can adequately identify low-risk patients by pre-hospital HEART score assessment.[15,16] However, rule-out of NSTE-ACS in the pre-hospital setting has not been investigated in a randomised trial and its impact on healthcare costs is currently unknown. Therefore, the "Acute rule-out of non-ST-segment elevation acute coronary syndrome in the (pre)hospital setting by HEART score assessment and a single point-of-care troponin" (ARTICA) randomised trial assessed the 30-day healthcare costs and incidence of major adverse cardiac events (MACE) of a pre-hospital rule-out strategy for patients with suspected NSTE-ACS.

## Methods

*Trial design*

The ARTICA trial is an investigator-initiated, multicentre, open-label, randomised controlled trial in five ambulance regions in the Netherlands, with a total of 112 ambulances and 552 ambulance paramedics. Combined, these regions have a population of approximately 2.5 million people. All ambulance paramedics were trained as sub-investigators in order to be able to include patients in the trial. The mandatory training for ambulance paramedics consisted of on-site sessions, online sessions, scheduled online "frequently asked questions" sessions, an instruction video and an e-learning module with a final test. The training was designed to instruct the ambulance paramedics on how to calculate the HEAR score, how to perform informed consent, how to perform randomisation and how to perform POC troponin measurements. Examples of the training materials are available in the Supplementary Appendix. In the Netherlands, ambulance paramedics are registered nurses with bachelor degrees in nursing and at least two subsequent specialisations in

critical care nursing. Every participating ambulance region had at least one ambulance paramedic who was appointed to coordinate the ARTICA trial within their respective region. The trial design has been published previously.[17] A clinical research organisation (Radboud University Technology Centre Clinical Trials) was responsible for maintaining and monitoring the patient data. An independent and blinded Clinical Events Committee (CEC) was installed to adjudicate MACE. A Data and Safety Monitoring Board (DSMB) oversaw the trial and performed interim analyses after 200, 500 and 750 recruited patients. Following each of these board meetings, the DSMB concluded after analysis of the number of adverse events and serious adverse events that there were no safety issues and that the trial could continue as planned. The members of the DSMB and CEC are listed in the Supplementary appendix. The study was conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO) and the statements of the Dutch Central Committee on Research Involving Human Subject (CCMO). The trial was approved by the medical ethics committee Oost-Nederland, the Netherlands on 27 November 2018 (NL66755.091.18).

*HEAR clinical risk score*

The HEAR score includes the History, ECG, Age and Risk factors components of the total HEART score (Supplementary figure S1). The History component was given 2 points for highly suspicious symptoms, 1 point for moderately suspicious symptoms and 0 points for slightly suspicious symptoms. The ECG component was given 2 points in case of significant ST-segment depressions, 1 point in case of non-specific repolarisation disturbances, a left bundle branch block or a ventricular paced rhythm and 0 points in case of a normal ECG. The Age component was given 2 points if the patient was 65 years or older, 1 point if the patient was 45 to 64 years and 0 points if the patient was below 45 years. The Risk factors component was given 2 points if the patient had a history of atherosclerotic disease (coronary revascularisation, myocardial infarction, stroke, or peripheral artery disease) or 3 or more risk factors, 1 point if the patient had 1 or 2 risk factors and 0 points in the absence of risk factors. The risk factors that were scored were active or recent (<90 days) smoking, hypertension, diabetes mellitus, obesity (body mass index [BMI] > 30 $kg/m^2$), hypercholesterolaemia and positive family history. Before informed consent was provided, the individual components of the HEAR score were entered into the case report form, resulting in an automatically calculated HEAR score.

*Participants*

The study population consisted of low-risk chest pain patients with suspected NSTE-ACS, who had an onset of symptoms at least 2 hours before ambulance presentation. Low-risk was defined as a HEAR score ≤3. The patients either called the emergency number or were reported by their general practitioner (GP) for emergency evaluation by ambulance personnel. In all patients, an on-site 12-lead ECG was performed and evaluated by ambulance paramedics and if there was any doubt, the ECG could be transmitted for immediate evaluation by an independent cardiologist. The patients were screened by ambulance paramedics, after which the patients were invited to participate in the study by the ambulance paramedics. In order to aid the ambulance paramedics in informing the patients, an animated version of the trial information for patients was available in all ambulances. Patients were not eligible for inclusion if they were suspected of another diagnosis requiring ED presentation (e.g. aortic dissection or pulmonary embolism [PE]) or if they were unable to provide written informed consent. The complete list of inclusion and exclusion criteria is provided in the Supplementary appendix (Table S1).



*Randomisation*

After providing written informed consent, patients were randomised to either the pre-hospital rule-out strategy or the ED rule-out strategy using Castor Electronic Data Capture (Castor EDC). The randomisation algorithm performed a 1:1 randomisation and included a variable block randomisation with block sizes of 4, 6 or 8.

*Intervention*

In the pre-hospital rule-out strategy, patients underwent an on-site POC troponin T measurement. If POC troponin T was low (<40 ng/L), the care for the patient was transferred to the GP, as is the normal procedure in patients who are not transported. If POC troponin T was elevated (≥40 ng/L), the patient was mandatory transported to the ED.

Patients in the ED rule-out strategy were transferred directly to the ED for evaluation without POC troponin measurement and evaluated according to standard practice.

*Procedures*

In the pre-hospital rule-out strategy, POC troponin T was measured using the Cobas h232 (Roche diagnostics, Basel, Switzerland). The detection limits are 40-2000 ng/L. Concentrations of 40-2000 ng/L on this assay are comparable to high-sensitivity troponin T concentrations in the laboratory.[18] The 99$^{th}$ percentile of normal on the laboratory high-sensitivity troponin T assay is 14 ng/L, which is below the detection limit of the Cobas h232. All ambulances were equipped with a refrigerator to store the strips at 2–8° C. Blood (150 µL) was obtained in a heparinized tube by venepuncture or venous line. The results were available after 12 minutes. Every seven days, the Cobas h232 was automatically locked until

functional testing of the optical system was performed with an internal quality control (IQC). Every year, all devices were maintained and tested with external quality controls.

In the ED rule-out strategy, high-sensitivity troponin (T or I) was measured at the ED according to the prevailing guidelines. Additional diagnostic tests were at the discretion of the cardiologist. Follow-up was performed for all patients after 30 days by contacting the patients by telephone and e-mail. If patients visited a hospital, that hospital was contacted to collect all data on procedures and events. In case of non-response of the patient, the GP and hospital were contacted. Data were collected on all healthcare resource use and productivity losses (assessed by the Institute for Medical Technology Assessment Productivity Cost Questionnaire).[17,19]

*Healthcare resource use and cost-prices*

Healthcare resource use data were collected for all randomised patients. The cost-prices were determined according to the 2018 reference list of the Dutch National Healthcare Institute.[20] Hospital procedure costs were based on standard 2018 list prices and the diagnosis-treatment combination, which is the current reimbursement system in the Netherlands. This diagnosis-treatment combination is comparable to the diagnosis-related group system in other countries.[21] No standard cost-prices were available for a POC troponin measurement and an ambulance visit without transporting the patient. Since no formal costing was available for these elements, the current cost analysis did not take into account additional costs for the POC troponin measurement, nor additional savings for not transporting the patient in the pre-hospital rule-out strategy. Hence, in the current analysis, the costs for the index ambulance visit were considered equal in both strategies. Supplementary Table S2 shows a detailed description of the average prices of ambulance transportations, hospital visits, procedures, hospitalisations, GP visits and additional tests.

*Outcomes*

The primary outcome was costs from a healthcare perspective at 30 days. Healthcare costs consisted of all costs related to healthcare consumption in-hospital, diagnostic tests and GP consultations. MACE at 30 days were a secondary outcome, which was defined as one or more of the following events: ACS, unplanned revascularisation or all-cause death. MACE at 30 days were compared between groups in the total population and in the ruled-out ACS population (all patients for whom an ACS was ruled out, either in the pre-hospital setting or in the ED). Costs from a societal perspective were a secondary outcome, which was defined as the sum of the healthcare costs and the productivity loss costs.

*Statistical analysis*

For the primary outcome, the mean cost difference was estimated to be €507 in an intention-to-treat analysis.[17] A small effect size (0.2 standard deviation [SD]) and equal SD

in both groups were assumed. A sample size of 392 per group was estimated to achieve 80% power to detect a difference of €507 between both groups with an alpha of 0.05 using a two-sample t-test. To compensate for potential loss to follow-up, the sample size was increased to a total of 866 patients. The complete statistical analysis plan is included in the Supplementary appendix.



For the cost analysis, mean differences and 95% confidence intervals (CI) for differences were calculated (univariable analysis). To take potentially skewed distribution into account as well as possible heteroscedasticity, a generalized linear model (GLM) with gamma distribution was included. Continuous data were summarized as means ± SD or medians (interquartile ranges [IQRs]). Categorical data were summarized by frequencies and percentages. Categorical variables were reported as (relative) frequencies and compared using the chi-squared test or Fisher's exact test, whichever was most appropriate. Pre-specified subgroups included sex, diabetes mellitus and age (≤64 years vs ≥65 years). For the subgroups, mean cost differences and 95% CI for differences were calculated. Data analyses were performed using the software package Stata version 16 (StataCorp LLC, College Station, TX, USA) or SPSS statistics version 25 (IBM, Armonk, NY, USA).

For the MACE endpoint, 30-day incidence was calculated in both groups in the total population and in the ruled-out ACS population. Risk differences were calculated along with 95% CI.

In post-hoc analyses, the ambulance on-scene time, transportation time and time to availability were calculated and expressed as medians (IQR). On-scene time was defined as the interval (in minutes) from the time of arrival at the location of the patient to the time of departure. Transportation time was defined as the interval (in minutes) from the time of departure from the location of the patient to the time of arrival at the hospital. Time to availability was defined as the interval (in minutes) from the time of arrival at the location of the patient to the time the ambulance was available for a new call. On-scene times and times to availability were compared between both strategies using the Wilcoxon rank sum test.

## Patient and Public Involvement

A patient member of the Harteraad (a Dutch patient federation for cardiovascular patients**)** was involved in the development of patient information. During the development of the trial information (i.e. patient information letters, letter to the general practitioner) valuable feedback was given which helped to improve the quality of these documents. During the conduct of the trial, the patient representative provided advice to the ambulance personnel on how to perform informed consent and how to increase communication skills from a patient perspective.

## Results

*Participants*

From March 1st, 2019 to May 4th, 2022, 1138 patients were screened and a total of 866 randomisations were performed. Three patients were excluded from the analyses because of withdrawn informed consent (n=3). No patients were lost to follow-up, resulting in a total of 863 patients available for analyses. The consort flow chart is depicted in Figure 1. Baseline characteristics were well balanced and are shown in Table 1. Mean age was 54±13 years and 57% of the patients were female. Median HEAR score was 3 (IQR 2-3). Median on-scene time was 63 minutes (IQR 52-73) in the pre-hospital rule-out strategy and 39 minutes (IQR 32-48) in the ED rule-out strategy (P<0.001). The median ambulance time to availability was 70 minutes (IQR 58-88) in the pre-hospital rule-out strategy and 76 minutes (IQR 63-89) in the ED rule-out strategy (P=0.006). The median on-scene times and times to availability are shown in Figure 2. Median transportation time was 15 minutes (IQR 8-19). Elevated POC troponin was observed in 4.1% of patients in the pre-hospital rule-out strategy and these patients were all transported to the ED. 8.5% of patients in the pre-hospital rule-out strategy were transferred to the ED because of elevated POC troponin (n=18), failed POC troponin test (n=12) or decision of the GP (n=7). In 836 patients (96.5% of the total population), ACS was ruled-out, either in the pre-hospital setting or at the ED.

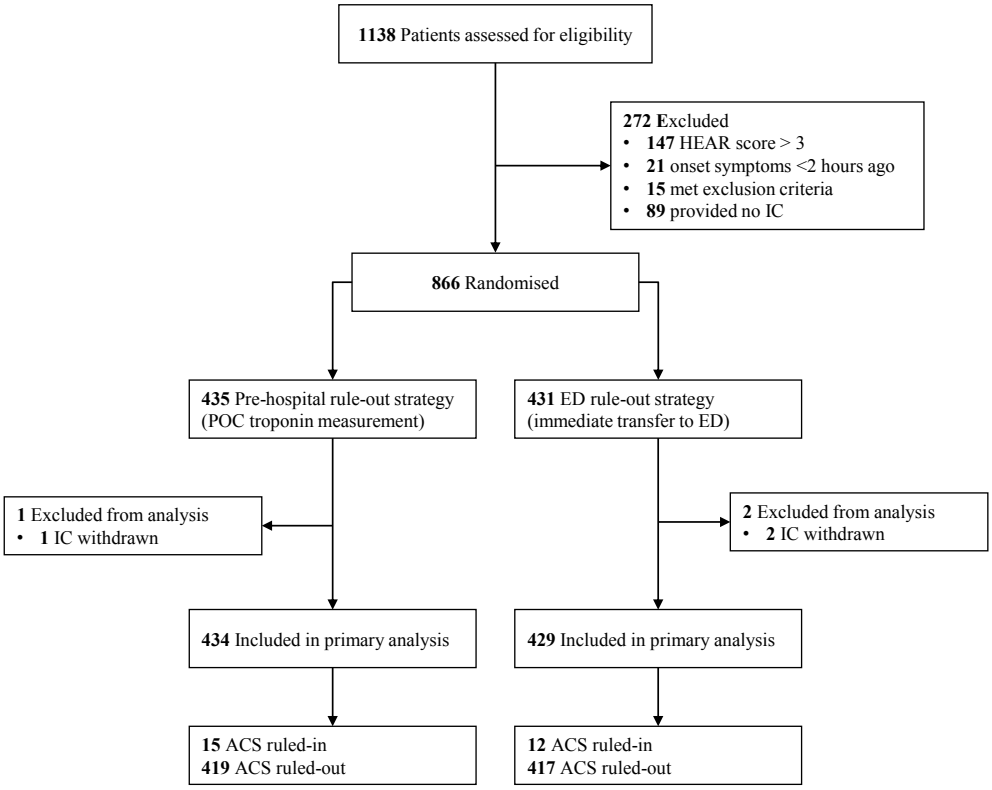



**Figure 1. Flow chart of recruitment and participants.** ED, emergency department; HEAR score, History Electrocardiogram Age Risk factors score; IC, informed consent; POC, point-of-care

**Table 1. Baseline characteristics**

| | Pre-hospital rule-out strategy (N=431) | ED rule-out strategy (N=414) |
|---|---|---|
| Age (years), mean (SD) | 53.7 (13.1) | 53.4 (12.5) |
| Female sex, N (%) | 246 (57.1%) | 238 (57.5%) |
| History (HEAR score), median (IQR) | 0 (0-1) | 1 (0-1) |
| ECG score (HEAR score), median (IQR) | 0 (0-0) | 0 (0-0) |
| History of atherosclerotic disease, N (%) | 34 (7.9%) | 22 (5.3%) |
| Hypertension, N (%) | 83 (19.3%) | 69 (16.7%) |
| Diabetes Mellitus, N (%) | 22 (5.1%) | 14 (3.4%) |
| Current Smoker, N (%) | 112 (26.0%) | 106 (25.6%) |
| Hypercholesterolemia, N (%) | 36 (8.4%) | 34 (8.2%) |
| Family history, N (%) | 154 (35.7%) | 149 (36.0%) |
| BMI ≥30 kg/m$^2$, N (%) | 86 (20.0%) | 78 (18.8%) |
| Mean HEAR score (SD) | 2.4 (0.7) | 2.4 (0.8) |
| Onset of symptoms (hours), mean (SD) | 7.1 (5.2) | 6.7 (5.3) |
| Elevated troponin, N (%) | 18 (4.2%) | 24 (5.8%) |
| Heart rate, bpm, mean (SD) | 77.9 (13.2) | 77.5 (13.5) |
| Systolic blood pressure, mmHg, mean (SD) | 145.9 (20.3) | 145.0 (21.3) |

Bpm = beats per minute, BMI = body mass index, ECG = electrocardiogram, ED = emergency department, HEAR score = History, ECG, Age and Risk factors score, IQR = interquartile range, SD = standard deviation.

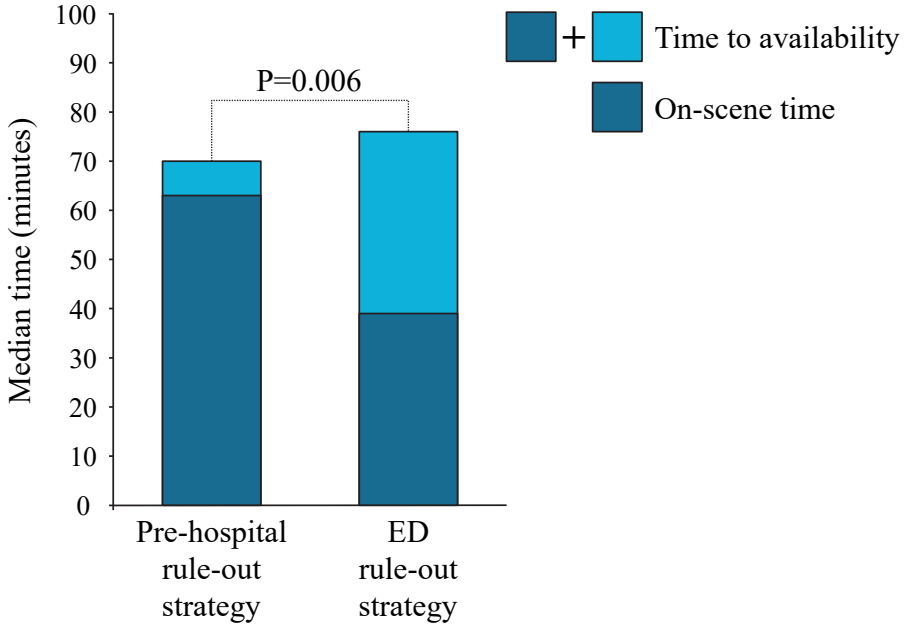



**Figure 2. Median on scene time and time to availability.** ED = emergency department

*MACE in the total population*

In the total population, MACE within 30 days occurred in 17/434 (3.9%) patients in the pre-hospital rule-out strategy versus 16/429 (3.7%) patients in the ED rule-out strategy, with a point estimate for the risk difference of 0.2% (95% CI -2.4% to 2.7%, P=0.89). (Figure 3) In the pre-hospital rule-out strategy, 17 (3.9%) patients had an ACS, of which four patients (0.9%) had an ST-segment elevation myocardial infarction (STEMI), 12 (2.8%) patients received unplanned revascularisation and no patients died. A total of 15 of these 17 patients were directly transferred to the ED because they did not have low POC troponin.

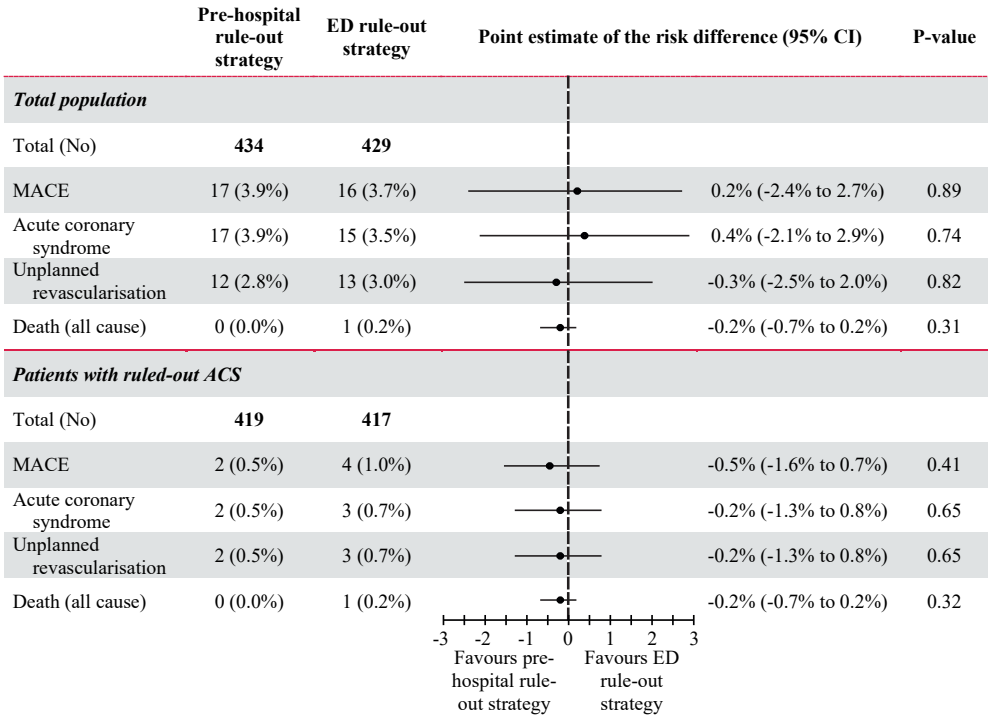



**Figure 3. MACE at 30 days.** MACE, major adverse cardiac events; ED, emergency department; ACS, acute coronary syndrome

*Safety of the pre-hospital rule-out strategy*

In the ruled-out ACS population, MACE within 30 days occurred in 2/419 (0.5%) patients in the pre-hospital rule-out strategy versus 4/417 (1.0%) patients in the ED rule-out strategy, with a point estimate for the risk difference of -0.5% (95% CI -1.6% to 0.7%, P=0.41). In the pre-hospital rule-out strategy, two (0.5%) patients had an ACS, two (0.5%) patients received unplanned revascularisation and no patients died after an ACS was ruled-out in the pre-hospital setting. In the ED rule-out strategy, three (0.7%) patients had an ACS, three (0.7%) patients received unplanned revascularisation and one (0.2%) patient died after an ACS was ruled-out at the ED. Of the four patients with a STEMI, three patients had normal ECGs and elevated POC troponin concentrations at home, after which ST-segment elevations were observed in the ED. In one patient, the GP decided not to refer the patient to the ED because the ECG and POC troponin measurement were normal. Two days later, the patient called the emergency number because of recurrence of chest pain, after which the ECG showed ST-segment elevations. In the ED rule-out strategy, 15 (3.5%) patients had an ACS, of which zero patients had a STEMI, 13 (3.0%) patients received unplanned revascularisation and one (0.2%) patient died after an out-of-hospital cardiac arrest one week after visiting the ED.

PE occurred in 2/434 (0.5%) patients in the pre-hospital rule-out strategy and in 1/429 (0.2%) patient in the ED rule-out strategy. No aortic dissections occurred in the total study population. Final diagnoses of all patients are provided in Supplementary Table S3.

*Healthcare costs*

Costs from a healthcare perspective at 30 days were significantly lower in the pre-hospital rule-out strategy (€1349±€2051 versus €1960±€1808), with a mean difference of €611 (95%CI €353 to €869), P<0.001) (Table 2).



**Table 2. Healthcare costs**

| | Pre-hospital rule-out strategy (N=431) | ED rule-out strategy (N=414) | Mean difference (95% CI) | P-value |
|---|---|---|---|---|
| **Mean costs (SD) in EURO** | | | | |
| Healthcare costs | 1340.62 (2014.10) | 1910.96 (1312.11) | 570.34 (339.83 – 800.86) | <0.001 |
| Productivity loss | 786.58 (1647.74) | 867.43 (1728.58) | 80.85 (-153.47 – 315.16) | 0.50 |
| Societal costs | 2147.02 (2874.07) | 2752.13 (2355.32) | 605.11 (239.51 – 970.71) | 0.001 |

CI = confidence interval; ED = emergency department; SD = standard deviation

This difference was mainly driven by the costs of ED visits and their associated diagnostic tests (ECGs, screening blood tests, second troponin measurements and chest X-rays). Of all patients in the pre-hospital rule-out strategy, 13.6% had one ED visit (n=59), 1.2% had two or more ED visits (n=5), 7.4% were hospitalised (n=32) and 4.8% were hospitalised directly after the initial transport to the hospital (n=21). Of all patients in the ED rule-out strategy, 95.8% had one ED visit (n=411) , 4.2% had two or more ED visits (n=18), 9.8% were hospitalised (n=42) and 8.4% were hospitalised directly after the initial transport to the hospital (n=36). The individual components of the healthcare costs are listed in Table 3. The GLM showed similar results to the T-tests: costs difference of €611 (standard error €131, 95%CI €353 to €869).

Costs of productivity losses showed no significant difference between the groups (€785±€1646 versus 893€±€1757), with a mean difference of €108 (95%CI €-128 to €344, P=0.37). Costs from a societal perspective were significantly lower in the pre-hospital rule-out strategy (€2157±€2900 versus €2842±€2819), with a mean difference of €685 (95%CI €289 to €1081, P=0.001).

The prespecified subgroup analyses were underpowered but are available in Supplementary Table S4.

Prescribed medications (in the hospital or by the GP) are shown in Supplementary Table S5. Proton pump inhibitors, analgesics and other medications (e.g. antiemetics and inhaled medications) were significantly more frequently prescribed in the ED rule-out strategy, whereas aspirin, P2Y12-inhibitors, statins, betablockers and antihypertensive medication did not differ between both strategies.

**Table 3. Healthcare resource use at 30 days**

| | **Pre-hospital rule-out strategy n = 434** | **ED rule-out strategy *n* = 429** | **P-value** |
|---|---|---|---|
| One additional ambulance transport, *n* (%) | 24 (5.5%) | 10 (2.3%) | 0.02 |
| Two or more additional ambulance transports, *n* (%) | 2 (0.5%) | 0 (0.0%) | 0.16 |
| One ED visit, *n* (%) | 59 (13.6%) | 411 (95.8%) | <0.001 |
| Two or more ED visits, *n* (%) | 5 (1.2%) | 18 (4.2%) | 0.006 |
| No. of additional tests at ED, mean ± SD | | | |
| ECGs | 0.56 (1.82) | 1.84 (1.87) | <0.001 |
| Screening blood tests | 0.16 (0.43) | 1.04 (0.22) | <0.001 |
| Second high-sensitivity troponin measurements | 0.08 (0.31) | 0.44 (0.51) | <0.001 |
| D-dimer measurements | 0.04 (0.21) | 0.27 (0.44) | <0.001 |
| Chest X-rays | 0.17 (0.43) | 0.62 (0.56) | <0.001 |
| One GP consultation, *n* (%) | 338 (77.9%) | 132 (30.8%) | <0.001 |
| Two or more GP consultations, *n* (%) | 96 (22.1%) | 31 (7.2%) | <0.001 |
| One outpatient clinic visit, *n* (%) | 54 (12.4%) | 46 (10.7%) | 0.43 |
| Two or more outpatient clinic visits, *n* (%) | 5 (1.2%) | 3 (0.7%) | 0.49 |
| CT, *n* (%) | 12 (2.8%) | 17 (4.0%) | 0.33 |
| MRI, *n* (%) | 1 (0.2%) | 0 (0.0%) | 0.32 |
| Echocardiography, *n* (%) | 54 (12.4%) | 44 (10.3%) | 0.31 |
| Treadmill, *n* (%) | 41 (9.4%) | 52 (12.1%) | 0.21 |
| Other additional tests, *n* (%) | 62 (14.3%) | 45 (10.5%) | 0.09 |
| CAG, *n* (%) | 20 (4.6%) | 20 (4.7%) | 0.97 |
| PCI, *n* (%) | 13 (3.0%) | 12 (2.8%) | 0.86 |
| CABG, *n* (%) | 1 (0.2%) | 1 (0.2%) | 0.99 |
| Hospitalisation, *n* (%) | 32 (7.4%) | 42 (9.8%) | 0.21 |
| Length of hospitalisation (days), median (IQR) | 0 (0-0) | 0 (0-0) | 0.24 |

CABG = coronary artery bypass grafting, CAG = coronary angiography, CT = computed tomography, ED = emergency department, GP = general practitioner, IR = interquartile range, MRI = magnetic resonance imaging

## Discussion

*Principal findings*

Our trial shows that pre-hospital rule-out of NSTE-ACS in low-risk patients by a single POC troponin measurement results in a significant reduction of healthcare costs in the first 30 days and that incidence of MACE is low in both strategies (Structured Graphical Abstract). In patients for whom an ACS was ruled out (either at home or at the ED), MACE at 30 days was very low and occurred in only 0.5% of the patients in the pre-hospital rule-out strategy, versus 1.0% of the patients in the ED rule-out strategy. In this study, 8.5% of the patients in the pre-hospital rule-out strategy were directly referred to the ED of whom only seven patients (1.6%) with a low POC troponin were referred to the ED by the GP.



*Safety*

Previous observational studies have shown that HEAR score assessment in combination with a POC troponin measurement by ambulance paramedics is a feasible strategy.[15,16] The HEART score has been shown to have a very strong overall inter-operator reliability between physicians and nurses and compared to physicians at the ED, ambulance paramedics tend to overestimate the History and ECG components of the HEART score.[14,22] Also, the risk of mortality and myocardial infarction is very low in patients with a HEART score ≤3.[9,15-23] To prevent missing very early onset myocardial infarction with a risk of a low troponin result, patients with symptom onset shorter than two hours before presentation were excluded from our trial. MACE occurred in 3.8% of the patients with similar percentages between groups. However, in the pre-hospital rule-out strategy, most of the MACE were diagnosed by POC troponin measurement and therefore not missed. Hence, the safety of pre-hospital rule-out of NSTE-ACS is best demonstrated by the comparison of the incidence of MACE after an ACS is ruled-out in both groups. In the ruled-out ACS population (96.5% of the total population), MACE occurred in 0.5% of the patients in the pre-hospital strategy versus 1.0% of the patients in the ED rule-out strategy, with a risk difference of -0.5% (95% CI -1.6% to 0.7%) in favour of the pre-hospital rule-out strategy. MACE were a secondary outcome measure and our trial was not formally powered to conclude that the pre-hospital rule-out strategy is non-inferior for safety. However, since the incidence of MACE in ruled-out ACS patients was very low and the risk difference is at most 0.7% higher in the pre-hospital rule-out strategy, the results of our trial demonstrate that implementation of the pre-hospital rule-out strategy in routine practice is likely to be safe. Moreover, when designing a trial powered to show non-inferiority for MACE in low-risk patients with ruled-out ACS by POC troponin measurement, the sample size should be based on the incidence of MACE in the ruled-out ACS population. Such a trial would require a total of 17820 patients, based on a mean incidence of MACE of 0.7% (observed in our ruled-out ACS population) and upper limit of a two-sided 95% CI to exclude a difference of more than 0.35% (50% of the incidence). Although a large trial like that is possible with a large number of international sites involved,

it will require significant funding and time. Another strategy that could be considered is the implementation of a pre-hospital rule out strategy in a large multinational registry with very strict monitoring of clinical outcomes.

*Healthcare costs and overcrowding*

Mean healthcare costs were significantly lower in the pre-hospital rule-out strategy. This difference was mainly driven by the costs of the ED visits and their associated diagnostic tests. Implementation of this pre-hospital rule-out strategy in low-risk patients could achieve a significant reduction in healthcare costs by more efficient use of ambulance services and less ED visits.[12,24] A recent study has shown that rule-out of NSTE-ACS in emergency primary care is cost-effective, which is in line with our results. In that study, the European Society of Cardiology 0/1-h algorithm with a high-sensitivity troponin assay in a hospital laboratory was used to identify low-risk patients, whereas our study offers an algorithm that does not require a laboratory and can be performed on-site.[12] A total of 91.5% of the patients in the pre-hospital rule-out strategy were not transferred to the ED, while all of these patients would have been transferred to the ED in the absence of a pre-hospital strategy. Hence, the pre-hospital rule-out strategy reduces the number unnecessary ED visits, which contributes to a reduction in ED overcrowding. Moreover, no significant differences were seen in downstream outpatient clinic visits, additional tests outside of the ED and hospitalisations. Although the POC troponin test requires the ambulance to stay longer on-site, the ambulance time to availability was actually shorter in the pre-hospital rule-out strategy. Since the study procedures (informed consent, case report form and randomisation) were performed by ambulance paramedics, the on-scene times in both strategies were longer than can be expected of routine ambulance visits. In countries with longer transportation distances and therefore longer transportation times, the time saved by pre-hospital rule-out of ACS is expected to be even more. If the pre-hospital rule-out strategy is implemented, considerable cost savings for transporting the patient will apply to the majority of cases, whereas the time to availability is also reduced. According to the Dutch Healthcare Authority, in the year 2018 almost 200.000 patients in the Netherlands were evaluated at the ED for chest pain without a cardiac diagnosis.[25] Given that 39.3% of all chest pain patients visiting the ED are low-risk patients, that the Netherlands has 714 ambulances and that the POC devices can be used for at least five years, the estimated POC troponin costs are €42,50 per measurement (all-in, including purchase of 714 POC devices, materials, time for the measurement and time for the maintenance of the device).[9] Therefore, we believe that the reduction in ambulance costs will outweigh the additional costs for the POC troponin test, which might further increase the cost savings of the pre-hospital rule-out strategy. However, according to the current analysis of the reduced healthcare costs (€611 per patient), the added value of our pre-hospital rule-out strategy on the Dutch population already would amount to an estimated €48 000 000 per year in the Netherlands alone.

*Generalizability*

We believe the results of our trial on pre-hospital rule-out of ACS in low-risk patients are, in general, applicable on a global level, given a well-functioning healthcare system is available. As mentioned, the HEART score has a very strong overall inter-operator reliability, regardless of the level of education.[14] HEART score assessment has already been shown to be applicable in the ED worldwide.[26] Pre-hospital rule-out of ACS has recently been shown to reduce healthcare costs in a trial in Norway.[12] Implementation of routine pre-hospital POC troponin measurement has been shown to effectively identify high-risk patients in Denmark, whereas pre-hospital HEART score assessment including a POC troponin measurement has been shown to adequately identify low-risk patients in the Netherlands and the United States.[15, 16, 27] The Netherlands is a country with highly developed ambulatory care and short distances. However, despite the short distances, the pre-hospital rule-out strategy showed significantly shorter ambulance time to availability. In countries with less ambulance capacity and longer distances, the benefit of pre-hospital rule-out of ACS could be larger. In the Netherlands, GPs cooperate to provide urgent primary care on rotation basis in so-called GP-posts, ensuring a gatekeeping function 24/7.[28] Implementation of the pre-hospital strategy therefore also depends on the accessibility of primary care. Furthermore, the average level of education of ambulance paramedics could be different in other countries. Therefore, the local healthcare infrastructure should be taken into account when extrapolating the results of this trial to other countries.

*Limitations*

The POC troponin assay is less sensitive than high-sensitivity assays in the hospital laboratory. Therefore, patients with a low POC troponin concentration could have mildly increased high-sensitivity troponin concentrations, which is associated with an increased mortality risk for which further investigation is necessary.[29] However, the combination of this POC assay and the HEAR score has been shown to identify low-risk chest pain patients with low MACE incidence. Moreover, all patients with elevated POC troponin were directly transferred to the hospital. The study algorithm was primarily focused on ACS rule-out. However, the incidence of MACE and other emergent cardiovascular events in ruled-out ACS patients in our trial is comparable with previous observational studies.[9,15] The current costs analysis did not include the additional costs for the POC troponin measurement in the pre-hospital rule-out strategy. However, additional cost savings by not transporting the majority of patients were also not included and we believe that this reduction in ambulance costs will outweigh the costs of the POC troponin test, which might further increase the cost savings of the pre-hospital rule-out strategy. Ambulance on-scene times seem very long, however one should realise that all study procedures (including data entry in Castor EDC) were performed on site by the ambulance paramedics.

## Conclusion

Pre-hospital rule-out of NSTE-ACS in low-risk patients with the use of POC troponin testing in combination with a clinical risk score leads to large healthcare cost reductions and is associated with a very low MACE occurrence.

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# Chapter 4

## Pre-hospital rule-out of non-ST-segment elevation acute coronary syndrome by a single troponin measurement: final one-year outcomes of the ARTICA randomised trial

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## ABSTRACT

### Background and aims

The healthcare burden of acute chest pain is enormous. In the randomised ARTICA trial, we showed that pre-hospital identification of low-risk patients and rule-out of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) with point-of-care (POC) troponin measurement reduces 30-day healthcare costs with a low major adverse cardiac events (MACE) incidence. Here we present the final one-year results of the ARTICA trial.

### Methods

Low-risk patients with suspected NSTE-ACS were randomised to pre-hospital rule-out with POC troponin measurement or emergency department (ED) transfer. Primary one-year outcome was healthcare costs. Secondary outcomes were safety, quality of life and cost-effectiveness. Safety was defined as one-year MACE, consisting of ACS, unplanned revascularisation or all-cause death. Quality of life was measured with EuroQol-5D-5L questionnaires. Cost-effectiveness was defined as one-year healthcare costs difference per quality-of-life difference.

### Results

Follow-up was completed in all 863 patients. Healthcare costs were significantly lower in the pre-hospital strategy (€1932±€2784 vs €2649±€2750), mean difference €717 (95% confidence interval [CI] €347 to €1087; P<0.001). In the total population, one-year MACE rate was comparable between groups (5.1% [22/434] in the pre-hospital strategy vs 4.2% [18/429] in the ED strategy; P=0.54). In the ruled-out ACS population, one-year MACE remained low (1.7% [7/419] vs 1.4% [6/417]), risk difference 0.2% (95% CI -1.4% to 1.9%;P=0.79). Quality of life showed no significant difference between strategies.

### Conclusions

Pre-hospital rule-out of NSTE-ACS with POC troponin testing in low-risk patients is cost-effective, expressed by a sustainable healthcare costs reduction and no significant effect on quality of life. One-year MACE remained low for both strategies.

## Introduction

Chest pain is the most common reason for emergency medical contact.[1] Due to a lack of validated pre-hospital algorithms to rule out a non-ST-segment elevation acute coronary syndrome (NSTE-ACS), patients with chest pain are routinely transported to the emergency department (ED).[2-3] Around 10% of all ED visits are due to chest pain, which contributes to ED overcrowding, a growing problem worldwide, which is associated with high costs, increased length of stay and worse clinical outcomes.[4,5] Importantly, for the majority (80-90%) of patients suspected of NSTE-ACS, an acute coronary syndrome (ACS) can be ruled-out.[6-8] Furthermore, low-risk patients are not likely to benefit from expensive, lengthy and resource intensive ED visits.[1,9,10] The HEART (History, Electrocardiogram [ECG], Age, Risk factors and Troponin) score enables rapid identification of low-risk patients, with low short-term major adverse cardiac event (MACE) incidence.[11,12] A point-of-care (POC) troponin measurement enables ambulance paramedics to assess the HEART score and identify low-risk patients in the pre-hospital setting.[13] Recently, in the 'Acute rule-out of non-ST-segment elevation acute coronary syndrome in the (pre)hospital setting by HEART score assessment and a single point-of-care troponin' (ARTICA) randomised trial, we found that pre-hospital rule-out of NSTE-ACS in low-risk patients with POC troponin testing leads to a large reduction in healthcare costs in the first 30 days, while occurrence of major adverse cardiac events (MACE) was very low. However, the long-term healthcare costs, impact on safety, quality of life and cost-effectiveness of pre-hospital rule-out of NSTE-ACS in low-risk patients with POC troponin testing are unknown. Here we present the final results of the ARTICA trial with respect to the one-year healthcare costs, quality of life, cost-effectiveness and safety of pre-hospital rule-out of NSTE-ACS in low-risk patients.



## Methods

*Trial design*

The ARTICA trial is an investigator-initiated, multicentre, open-label, randomised controlled trial. The design of the study and the primary 30-day results have been published previously.[14,15] An independent and blinded Clinical Events Committee (CEC) was responsible for the adjudication of the MACE and a Data and Safety Monitoring Board (DSMB) oversaw the trial. More information about the members of the CEC and the DSMB is provided in the Supplementary Appendix. The study was conducted in accordance with the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO) and the statements of the Dutch Central Committee on Research Involving Human Subjects (CCMO). The medical ethics committee Oost-Nederland, The Netherlands, approved the trial on November 27th 2018 (NL66755.091.18). The trial was registered at Clinicaltrials.gov (NCT05466591).

*Participants*

The study population consisted of low-risk patients suspected of having a NSTE-ACS, who had an onset of symptoms at least two hours before arrival of the ambulance. Patients were considered low-risk patients if they had a HEAR score of ≤3. The HEAR score is depicted in Supplementary Table S1. The ambulance paramedics performed the screening of the patients, the informed consent procedure, the randomisation and the POC troponin measurement. Patients were not eligible for participation if they were suspected of another diagnosis requiring ED presentation (e.g. aortic dissection or pulmonary embolism [PE]) or if they were unable to provide written informed consent. Table S1 in the Supplementary Appendix depicts the complete list of inclusion- and exclusion criteria.

*Randomisation and intervention*

Eligible patients were randomised to either the pre-hospital rule-out strategy or the ED rule-out strategy. Patients who were randomised to the pre-hospital rule-out strategy underwent POC troponin T measurement on-site. If POC troponin T was low (<40 ng/L), an ACS was considered ruled-out and the care for the patient was transferred to the general practitioner (GP), as is the normal procedure for not transporting patients. If POC troponin T was not low (≥40 ng/L), the patient was transported to the ED, according to standard practice. In the ED rule-out strategy, patients were directly transported to the ED for evaluation without POC troponin measurement, according to standard practice. POC troponin T was measured using the Cobas h232 (Roche diagnostics, Basel, Switzerland). The detection limits are 40-2000 ng/L. Concentrations of 40-2000 ng/L on this assay are comparable to high-sensitivity troponin T concentrations in the laboratory.[16]

*Follow-up at one year*

For all patients, follow-up was performed by telephone and e-mail. If patients visited a hospital, medical records were collected to record all data on procedures and events. In case of non-response of a patient, the GP and hospital were contacted. Data were collected on the use of all healthcare resources. All patients received questionnaires regarding quality of life.

*Healthcare resources*

Data on healthcare resources were collected for all randomised patients over the entire period of evaluation (one year). The prices for the healthcare resources were determined in accordance with the 2018 reference list of the Dutch National Healthcare Institute.[17] The costs for hospital procedures were based on the standard 2018 list prices and the diagnosis-treatment combination (reimbursement system in the Netherlands). The diagnosis-treatment combination is comparable to the diagnosis related group system in other countries.[18] The costs for the index ambulance visit were considered equal in both strategies. Supplementary Table S2 shows a detailed description of the average prices of

ambulance transportations, hospital visits, procedures, inpatient hospitalisations, GP visits and additional tests.

*Primary outcome*

The primary outcome was healthcare costs at one year. Healthcare costs at one year consisted of the sum of all costs related to healthcare consumption, namely costs for ambulance transports, GP visits, hospital visits, additional tests, newly prescribed medications and inpatient hospitalisations.

*Secondary outcomes*

Secondary outcomes were safety, quality of life and cost-effectiveness. Safety was assessed by incidence of MACE at one year, which was defined as one or more of the following events: ACS, unplanned revascularisation and all-cause death. Incidence of MACE at one year was compared between groups in the total population and in the ruled-out ACS population (all patients for whom an ACS was ruled out, either in the pre-hospital setting or in the ED). Quality of life was assessed at 30 days and one year and was measured with a validated health-related quality of life (HRQoL) instrument, the EuroQol-5D-5L (EQ-5D-5L), for which a Dutch version is available.[19] The EQ-5D-5L is a generic HRQoL instrument comprising five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D-5L utility was obtained by applying predetermined weight to these five domains. Utility gives a global quantification of the patient's health status on a scale ranging from 0 (death) to 1 (perfect health). Cost-effectiveness adheres an incremental approach and was defined as the difference in healthcare costs divided by the difference in EQ-5D-5L utility scores at one year.

*Statistical analysis*

The statistical analysis plan of the entire study was published previously.[15] Categorical data were summarised by (relative) frequencies and percentages. Categorical variables were compared using Fisher's exact test or the chi-squared test, whichever was most appropriate. Continuous data were summarised as means ±SD or medians (interquartile ranges [IQRs]). Healthcare costs were expressed as means ±SD. Mean cost differences and their 95% confidence intervals (CIs) were calculated (univariable analysis). To take potentially skewed distribution into account, as well as possible heteroscedasticity, a generalized linear model (GLM) with a gamma distribution for the dependent variable (total healthcare costs) was included. For the MACE endpoints, one-year incidence was calculated in both groups in the total population and in the ruled-out ACS population. Point estimates for the risk differences were calculated along with their 95% CIs. For the incidence of MACE in the total population, a cumulative incidence curve was plotted and the time to event was compared between strategies using the Log-Rank test. The EQ-5D-5L utility scores for the quality of life were analysed using tobit regression with right-censoring at 1. For cost-effectiveness and the

EQ-5D-5L utility scores, two missing data scenarios were performed: a scenario with complete cases and a scenario with multiple imputation by chained equations with predictive mean matching. Missing data were assumed to be missing at random. Cost-effectiveness was presented as the difference in costs between the pre-hospital rule-out strategy and the ED rule-out strategy, compared to the difference in their effect (EQ-5D-5L utility score at one year). Moreover, cost-effectiveness incorporating parameter uncertainty using bootstrapping was presented as a Cost-Effectiveness plane (CE-plane). With the ED rule-out strategy occupying the origin of the graph, the CE plane plotted the incremental costs (y-axis) and utilities (x-axis) of the pre-hospital rule-out strategy relative to this standard care in a two-dimensional (costs and utility scores) space. In the CE plane, the area above the horizontal axis represents an increase in costs and the area to the right of the vertical axis represents a gain in quality of life. There are four quadrants. In two quadrants there is an Incremental Cost Effectiveness Ratio (ICER) (upper right-hand quadrant and lower left-hand quadrant), in the other two quadrants there is no interpretable ICER as there is no trade-off between costs and effects. The CE plane, incorporating uncertainty, shows the joint distribution of differences in costs and utility scores at one year recalculated over 1000 replications of the imputed study data using bootstrap resampling method. Each point in the scatterplot represents 1 bootstrap sample. The scatter cloud may lay in more than one quadrant. From a CE plane, a Cost-Effectiveness Acceptability Curve (CEAC) can be inferred. A CEAC shows the likelihood that the pre-hospital rule-out strategy is cost-effective across a range of cost-effectiveness thresholds (willingness to pay [WTP] for an effect). The software package Stata version 17 (StataCorp LLC, College Station, TX, USA) and SPSS statistics version 27 (IBM, Armonk, NY, USA) were used to perform the data analyses.

*Patient and public involvement*

The patient information was developed in consultation with a patient member of the Harteraad (a Dutch patient federation for cardiovascular patients). During the development of the trial information (i.e. patient information letters, letter to the GP), the patient representative gave feedback to improve the quality of these documents. The patient representative also advised the ambulance paramedics on how to perform informed consent.

## Results

*Participants*

From March 1st 2019 to May 4th 2022, 1138 patients were screened and a total of 866 patients were randomised. Three patients were excluded from the analyses after withdrawal of informed consent (n=3). One-year follow-up was completed for all patients, resulting in a total of 863 patients available for analyses. The study flow chart is depicted in Figure 1. The patients had a mean age of 54 ±13 years, a median HEAR score of 3 (IQR 2-3) and 57%

of the study population was female. In the pre-hospital rule-out strategy, 37/434 patients (8.5%) were transported to the ED because of elevated POC troponin T (n=18), failed POC troponin T test (n=12) or decision of the GP (n=7). In the ED rule-out strategy, 100% of the patients were transported to the ED. In 836 patients (96.9% of the total population), ACS was ruled-out, either in the pre-hospital setting or at the ED. Table 1 shows the baseline characteristics, which were well balanced.

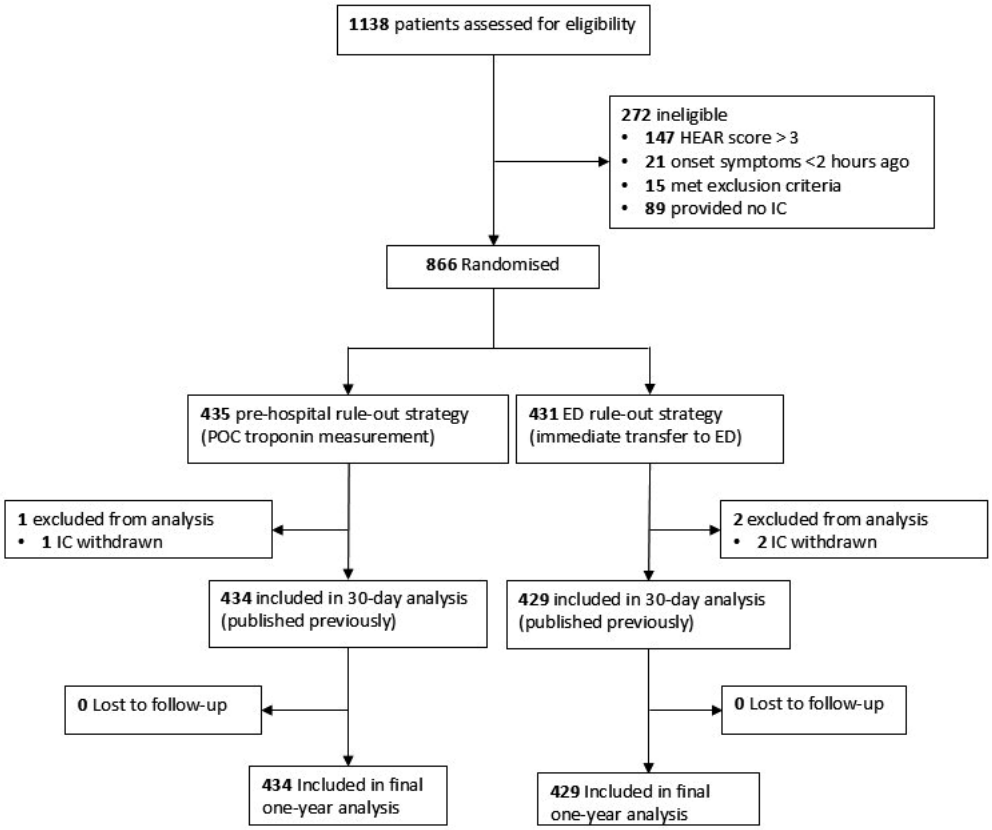



**Figure 1. Study flow chart**

**Table 1. Baseline characteristics**

| | Pre-hospital rule-out strategy (N=434) | ED rule-out strategy (N=429) |
|---|---|---|
| Age (years), mean (SD) | 53.7 (13.1) | 53.4 (12.5) |
| Female sex, N (%) | 247 (56.9%) | 248 (57.8%) |
| History (HEAR score), median (IQR) | 3 (2-3) | 3 (2-3) |
| ECG score (HEAR score), median (IQR) | 0 (0-1) | 1 (0-1) |
| History of atherosclerotic disease, N (%) | 34 (7.8%) | 23 (5.4%) |
| Hypertension, N (%) | 85 (19.6%) | 71 (16.6%) |
| Diabetes Mellitus, N (%) | 22 (5.1%) | 14 (3.3%) |
| Current Smoker, N (%) | 112 (25.8%) | 110 (25.6%) |
| Hypercholesterolemia, N (%) | 37 (8.5%) | 35 (8.2%) |
| Family history, N (%) | 155 (35.7%) | 152 (35.4%) |
| BMI ≥30 kg/m$^2$, N (%) | 86 (19.8%) | 80 (18.6%) |
| Onset of symptoms > 24 h, N (%) | 130 (30.0) | 123 (28.7) |
| Onset of symptoms < 24 h, N (%) | 304 (70.0) | 306 (71.3) |
| Onset of symptoms (if onset <24h), mean (SD) | 7.1 (5.2) | 6.8 (5.3) |
| Elevated troponin, N (%) | 18 (4.1%) | 24 (5.6%) |
| Heart rate, bpm, mean (SD) | 77.9 (13.2) | 77.4 (13.4) |
| Systolic blood pressure, mmHg, mean (SD) | 146 (20.5) | 145.1 (21.2) |

BMI = body mass index, Bpm = beats per minute, ECG = electrocardiogram, ED = emergency department, h = hours, HEAR score = History, ECG, Age and Risk factors score, IQR = interquartile range, SD = standard deviation.

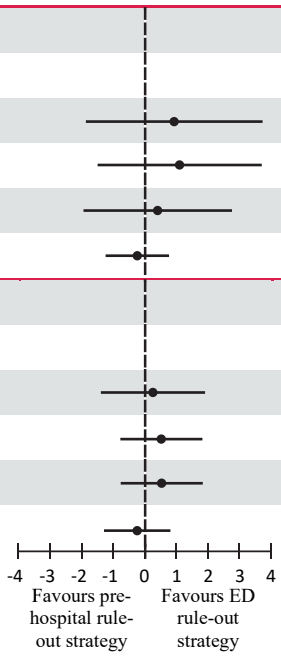
*MACE in the total population*

In the total population, MACE at one year (including MACE at index presentation) occurred in 22/434 patients (5.1%) in the pre-hospital rule-out strategy versus 18/429 patients (4.2%) in the ED rule-out strategy, with a point estimate for the risk difference of 0.9% (95% CI -1.9 to 3.7%, P=0.54). (Figure 2) In the pre-hospital rule-out strategy, 20 patients (4.6%) had an ACS, of which 14 patients (3.2%) had a non-ST-segment elevation myocardial infarction (NSTEMI), 5 patients (1.2%) had an ST-segment elevation myocardial infarction (STEMI) and 1 patient (0.2%) had unstable angina. Unplanned revascularisation was

performed in 15 patients (3.5%) and 2 patients (0.5%) died. A total of 15 of these 22 patients were directly transported to the ED after not having low POC troponin T concentrations. In the ED rule-out strategy, 15 patients (3.5%) had an ACS, of which 11 patients (2.6%) had an NSTEMI and 4 patients (0.9%) had unstable angina. Unplanned revascularisation was performed in 13 patients (3.0%) and 3 patients (0.7%) died. Figure 3 shows a cumulative incidence curve for the incidence of MACE in both strategies in the total study population (P=0.54).

**Figure 2. Incidence of major adverse cardiac events at one year**

| | Pre-hospital rule-out strategy | ED rule-out strategy | Point estimate of the risk difference (95% CI) | P-value |
|---|---|---|---|---|
| ***All randomised patients*** | | | | |
| Total (No) | **434** | **429** | | |
| MACE | 22 (5.1%) | 18 (4.2%) | 0.9% (-1.9% to 3.7%) | 0.54 |
| Acute coronary syndrome | 20 (4.6%) | 15 (3.5%) | 1.1% (-1.5% to 3.7%) | 0.41 |
| Unplanned revascularisation | 15 (3.5%) | 13 (3.0%) | 0.4% (-1.9% to 2.8%) | 0.72 |
| Death (all cause) | 2 (0.5%) | 3 (0.7%) | -0.2% (-1.2% to 0.8%) | 0.64 |
| ***Patients with ruled-out ACS*** | | | | |
| Total (No) | **419** | **417** | | |
| MACE | 7 (1.7%) | 6 (1.4%) | 0.2% (-1.4% to 1.9%) | 0.79 |
| Acute coronary syndrome | 5 (1.2%) | 3 (0.7%) | 0.5% (-0.8% to 1.8%) | 0.48 |
| Unplanned revascularisation | 5 (1.2%) | 3 (0.7%) | 0.5% (-0.8% to 1.8%) | 0.48 |
| Death (all cause) | 2 (0.5%) | 3 (0.7%) | -0.2% (-1.3% to 0.8%) | 0.65 |



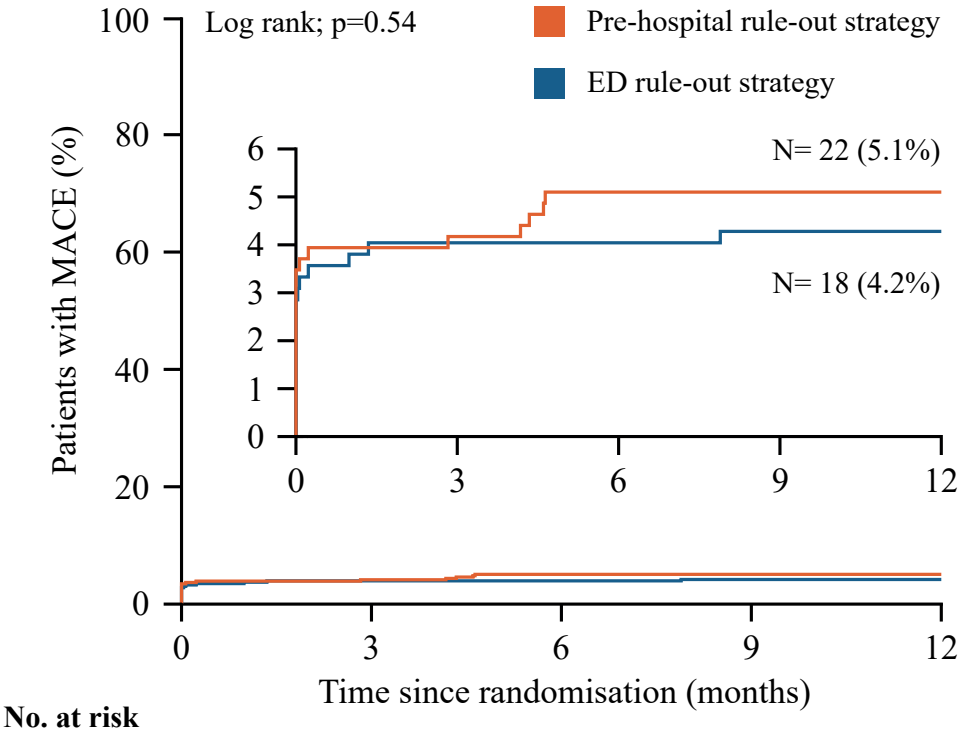



**Figure 3. Cumulative incidence curve for the incidence of major adverse cardiac events at 1 year**

*Safety pre-hospital rule-out of ACS*

In the ruled-out ACS population (96.9% of the total population), MACE at one year occurred in 7/419 patients (1.7%) in the pre-hospital rule-out strategy versus 6/417 patients (1.4%) in the ED rule-out strategy, with a point estimate for the risk difference of 0.2% (95% CI -1.4% to 1.9%, P=0.79). In the pre-hospital rule-out strategy, 5 patients (1.2%) had an ACS, of which 2 patients (0.5%) had a NSTEMI, 2 patients (0.5%) had a STEMI and 1 patient (0.2%) had unstable angina. Unplanned revascularisation was performed in 5 patients (1.2%) and 2 patients (0.5%) died. MACE after the first 30 days occurred in 5 patients (1.2%) in the pre-hospital rule-out strategy; 3 patients had an ACS (0.7%), and 2 patients (0.5%) died. One patient had a NSTEMI (0.2%) after 141 days, one patient had a STEMI (0.2%) after 127 days and one patient had unstable angina (0.2%) after 132 days. All three of these patients presented with new symptoms and received revascularisation. One patient died

from end-stage myelodysplastic syndrome. One patient was found in a confused state and died while being transferred into the ambulance, no autopsy was performed. In the ED rule-out strategy, 3 patients (0.7%) had an ACS, of which 3 patients (0.7%) had unstable angina. Unplanned revascularisation was performed in 3 patients (0.7%) and 3 patients (0.7%) died.

MACE after the first 30 days occurred in 2 patients (0.5%) in the ED rule-out strategy; 0 patients (0.0%) had an ACS and 2 patients (0.5%) died. One patient died from thyroid cancer and one patient committed suicide. A list with details about all patients with MACE is available in the Supplementary Appendix (Table S3).



*Healthcare costs*

Healthcare costs at one year were significantly lower in the pre-hospital rule-out strategy (€1932 ±€2784 versus €2649 ±€2750) with a mean difference of €717 (95% CI €347 to €1087, P<0.001). Table 2 shows the healthcare costs and its components at one year. The costs for GP visits were significantly higher in the pre-hospital rule-out strategy, with a mean difference of €-27 (95% CI €-32 to €-22, P<0.001), and the costs for hospital visits were significantly lower in the pre-hospital rule-out strategy, with a mean difference of €710 (95%CI €511 to €909, P<0.001). Table 3 shows the healthcare resource use at one year. Figure 4A shows the healthcare costs.

**Table 2. Mean healthcare costs and its components**

| Costs at one year (€) | Pre-hospital rule-out strategy (N=434) | ED rule-out strategy (N=429) | Mean difference (95% CI) | P-value |
|---|---|---|---|---|
| Healthcare costs | 1931.83 (2784.01) | 2648.63 (2749.56) | 716.80 (347.07 – 1086.51) | <0.001 |
| Ambulance transports | 846.00 (291.07) | 831.94 (319.67) | -14.06 (-54.90 to 26.78) | 0.50 |
| GP visits | 52.09 (33.11) | 25.00 (38.55) | -27.09 (-31.89 to -22.29) | <0.001 |
| Hospital visits | 603.94 (1530.36) | 1314.17 (1450.37) | 710.23 (510.97 to 909.48) | <0.001 |
| Additional tests and procedures | 83.47 (386.13) | 128.22 (367.03) | 44.75 (-5.59 to 95.10) | 0.08 |
| Newly prescribed medication | 66.78 (253.25) | 86.52 (347.46) | 19.74 (-20.85 to 60.33) | 0.34 |
| Hospitalizations | 279.54 (1102.95) | 262.77 (1185.29) | -16.77 (-169.73 to 136.18) | 0.83 |

**Table 3. Healthcare resource use at 1 year**

| | Pre-hospital rule-out strategy (N=434) | ED rule-out strategy (N=429) | P-value |
|---|---|---|---|
| One additional Ambulance transport, *n* (%) | 63 (14.7%) | 29 (6.8%) | <0.001 |
| Two or more additional Ambulance transports, *n* (%) | 13 (3.0%) | 9 (2.1%) | 0.40 |
| One ED visit, *n* (%) | 76 (17.5%) | 360 (83.9%) | <0.001 |
| Two or more ED visits, *n* (%) | 25 (5.8%) | 69 (16.1%) | <0.001 |
| One GP consultation, *n* (%) | 301 (69.4%) | 138 (32.2%) | <0.001 |
| Two or more GP consultations, *n* (%) | 133 (30.6%) | 57 (13.3%) | <0.001 |
| One outpatient clinic visit, *n* (%) | 74 (17.1%) | 94 (21.9%) | 0.071 |
| Two or more outpatient clinic visits, *n* (%) | 101 (23.3%) | 122 (28.4%) | 0.083 |
| CT cardiac, *n* (%) | 29 (6.7%) | 44 (10.3%) | 0.059 |
| MRI cardiac, *n* (%) | 4 (0.9%) | 4 (0.9%) | 0.99 |
| Echocardiography, *n* (%) | 93 (21.4%) | 94 (21.9%) | 0.86 |
| Treadmill, *n* (%) | 64 (14.7%) | 83 (19.3%) | 0.072 |
| SPECT, *n* (%) | 10 (2.3%) | 12 (2.8%) | 0.65 |
| Other additional tests, *n* (%) | 137 (31.6%) | 135 (31.5%) | 0.98 |
| CAG, *n* (%) | 28 (6.5%) | 28 (6.5%) | 0.96 |
| PCI, *n* (%) | 18 (4.1%) | 14 (3.3%) | 0.49 |
| CABG, *n* (%) | 1 (0.2%) | 1 (0.2%) | 0.99 |
| Hospitalization, *n* (%) | 58 (13.4%) | 58 (13.5%) | 0.95 |
| Length of hospitalization (days), median (IQR) | 0 (0-0) | 0 (0-0) | 0.99 |

CABG = coronary artery bypass grafting; CAG = coronary angiography; CT= computed tomography; ED = emergency department; GP = general practitioner; IQR = interquartile range; MRI = magnetic resonance imaging; PCI = percutaneous coronary intervention.

*Quality of life*

The EQ-5D-5L questionnaire at 30 days was completed by 331 (76.3%) patients in the pre-hospital rule-out strategy and 311 (72.5%) patients in the ED rule-out strategy. At 30 days, the mean difference in EQ-5D-5L utility score was -0.009 (95% CI -0.048 to 0.030, P=0.65) in the complete cases analysis and -0.011 (95% CI -0.038 to 0.015, P=0.39) in the multiple

imputation analysis. The EQ-5D-5L questionnaire at one year was completed by 376 (86.6%) patients in the pre-hospital rule-out strategy and 362 (84.4%) patients in the ED rule-out strategy. The mean difference at one year in EQ-5D-5L utility score, was 0.008 (95% CI -0.033 to 0.050, P=0.69) in the complete cases analysis and 0.005 (95% CI -0.022 to 0.031, P=0.73) in the multiple imputations analysis (Figure 4B).

*Cost-effectiveness*

The fact that the pre-hospital rule-out strategy resulted in a significant reduction of healthcare costs, without significantly affecting quality of life, implicates that the pre-hospital rule-out strategy was the dominant strategy regarding cost-effectiveness. Figure 4C shows the CE plane and Figure 4D the CEAC. From the CE plane, it can be inferred that the point estimate (ICER) lies in the lower right-hand quadrant, meaning that the pre-hospital rule-out strategy was dominant by reducing healthcare costs with slightly better quality of life. Consequently, there was no trade-off between healthcare costs and quality of life. The CEAC shows that the probability that the pre-hospital rule-out strategy is cost-effective is 100% when the willingness to pay (WTP) for an effect equals zero. When the WTP for an effect increases, more uncertainty in the cost-effectiveness analysis is introduced and the probability of the pre-hospital rule-out strategy being cost-effective decreases slightly across a range of increasing WTPs but remains well above 80%.

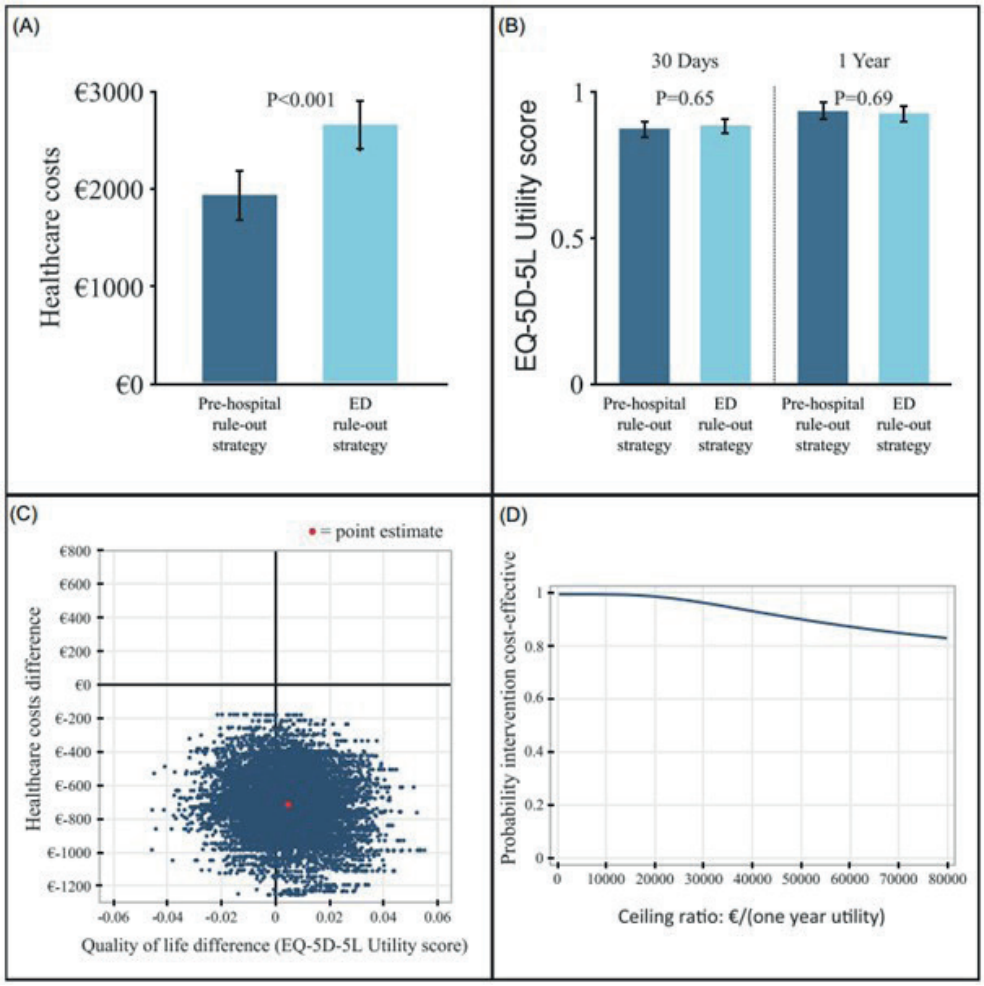



**Figure 4. Mean healthcare costs (A), EQ-5D-5L utility score (B), CE plane (C) and CEAC (D)**

## Discussion

*Principal findings*

Our trial shows that pre-hospital rule-out of NSTE-ACS in low-risk patients by a single POC troponin measurement is cost-effective at one year, as demonstrated by a sustainable significant reduction in healthcare costs without affecting quality of life. Incidence of MACE at one year was low in both the pre-hospital rule-out strategy (POC troponin measurement) and the ED rule-out strategy (standard transport to the hospital), especially when ACS was ruled out, irrespective of whether rule-out was performed at home or in-hospital.

*Safety*

Previously we showed that 30-day incidence of MACE in the ARTICA trial was low in patients with a low (≤3) pre-hospital HEAR score and very low in patients for whom an NSTE-ACS was ruled out.[15] These findings were comparable to previous studies regarding identification of low-risk patients by HEART score assessment at the ED.[12] Although the ARTICA trial was not powered to estimate the safety of pre-hospital rule-out, long-term follow-up was expected to provide more insight in the safety. At one year, incidence of MACE was 4.6% and comparable between the pre-hospital rule-out strategy and the ED rule-out strategy, including MACE at index presentation. In 97% of the patients, an ACS was ruled-out at index presentation (either at home by POC troponin measurement, or at the ED). In patients with a ruled-out ACS, one-year incidence of MACE was 1.6% and also comparable between both strategies. Although most studies on HEART score assessment for risk stratification in chest pain patients at the ED focused on short-term outcomes, some studies elaborated on the long-term outcomes after assessment of a HEART score of ≤3 at the ED. However, all of these studies were observational, the follow-up duration varied from 3 months to one year and the reported endpoints were heterogenous.[20-24] In a study from Sweden with 247 low-risk patients, 3-month incidence of MACE was 0.4%.[21] However, 3-month incidence of MACE in the total population (not just low-risk patients) in that study was only 7.3%, which is much lower than the short-term incidence of MACE in most studies.[25] In a study from Texas, USA, with 840 low-risk patients, 6-month incidence of MACE was 0.7%.[22] However, 1157 of the 2143 assessed patients were excluded from the long-term analysis because of missing follow-up. In a study from Michigan, USA, with 175 low-risk patients, one-year mortality was 2.7%, whereas 30-day incidence of MACE was 0.6%.[20] In a study from Italy with 512 low-risk patients, 180-day incidence of MACE was 0%.[24] However, this study had a possible selection bias and incomplete follow-up. In a study from Philadelphia, USA, with 98 low-risk patients, one-year incidence of MACE was 3.1%.[23] To summarize, long-term incidence of MACE in patients with a HEART score of ≤3 at the ED varied from 0% to 3.1% during follow-up of 3 months to one year. The incidence of one-year MACE in our total study population (4.6%) was higher than the incidences of long-term MACE in the aforementioned studies. However, an important difference is that the patients in the aforementioned studies had a HEART score of ≤3 (including troponin measurement), while the patients in our study had a HEAR score of ≤3. As can be seen in the Supplementary Appendix (Table S3), 25 of the 27 patients with a ruled-in ACS at index presentation had a HEAR score of 2 or 3 and elevated troponin concentrations because of STEMI or NSTEMI. Adding the Troponin component to the HEAR score in these patients would result in a HEART score >3. Therefore, long-term safety of true low-risk patients is better demonstrated by the ruled-out ACS population instead of the total population. In our study, one-year incidence of MACE was 1.7% after ruled-out ACS in the pre-hospital rule-out strategy and 1.4% after ruled-out ACS in the ED rule-out strategy. The difference in risk between strategies was negligible at 0.2% (95% CI -1.4% to 1.9%, P=0.79). Therefore, in addition to the low incidences of MACE at 30 days, the final one-year results

of our trial show that the one-year MACE incidence after pre-hospital rule-out of NSTE-ACS by POC troponin measurement in low-risk patients remains low and is comparable to the patients with a ruled-out ACS at the ED.[15] However, in the ruled-out ACS population, three patients (0.7%) in the pre-hospital rule-out strategy had an ACS after the first 30 days, in comparison to zero patients in the ED rule-out strategy. Also, it should be noted that our study was not formally designed nor powered to show non-inferiority regarding the safety of the pre-hospital rule-out strategy as compared to the ED strategy. These results emphasise the importance of a future trial powered to show non-inferiority regarding the safety of pre-hospital rule-out of ACS.

*Cost-effectiveness*

The mean healthcare costs at one year were significantly lower in the pre-hospital rule-out strategy. Since quality of life at one year showed no significant difference between the strategies, a reduction in healthcare costs automatically indicates that the strategy is cost-effective. At one year, the patients in the pre-hospital rule-out strategy had significantly more ambulance transports in addition to the index presentation. As could be expected with this trial design, patients in the ED rule-out strategy had significantly more ED visits, while the patients in the pre-hospital rule-out strategy had significantly more GP visits. However, numbers of outpatient clinic visits, additional tests, procedures and hospitalisations showed no significant differences between the strategies. The final one-year results of our trial show that pre-hospital rule-out of NSTE-ACS was cost-effective demonstrated by a sustainable healthcare costs reduction, without affecting quality of life. Moreover, the mean difference in healthcare costs at one year was €717 per patient, whereas the difference in healthcare costs at 30 days was €611. As discussed in our previous paper, a healthcare costs reduction of €611 per patient would save an estimated €48M per year if the pre-hospital strategy were to be implemented in all of the Netherlands.[15] Therefore, with a healthcare costs reduction of €717 per patient, country-wide implementation would save an even larger amount per year (estimated €56M). These results are in line with a recent economic evaluation from Australia, which has also shown that pre-hospital risk stratification and POC troponin measurement leads to large long-term healthcare costs reductions.[26]

*Future implications*

We believe that the final results of the ARTICA trial indicate that implementation of the pre-hospital rule-out strategy will reduce long-term costs and will help to alleviate the overcrowded ED. The possibility to implement the pre-hospital rule-out strategy depends on multiple factors. First, the level of education of ambulance professionals differs between countries, which might influence the reliability of HEAR score assessment. However, the overall inter-operator reliability of the HEART score is very strong, regardless of the level of education.[27] Second, ambulance availability differs between countries.[28] The Netherlands is a relatively small and well-organized country with short distances and consequently short

transportation times. Therefore, in countries with less ambulance availability and longer distances, the amounts of time and money saved by not transporting patients could be even larger. Third, the pre-hospital rule-out strategy relies on a well-functioning primary care system. In our trial, after rule-out of NSTE-ACS and not transporting the patient to the ED, the care for the patient was transferred to the GP. In the Netherlands, GPs provide out-of-hours urgent primary care in so-called GP cooperatives, facilitating transfer of the care for the patient to a GP at every moment of the day.[29]

## Limitations



Follow-up was performed by telephone and e-mail, which could result in a certain degree of misclassification.[28] However, if patients visited a hospital, the medical records were requested from the relevant hospitals. Therefore, relevant events and utilized healthcare resources were objectively assessed and not subject to recall bias. The EQ-5D-5L questionnaires regarding quality of life were not completed by all patients. However, the numbers of missing questionnaires were comparable between groups and the results before and after multiple imputation were comparable. Finally, the point-of-care troponin used in this study is not a high-sensitivity troponin assay.

## Conclusion

Pre-hospital rule-out of NSTE-ACS in low-risk patients with a single POC troponin measurement was cost-effective demonstrated by a sustainable healthcare costs reduction at one year, without affecting quality of life. One-year MACE occurrence remained low after pre-hospital rule-out of NSTE-ACS.

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# Chapter 5

## Agreement between ambulance paramedics and physicians on the (pre)hospital identification of low-risk chest pain patients

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Patients with suspected non-ST-segment elevation acute coronary syndrome (NSTE-ACS) are routinely transported to the emergency department (ED) by ambulance.[1] However, in the majority of the suspected NSTE-ACS patients, no acute coronary syndrome (ACS) is found.[2,3] Identification of patients who are not likely to have an ACS is possible with the HEART (History, Electrocardiogram, Age, Risk factors and Troponin) score, which is a widely validated risk stratification tool for chest pain patients at the ED.[4] Implementing a point-of-care (POC) troponin measurement enables ambulance paramedics to assess the HEART score in the pre-hospital setting.[5,6] To widely implement such strategy of pre-hospital rule-out, a correct low-risk classification (HEART score of ≤3) is essential. In this prespecified sub-analysis of the ARTICA trial, we evaluated the level of agreement between ambulance paramedics and physicians regarding the classification of patients as low-risk, within a pre-hospital population deemed eligible for early rule-out of NSTE-ACS. The ARTICA trial is a randomised trial on pre-hospital rule-out of NSTE-ACS in low-risk patients using a POC troponin measurement and primary results and design were published previously.[7,8]

Suspected NSTE-ACS patients ≥ 18 years, with a low pre-hospital HEAR score (≤3) were included in the current study if they were transported to the hospital as part of the ARTICA trial design and if data was available to assess an in-hospital HEAR score. Assessment of the HEAR score by ambulance paramedics was performed on-site. The in-hospital HEAR score was retrospectively assessed by two independent physicians. The pre-hospital and in-hospital HEAR scores were compared and the intraclass correlation coefficient (ICC) was calculated.

A total of 388 patients were included. Mean age was 53.1 (±12.4) years and 56.2% were female. Agreement on the low-risk classification (HEAR score of ≤3) was achieved in 88.9%. The pre-hospital total HEAR score was identical to the in-hospital HEAR score in 152 patients (39.2%), lower in 86 (22.2%) and higher in 150 (38.7%). The overall ICC was 0.67 (95% CI 0.59 – 0.73). Pre-hospital History scores were significantly higher and pre-hospital ECG scores were significantly lower. The mean pre-hospital History score was significantly higher than the mean in-hospital History score, with a mean difference of +0.35 (95% CI 0.28 to 0.42, P<0.001). The mean pre-hospital ECG score was significantly lower than the mean in-hospital ECG score, with a mean difference of -0.19 (95% CI -0.24 to -0.15, P<0.001) (figure 1).

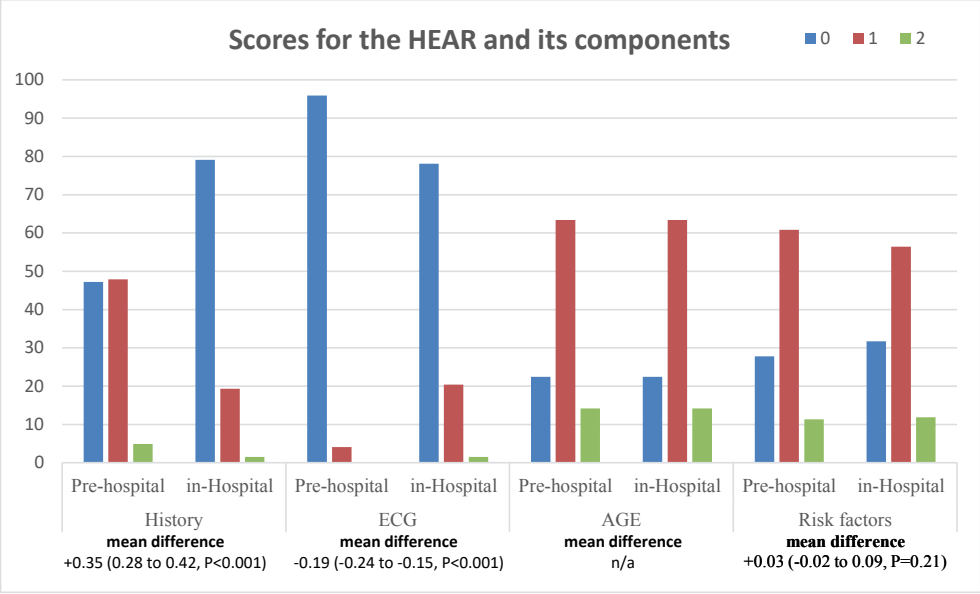



**Figure 1. Scores for the HEAR score and its components. HEAR, History, ECG, Age, and Risk factors**

This study demonstrated that physicians in the hospital agreed with ambulance paramedics on a low-risk classification (HEAR score ≤3) for NSTE-ACS in a high percentage (88.9%). The mean HEAR score was similar. Overall agreement of the HEAR score, as assessed by physicians in-hospital and ambulance paramedics pre-hospital, was moderate with an ICC of 0.66. This was primarily influenced by the history and ECG components, which yielded the lowest ICC values. Only 39.2% of patients that had exactly identical pre-hospital and in-hospital HEAR scores (table 1).

**Table 1 Differences in the assessment of the HEAR score and its components**

| | History | ECG | Age | Risk factors | HEAR score |
|---|---|---|---|---|---|
| Pre-hospital lower | 31 (8.0%) | 77 (19.8%) | 0 | 44 (11.3%) | 86 (22.2%) |
| Equal | 200 (51.5%) | 304 (78.4%) | 388 (100.0%) | 287 (74.0%) | 152 (39.2%) |
| Pre-hospital higher | 157 (40.5%) | 7 (1.8%) | 0 | 57 (14.7%) | 150 (38.7%) |

ECG = electrocardiogram; HEAR = History, Electrocardiogram, Age and Risk factors.

Of the 388 patients identified as low-risk patients by ambulance paramedics, 43 (11%) had an in-hospital HEAR score of >3. In these patients, the underestimation of the HEAR score was mostly caused by an underestimation of the ECG component. In the group with disagreement regarding low-risk classification, the incidence of MACE was significantly higher compared to the group with consensus on low-risk classification. However, five patients in the disagreement group had elevated troponin levels at first presentation at the ED, which could also have been addressed through prehospital POC troponin analysis.

More correct assessment of the ECG component can probably be achieved by transmission of the ECG to a hospital if POC troponin measurement to rule-out an NSTE-ACS is being considered. Also, adding a POC troponin increases agreement between pre-hospital and in-hospital risk classification. Finally, the assessment of ECGs using artificial intelligence algorithms is expected to advance significantly in the near future.

Limitations include the retrospective calculation based on the medical records and in contrast to the ambulance paramedics on-site, the physicians at the ED had access to the more detailed medical history of the patients. Moreover, the treating physicians at the ED had more information about the course of the symptoms, the reaction to sublingual nitrates and troponin levels.

**In summary,** in a population of pre-hospital identified low-risk patients, physicians in the hospital agreed with the ambulance paramedics on the low-risk classification in a high percentage of patients. Continuous history training and multidisciplinary ECG assessments are strongly recommended to further enhance the pre-hospital use of the HEAR score.

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# Chapter 6

## Less concern about missing NSTEMIs, more prospective randomized controlled trials warranted

Cyril Camaro , Goaris W.A. Aarts, Niels van Royen on behalf of the ARTICA Investigators

*European Heart Journal, 2024*

## Invited discussion forum

This commentary refers to 'Rule-out of non-ST-segment elevation acute coronary syndrome by a single, pre-hospital troponin measurement: a randomised trial', by C. Camaro et al., https://doi.org/10.1093/eurheartj/ehad056 and the discussion piece 'Concern regarding missed non-ST-segment elevation myocardial infarctions when applying a single, pre-hospital cardiac troponin measurement', by J. Glaeser et al., https://doi.org/10.1093/eurheartj/ehad642.

We would like to thank colleagues dr Glaeser, dr Lopez-Ayala and prof. Mueller for their interesting comments and questions regarding our ARTICA randomized trial.

First, the point-of-care (POC) troponin device used in our trial is indeed relatively low sensitive. The limit of detection (LOD) of the POC troponin T assay used in our trial (40 ng/l) is higher than the 99$^{th}$ percentile upper reference limit recommended for clinical use, which is 14 ng/L for high sensitivity cardiac troponin T. Dr Glaeser and colleagues state that this translates into 41 missed NSTEMIs for every 100 patients. In ARTICA this was definitely not the case, also in the standard care arm the total number of NSTEMI patients was very low and not increased as compared the pre-hospital arm (3.0% vs 2.6%). This was not only at first presentation, but also after 30 days. The one-year follow-up data are currently prepared for publication. This low number has off course to do with the low *a priori* chance after clinical judgment and risk scoring by ambulance personnel. In the ARTICA trial a NSTEMI was ruled out if patients had a low HEAR (HEART score without the Troponin component) score and a low POC troponin concentration.[1] Thus, we believe that the ARTICA algorithm indeed is capable of compensating for the lack of sensitivity of the POC troponin assay in the total population of patients presenting with chest pain. We agree that extra pre-hospital blood samples to analyze the value of high sensitive troponin could have provided additional insights, but this was not part of the protocol. The difference between the postulated number of missed NSTEMIs by dr Glaeser and the reality of the data from the ARTICA trial stresses the fact that every biomarker needs to be accompanied by additional *clinical* decision rules to take into account the clinical pre-test probability. This is also the case for high sensitivity troponin assays that are becoming increasingly available as POC assays.[2] A potential concern on high sensitivity POC troponin assays is a decrease in specificity, leading to a higher number of unnecessary hospital referrals.

Finally, the reported proportion of screened patients with a low HEAR score in the ARTICA trial is high because ambulance paramedics only entered patients into the electronic case report form if they thought the patient could be eligible for participation. However, our projected annual cost savings of implementation of the pre-hospital algorithm was based on a proportion of low-risk patients of 39.3%, as reported in a large meta-analysis and not

on the proportion of eligible low-risk patients in our trial.[3] Future randomized trials are needed to provide definite answers regarding safety of pre-hospital triage of patients with chest pain.

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# Chapter 7

## Pre-hospital risk stratification in suspected non-ST-segment elevation acute coronary syndrome with point-of-care troponin – An individual patient data meta-analysis

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## ABSTRACT

### Background

Emergency Medical Services (EMS) patients with chest pain are often suspected of having non-ST-elevation acute coronary syndrome (NSTE-ACS). Current risk stratification protocols for NSTE-ACS have limitations, leading to a lack of a well-organized prehospital diagnostic pathway. Recent studies have demonstrated that using clinical risk scores (CRS) including point-of-care (POC)-troponin in the EMS can improve prehospital diagnostic pathways for suspected NSTE-ACS. The primary aim of this systematic review and individual patient data meta-analysis was to assess safety of low-risk stratification for suspected NSTE-ACS patients in the prehospital setting.

### Methods

Prospective studies using CRS or POC-troponin for risk stratification in suspected NSTE-ACS patients within the EMS setting were included. Safety was assessed using sensitivity and negative predictive value (NPV) for patients identified as low-risk, based on CRS or POC-troponin measurement, for three different endpoints within 30 days: 1. all-cause mortality, 2. composite of mortality and/or acute myocardial infarction (AMI), 3. Major Adverse Cardiac Events (MACE).

### Results

Of 1526 articles screened, six were included, comprising 5.239 patients, and all utilized CRS derived from the HEART score. The summary low-risk CRS diagnostic performance predicted: all-cause mortality with a sensitivity of 93.2% (83.5-98.1) and NPV of 99.8% (99.5-99.9); mortality and/or AMI with a sensitivity of 91.8% (83.0-96.2) and a NPV of 97.3% (89.9-99.3); and MACE with a sensitivity of 92.8% (88.7-95.5) and a NPV of 97.2% (92.1-99.0). Lowering the CRS cut-off value for identifying low-risk patients, increased sensitivity and NPV but decreased the proportion of patients classified as low-risk.

### Conclusion

In well-trained EMS systems, where prompt and accurate follow-up of low-risk patients is possible, HEART-derived clinical risk scores effectively identify patients with a very low risk of 30-day mortality and MACE. However, implementation in other healthcare systems requires additional validation, given the variations in healthcare structure, risk stratification processes, and follow-up capabilities.

## Introduction

Chest pain is among the most common reasons for contacting Emergency Medical Services (EMS).[1] Current guidelines from the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) recommend that EMS paramedics perform immediate risk stratification of patients with symptoms suspicious for an acute coronary syndrome (ACS) according to regional protocols that primarily relies on clinical history and electrocardiogram (ECG) findings to identify patients with suspected ST-elevation myocardial infarction (STEMI).[2-4] In patients suspected of STEMI, healthcare is well-organized in prehospital networks leading to improved outcomes over the past decades.[5]

However, the majority of patients with suspected ACS do not have ECG evidence of ST-elevation and are suspected of having non-ST-elevation acute coronary syndrome (NSTE-ACS).[2,3] Within this group, clinical history and ECG findings are of low predictive value for effective risk stratification.[6] Due to the limitations of current risk stratification protocols for NSTE-ACS, a well-organized prehospital diagnostic pathway is lacking.[7] Consequently, these patients are transferred to the nearest emergency department (ED) for further diagnostic evaluations, contributing to ED overcrowding and elevated healthcare costs.[8] Upon arrival at the ED, diagnostic pathways based on troponin algorithms and clinical risk scores are implemented, allowing for same-day discharge in the majority of the patients.[2,3,9]



Recent studies have demonstrated that using clinical risk scores (CRS) including a single point-of-care (POC) troponin, to classify low-, intermediate-, and high risk, in the EMS setting is feasible and may improve prehospital diagnostic pathways for patients with suspected NSTE-ACS.[6,8,10-17] Most of these studies have explored whether patients identified as low-risk for NSTE-ACS could be safely left at home and referred to their general practitioner (GP) for further evaluation.[8,12,14] Findings suggest that prehospital risk stratification with CRS is feasible, improves both prehospital and in-hospital logistics, and reduces healthcare costs.[8,13,18] Although this pre-hospital rule-out strategy appeared safe, with similar rates of major adverse cardiovascular events (MACE), none of these studies were adequately powered to assess safety.

Some countries are now considering the implementation of CRS within the EMS setting as part of standard care but discussions about safety, cost-effectiveness and generalizability of this approach remains a topic of debate.[7] In order to inform these discussions, it is important to review, and synthesize where possible, the current available evidence.
This systematic review and individual patient data (IPD) meta-analysis aims to evaluate the safety of prehospital risk stratification using a CRS and POC-troponin in patients with suspected NSTE-ACS with respect to identification of patients at low-risk of mortality, acute myocardial infarction and MACE.

## METHODS

**Search strategy and selection criteria**

This systematic review and IPD meta-analysis was conducted and reported in accordance to the Cochrane Handbook for IPD Systematic Reviews and the PRISMA guidelines.[19,20]

The primary search was conducted in MEDLINE and Embase up to July 21, 2023, using the following key terms: 'prehospital', 'troponin', 'risk scores', and 'ACS'. No language restrictions were applied. The search was updated on October 10, 2025, and expanded to include Scopus and Web of Science. The full search strategy is provided in the Supplemental Data (sTable 1). In brief, prospective studies that performed risk stratification of suspected NSTE-ACS patients within the EMS setting using a CRS or POC-troponin were included and that provided clinical endpoint data regarding the diagnosis of NSTE-ACS upon hospital admission or MACE within 30 days. Studies were excluded if the CRS or POC-troponin measurement were not completely calculated or measured within the EMS setting by EMS paramedics or were calculated retrospectively. Study selection was conducted independently by two authors (JD and VH), a third author (PJV) was consulted if no consensus was reached. This IPD meta-analysis was preregistered on PROSPERO (CRD42023453409) and ClinicalTrials.gov (NCT06051110).

### Data management

The corresponding author of each included study was invited via email to participate in the IPD meta-analysis. If unavailable or unresponsive, the invitation was extended to the first or last author. Authors who did not respond after three email attempts were considered non-responders and excluded from the analysis. Respondents were asked to provide data for inclusion in a general database designed for this study. The requested data included baseline characteristics, information on CRS and POC-troponin measurement, prehospital and hospital data, and follow-up information.

Three authors (JD, MV and PJV) verified the data, and any discrepancies were resolved through correspondence with the original investigators. After receiving the individual patient data, the data was re-coded and harmonized into a common format. Patients without complete CRS, POC-troponin measurement, or endpoint data were excluded from the analysis.

The methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool by two authors (JD and VH).[21]

## Clinical Risk Scores

The CRS most often investigated in the prehospital setting are derived from the History, ECG, Age, Risk-factor, and Troponin (HEART) score and the Troponin-only Manchester Acute Coronary Syndromes score (T-MACS).[8,10-14,16,22,23] The HEART score is calculated based on five key components: history, ECG, age, risk-factors, and a POC-troponin measurement, with each component scored 0, 1 or, 2 to give a total score between 0 and 10. Patients with a HEART score of ≤3 are classified as low-risk, patients with a score of ≥4 are classified as intermediate/high risk for having NSTE-ACS. The T-MACS decision aid is calculated mathematically to give a probability, aligning patients into four different risk groups, with those at very-low risk considered for early ED discharge.

## Aims and endpoints

The primary aim of this IPD meta-analysis was to assess the safety of risk stratification for suspected NSTE-ACS patients in the EMS setting. Safety was assessed using summary values for sensitivity and negative predictive value (NPV) with 95% confidence intervals (95-CI) for patients identified as low-risk, based on CRS or solely POC-troponin measurement. Patients were identified as low-risk based on the total CRS score, as defined for the specific CRS used. Patients were classified as low-risk based solely on POC-troponin measurement if they had a score of 0 for the troponin component within the CRS. If complete CRS data were unavailable and only the POC troponin value was accessible, patients were considered low-risk if the troponin level was at or below the Limit of Detection (LoD) of the POC analyzer used or if the troponin level was below the detectable range of the analyzer. Safety was assessed for three different endpoints evaluated within 30 days after inclusion (including the index event): 1. all-cause mortality; 2. composite of all-cause mortality and/or acute myocardial infarction (AMI); 3. MACE.



Acute myocardial infarction was defined as the diagnosis of non-ST-elevation myocardial infarction (NSTEMI) as adjudicated in the included studies. MACE was defined as a composite of all-cause mortality, ACS (NSTEMI or unstable angina pectoris), or revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)).

In current practice, there are variations in the POC analyzers and POC troponin assays used in different healthcare environments in which studies have been conducted, hence differences exists in the troponin diagnostic cut-off thresholds used across studies. In addition to the primary aim, an adjusted CRS was calculated using standardized troponin cut-off points, to make the approach as uniform as possible. For the adjusted CRS, patients will be classified as low-risk if their measured troponin value is at, or below, the LoD for the POC troponin assay used, and if the total score of the CRS is ≤3. If the LoD is not specified for a given POC

troponin assay, low-risk classification will be based on troponin values below the detectable range of the test on the respective POC platform tested. Patients with POC troponin results above the LoD (or within the detectable range of the POC assay if no LoD specified) or if the CRS score is ≥ 4, will be classified as intermediate/high risk within the adjusted CRS.

Secondary aims were to examine the influence of time between symptom onset and risk stratification performed within the EMS setting and to assess the impact of using different cut-off value in CRS on the classification of patients as low-risk, with regard to both safety and the number of patients classified as low-risk (efficacy). To assess the diagnostic performance of CRS and POC-troponin in different populations, subgroup analyses were performed based on age, sex, country, and POC analyzer type.

## Data analysis

Continuous variables were considered normally distributed if skewness and kurtosis were between -1 and 1, and were expressed as means ± standard deviation (SD). Variables that were not normally distributed were presented as medians with interquartile ranges (IQR)]. Categorical variables were reported as frequencies and percentages.

Given the potential importance of inter-study differences for the primary aim, a two-stage approach was employed.[19] In the two-stage approach, each study was first analyzed independently. These data were then combined using the *meta* package using R Statistical Software (v4.4.2).[24] Depending on the level of heterogeneity, either a fixed common-effect model or a random-effects model according to Hartung and Knapp methods was selected to compute summary sensitivities and NPV. In case of severe heterogeneity, defined as an $I^2$> 40% with a significant Q-test (p-value < 0·10), a random-effects model was applied, otherwise, a fixed-effect model was used.[25] To account for the potential influence of individual studies, a leave-one-out meta-analysis was performed to identify influential studies. A quantitative sensitivity analysis was conducted to evaluate the number of missed events per 1,000 patients for different prevalences and NPV for the endpoints of mortality and MACE.

For the baseline characteristics and the secondary aims, a one-stage approach was primarily used for the analysis.[19] In this approach, data from all studies were combined, and 2x2 tables were generated from the raw data to calculate summary sensitivities and NPVs. The 95% confidence intervals for efficacy, sensitivity, and NPV were calculated according to the Wilson score methods.[26]

All analyses were performed using SPSS V.29.0 and R-studio V2024.04.2 (R Foundation for Statistical Computing, Vienna, Austria).

## Ethics approval

The study was reviewed and approved by the regional and local Medical Ethics Committees of the participating medical centers (MEC-U W23.140).


## Funding

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## Results

Out of 1,526 full-text articles screened, a total of six studies were eligible and all studies were included in this systematic review and IPD meta-analysis. No studies were missed or excluded (sFigure 1).[8,10-14] All included studies were conducted in the EMS setting, where EMS paramedics prospectively calculated the CRS and analyzed POC-troponin levels. Four of the six included studies were conducted in the Netherlands, one in the United Kingdom (UK), and one in the United States of America (USA). Additional information for the included studies are provided in the supplementary materials (sTable 2 and sTable 3). All eligible studies utilized CRS derived from the HEART score, with varying cut-off values applied to the troponin component. The risk of bias for the included studies was evaluated using the QUADAS-2 tool (sTable 4 and sTable 5).

Published and unpublished individual patient data were obtained from all included studies. Data were available for 5,826 patients, 587 (10%) patients were excluded due to missing data for one or more endpoints. The final analysis included 5,239 patients, with a mean age of 63 (SD 15) years of whom 2,485 (47%) were female. The median time from symptom onset to POC troponin measurement by an EMS paramedic was 180 [IQR 74 – 480] minutes and the median CRS was 4 [IQR 3 – 5]. Mortality status within 30 days of inclusion was available for all patients, with a total of 60 (1%) patients deceased. Among the 3,242 patients with data available for the combined endpoint of mortality and/or AMI, 486 (15%) experienced an event. MACE data were available for 4,231 patients, of whom 750 (18%) experienced a MACE. Additional baseline characteristics are presented in Table 1.

**Table 1. Baseline characteristics**

| | **n=5239** |
|---|---|
| Age (years), mean (SD) | 63 (15) |
| Female sex, n (%) | 2485/5239 (47) |
| Hypertension, n (%) | 1531/3088 (50) |
| Diabetes Mellitus, n (%) | 551/3108 (18) |
| Current smoker, n (%) | 744/3012 (25) |
| Hypercholesterolemia, n (%) | 1463/3076 (48) |
| Family history of ACS, n (%) | 1235/2899 (43) |
| BMI, median [IQR} | 26 [24 – 29] |
| BMI ≥ 30 kg/m$^2$, n (%) | 751/2588 (29) |
| History of atherosclerotic disease, n (%) | 559/1817 (31) |
| History of PCI, n (%) | 363/1595 (23) |
| History of CABG, n (%) | 153/1596 (10) |
| Time from symptom onset until POC-troponin measurement by EMS paramedic (minutes), median [IQR] | 180 [74 – 480] |
| Clinical risk score, median [IQR] | 4 [3 – 5] |
| Hb (mmol/L), median [IQR] | 8·4 [7·7 – 9·0] |
| Creatinine (µmol/L), median [IQR] | 77 [66 – 90] |
| Mortality within 30 days, n (%) | 60/5239 (1) |
| Mortality and/or AMI within 30 days, n (%) | 486/3242 (15) |
| MACE within 30 days, n (%) | 750/4213 (18) |

ACS = Acute Coronary Syndrome, BMI = Body Mass Index, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting; POC = point-of-care, EMS = Emergency Medical Services, Hb = hemoglobin, NSTE-ACS = non-ST-segment elevation Acute Coronary Syndrome, AM = Acute Myocardial Infarction, MACE = Major Adverse Cardiac Events

The diagnostic performance of the CRS for identifying patients at low-risk for mortality in the EMS setting showed a sensitivity of 93.2% (95 CI 83.5% - 98.1%) and NPV of 99.8% (95-CI 99.5% - 99.9%). The POC-troponin had a sensitivity of 53.1% (95-CI 39.2% - 66.5%) and an NPV of 99.2% (95-CI 98.9% - 99.5%) (Table 2, sTable 6 and sTable 7).

**Table 2: Diagnostic performance of CRS and POC-troponin for identifying patients at low-risk**

| | Clinical risk score (≤ 3) | | | | POC-troponin | | | |
|---|---|---|---|---|---|---|---|---|
| **Endpoint** | **N** | **Efficacy*, % (95-CI)** | **Sensitivity, % (95-CI)** | **NPV, % (95-CI)** | **N** | **Efficacy*, % (95-CI)** | **Sensitivity, % (95-CI)** | **NPV, % (95-CI)** |
| **Mortality** | 5199 | 36.1 (34.8 – 37.5) | 93.2 (83.5 – 98.1) | 99.8 (99.5 – 99.9) | 4341 | 89.5 (88.5 – 90.5) | 53.1 (39.2 – 66.5) | 99.2 (98.9 – 99.5) |
| **Mortality + AMI** | 3202 | 32.7 (30.9 – 34.4) | 91.8 (83.0 – 96.2) | 97.3 (89.8 – 99.3) | 2790 | 82.7 (81.2 – 84.2) | 54.0 (49.4 – 58.6) | 93.5 (79.6 – 98.1) |
| **MACE** | 4173 | 33.8 (32.3 – 35.3) | 92.8 (88.7 – 95.5) | 97.2 (92.1 – 99.0) | 3617 | 84.0 (82.7 – 85.3) | 50.9 (34.1 – 67.4) | 91.6 (79.3 – 96.8) |

Abbreviations: CRS; clinical risk score, POC; point-of-care, 95-CI; 95% confidence intervals, AMI; acute myocardial infarction, MACE; major adverse cardiac events, NPV; negative predictive value

* Efficacy defined as the number of patients classified as low-risk. Calculated with exclusion of the study of Camaro et al. (study only aimed at low-risk patients)[54]



For the combined endpoint of mortality and/or AMI, the CRS demonstrated a sensitivity of 91.8% (95-CI 83.0% - 96.2%) and an NPV of 97.3% (95-CI 89.9% - 99.3%). The POC-troponin test showed a sensitivity of 54.0% (95-CI 49.4% - 58.6%) and an NPV of 93.5% (95-CI 79.6% - 98.1%).

For 30-day MACE, the CRS achieved a sensitivity of 92.8% (95-CI 88.7% - 95.5%) and an NPV of 97.2% (95-CI 92.1% - 99.0%). The POC-troponin test had a sensitivity of 50.9% (95-CI 34.1% - 67.4%) and an NPV of 91.6 (95-CI 79.3% - 96.8%) (Figure 1).

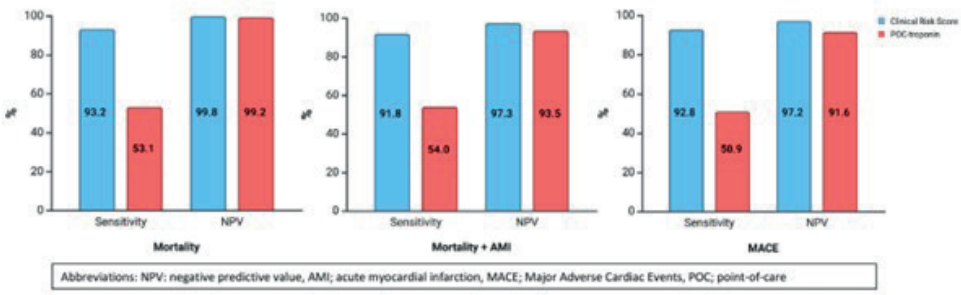



**Figure 1. Diagnostic performance of CRS and POC-troponin. CRS = clinical risk score**

After adjusting the cut-off points for the troponin component of CRS to the LoD (Abbott i-stat TnI) or lowest reported threshold (Roche TnT and Samsung TnI) and classifying patients with a POC-troponin above these thresholds as intermediate/high risk, the sensitivity of the adjusted CRS could be increased to a maximum of 93.8% (95-CI 91.8% – 95.3%) (sTable 8).

Subgroup analyses are presented in the supplementary material (sTables 9 - 12). For the combined endpoint of mortality and/or AMI and MACE, the sensitivity of CRS was lower in females compared to males, while no differences were found in NPV. Sensitivity of CRS increased with age category, with no differences observed in NPV. In the Netherlands, CRS showed higher sensitivity compared to the USA and the UK across all endpoints. When the CRS were adjusted, the sensitivity of CRS in the USA and UK increased.

To assess the potential influence of individual studies on the results, a leave-one-out analysis was performed (sTable 13). No influential studies were identified. A quantitative sensitivity analysis was conducted to evaluate the number of missed events per 1,000 patients for different prevalences and NPV for the endpoints of mortality and MACE. If the prevalence increased or the NPV decreased, the number of missed patients per 1,000 patients also increased (sTable 14 and sTable 15).

No differences in diagnostic performance across all endpoints were observed with respect to the time interval from symptom onset to prehospital risk stratification using the CRS. Using solely POC-troponin according to the study reported thresholds, sensitivity and NPV increased with longer durations between symptom onset and performing prehospital risk stratification (Table 3).

Reducing the CRS low-risk cut-off point from ≤ 3 to ≤ 2 resulted in an improved sensitivity for 30-day outcomes: mortality (93.2% (83.5 – 98.1) to 95.4% (91.0 – 99.7); mortality and AMI (91.8% (83.0 – 96.2) to 97.7% (96.5 – 99.0); and MACE (92.8% (88.7 – 95.5) to 97.7% (96.7 – 98.8)), but the proportion of patients classified as low-risk correspondingly reduced by over in each group. Conversely, elevating CRS low-risk cut-off point from ≤3 to ≤4, identified more patients as low-risk but significantly reduced diagnostic sensitivity (Table 4).

**Table 3: Influence of time between symptom onset and risk stratification by CRS and POC-troponin**

| **Clinical Risk Scores** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Mortality** | | | **Mortality + AMI** | | | **MACE** | | |
| **Time duration** | **N=2342** | **Sensitivity, % (95-CI)** | **NPV, % (95-CI)** | **n=1652** | **Sensitivity, % (95-CI)** | **NPV, % (95-CI)** | **n=2051** | **Sensitivity, % (95-CI)** | **NPV, % (95-CI)** |
| **< 1 hour** | **n=481** | 75.5 (51.0 – 100) N= 4/4* | 98.9 (97.7 – 100) | **n=321** | 90.2 (83.7 – 96.8) | 92.9 (88.0 – 97.7) | **n=413** | 92.9 (88.0 – 97.7) | 94.9 (91.5 – 98.4) |
| **< 2 hours** | **n=915** | 86.1 (72.2 – 100) N= 10/10* | 99.4 (98.8 – 100) | **n=645** | 89.4 (84.7 – 94.1) | 91.5 (87.7 – 95.3) | **n=801** | 91.0 (87.2 – 94.8) | 92.8 (89.7 – 95.8) |
| **< 3 hours** | **n=1198** | 87.1 (74.1 – 100) N= 11/11* | 99.6 (99.1 – 100) | **n=850** | 90.3 (86.1 – 94.5) | 94.1 (91.5 – 96.7) | **n=1042** | 92.0 (88.7 – 95.3) | 94.7 (92.5 – 96.9) |
| **> 3 hours** | **n=1144** | 83.6 (68.5 – 98.7) N= 13/14* | 99.4 (98.8 – 100) | n=802 | 90.8 (86.2 – 95.5) | 96.4 (94.5 – 98.3) | **n=1009** | 91.6 (87.8 – 95.3) | 96.1 (94.3 – 97.9) |
| **POC-troponin** | | | | | | | | | |
| **< 1 hour** | **n=408** | 37.2 (4.6 – 69.9) N= 1/4* | 98.7 (97.6 – 99.7) | **n=293** | 34.8 (23.3 – 46.3) | 82.6 (78.0 – 87.1) | **n=360** | 29.2 (19.8 – 38.6) | 80.4 (76.1 – 84.7) |
| **< 2 hours** | **n=786** | 57.2 (31.3 – 83.2) N= 6/10* | 99.1 (98.5 – 99.8) | **n=592** | 38.3 (30.6 – 46.0) | 81.4 (78.0 – 84.8) | **n=702** | 33.8 (27.2 – 40.4) | 78.2 (74.9 – 81.5) |
| **< 3 hours** | **n=1043** | 53.4 (28.0 – 78.7) N= 6/11* | 99.2 (98.7 – 99.8) | **n=789** | 41.3 (34.1 – 48.5) | 84.5 (81.8 – 87.2) | **n=928** | 36.0 (29.9 – 42.2) | 81.2 (78.4 – 83.9) |
| > 3 hours | **n=1012** | 56.3 (32.0 – 80.7) N= 7/12* | 99.2 (98.6 – 99.7) | **n=750** | 67.7 (59.8 – 75.6) | 93.1 (91.1 – 95.0) | **n=908** | 60.5 (53.5 – 67.6) | 90.1 (88.0 – 92.3) |

Abbreviations: CRS = clinical risk score, POC = point-of-care, 95-CI = 95% confidence intervals, AMI = acute myocardial infarction, MACE = major adverse cardiac events, NPV = negative predictive value.

***** In cases when denominator is less than 20, the number of test- and disease positive persons are added

**Table 4: Influence of adjusting the cut-off value of CRS for identifying patients at low-risk**

| | Mortality | | | Mortality + AMI | | | MACE | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cut-off value** | **Sensitivity, %** | **NPV, %** | **Efficacy*, % (95-CI)** | **Sensitivity, %** | **NPV, %** | **Efficacy*, % (95-CI)** | **Sensitivity, %** | **NPV, %** | **Efficacy*, % (95-CI)** |
| **≤ 2** | 95.4 (91.0 – 99.7) | 99.7 (99.4 – 100) | 17.1 (16.1 – 18.2) | 97.7 (96.5 – 99.0) | 98.2 (97.2 – 99.2) | 15.0 (13.7 – 16.4) | 97.7 (96.7 – 98.8) | 97.8 (96.9 – 98.8) | 15.8 (14.7 – 17.0) |
| **≤ 4** | 79.4 (69.6 – 89.3) | 99.6 (99.4 – 99.8) | 56.3 (54.9 – 57.7) | 80.5 (76.9 – 84.0) | 94.9 (93.9 – 95.9) | 52.6 (50.8 – 54.5) | 79.5 (76.6 – 82.4) | 93.7 (92.7 – 9.,6) | 53.6 (52.0 – 55.2) |

Abbrevations: CRS = clinical risk score, AMI = acute myocardial infarction, MACE = major adverse cardiac events, NPV = negative predictive value

* Efficacy defined as the number of patients classified as low-risk. Calculated with exclusion of the study by Camaro et al. (study only aimed at low-risk patients)[8]

## Discussion

This is the first international IPD meta-analysis, based on prospective data from 5,239 patients, serving as a benchmark for safety in patients with suspected NSTE-ACS. We demonstrated that in well-trained EMS systems similar to those included in this study, HEART-derived CRS, including POC-troponin, accurately identify patients with a very low 30-day mortality and MACE risk. This approach outperforms prehospital risk stratification based solely on POC-troponin measurement and is not influenced by the time interval between symptom onset and risk stratification. Lowering the cut-off value of the CRS to classify patients as low-risk can further increase sensitivity, though this comes at the cost of reduced efficacy. However, implementation in other healthcare systems requires additional validation, as NPV depends on baseline event rates and EMS structure.

*Diagnostic performance of CRS and POC-troponin*

As previously mentioned, current risk stratification within the EMS is mainly based on clinical history and ECG findings and does not provide additional diagnostic value in suspected NSTE-ACS patients.[6] Our IPD meta-analysis included all available prospective EMS studies worldwide and our results show that prehospital risk stratification using CRS and POC-troponin testing both yield very high NPVs. However, sensitivity is higher when using CRS compared to POC-troponin alone and these findings are consistent with previous studies.[6,16] The time interval between symptom onset and risk stratification appears to have little impact

when using CRS. We hypothesize that this is because CRS incorporates multiple component evaluated by EMS paramedics, including clinical history, ECG findings, and cardiovascular risk factors. Patients classified as low-risk using CRS are less likely to exhibit a history suggestive of ACS or significant ECG abnormalities, making the likelihood of an elevated troponin value inherently low. Within the subgroup analyses, lower sensitivity of the CRS was found in women and in younger age categories. The lower sensitivity is likely due to the statistical method used (Wald method) in combination with the low event rate. Previous studies have not found any differences in the diagnostic performance of HEART-derived CRS between men and women.[27] Nevertheless, this difference in sensitivity warrants further investigation in future studies. Furthermore, it is important to keep in mind that the NPV depends on disease prevalence, and that sensitivity may vary across populations. Therefore, the diagnostic performance of the CRS in classifying patients as low risk may differ between populations and clinical settings (GP, EMS, ED).

The diagnostic performance of CRS and POC-troponin testing could be further optimized in the future. All studies included in this IPD meta-analysis used conventional troponin assays, as high-sensitivity assays were not yet available for POC-analyzers at the time of patient enrollment. Compared to high-sensitivity troponin assays, conventional troponin assays have lower sensitivity and precision, particularly at low concentration ranges, and should therefore always be used in combination with a CRS.[28] Previous research comparing prehospital CRS performance using conventional versus a high-sensitivity troponin assay in-hospital did not result in a patient risk reclassification, although the POC troponin cut-off values chosen in this study were high.[29] Research has also shown that lowering the cut-off value for the troponin component (high-sensitivity or conventional) within the CRS improves sensitivity, a trend also observed in our results (sTable 8).[30,31] Current studies utilizing high-sensitivity troponin assays are ongoing and may further enhance sensitivity and NPV of CRS (URGENT 2.0 study, NCT04904107). Therefore, our results can be used as baseline evidence pending the outcomes of ongoing studies using POC high-sensitivity troponin assays. Additionally, the introduction of AI in prehospital risk stratification and ECG analysis could potentially improve the diagnostic performance of CRS in the near future.[32]

*Feasibility of prehospital risk stratification*

This IPD meta-analysis included studies conducted in the USA, the UK, and the Netherlands. In these countries, approximately 8 million people per year attend the ED because of chest pain.[8,13,33,34] Previous studies have demonstrated the feasibility of training EMS paramedics to use HEART-derived clinical risk scores for prehospital risk stratification in patients with suspected NSTE-ACS, showing very strong overall inter-operator reliability.[8,10-14,35] Such training enables paramedics to systematically assess chest pain patients and provides them with a structured tool to optimize diagnostic pathways for suspected NSTE-ACS within the EMS.

*Potential impact on emergency department overcrowding and system efficiency*

Patients with chest pain suspected for NSTE-ACS may present to a GP, EMS or ED. Therefore, they contribute significantly to ED overcrowding and comprise a major burden on healthcare resources.[1] Improving prehospital pathways for patients classified as low-risk could improve system efficiency and decrease emergency department overcrowding. As safety and accuracy levels are well defined for rule-out and rule-in algorithms at the ED, it is not well determined for the prehospital setting. Evaluations that balance safety with the clinical and health economic impact of these new prehospital strategies are required.[36]

Prehospital healthcare systems differ very significantly across countries, and the feasibility and safety of implementing diagnostic pathways depends on the structure of the healthcare organization. Therefore, it is not possible to generalize these results to all other healthcare services. In countries with highly trained EMS paramedics and networks involving general practitioners to manage patients who do not require emergency department referral, approximately 20-25% of patients with chest pain are already left at home or transferred to the GP.[37,38] In such countries, studies have demonstrated that using CRS to identify a significant proportion of patients as low-risk, and avoiding ED transport, can alleviate ED overcrowding (by not conveying an additional 10% of the patients to the ED) and potentially improve patient outcomes, while no differences in MACE rates were found.[8,12,23,38] However, to safely rule-out MACE, a second assessment by EMS paramedics was required in 25% of patients one study.[12] In these healthcare organizations, the high sensitivity and NPV of prehospital risk stratification using CRS, as identified in our meta-analysis, supports its implementation for ruling out suspected NSTE-ACS patients.

For healthcare organizations requiring a more conservative approach to non-conveyance of patients with suspected NSTE-ACS, lowering the CRS cut-off value for identifying low-risk patients could be a solution. Lowering the CRS cut-off value to 2 could increase sensitivity to 98%, while still avoiding hospital transfer for approximately 16% of patients. In systems where prehospital diagnostic pathways do not permit leaving patients at home or transferring them to general practitioners, CRS-based prehospital risk stratification can still provide valuable information for guiding conveyance decisions between local and more specialized hospitals and improving and expediting in-hospital ED diagnostics. This approach could lead to shorter hospital stays, improved in-hospital logistics, fewer invasive diagnostic procedures, and reduced healthcare costs.[13,18,39]

*Health-economic implications*

The ARTICA study found that avoiding ED transfers for low-risk patients reduces healthcare costs by €717 ($ 753) per patient within one year.[40] While the TRIAGE-ACS study found that healthcare costs could also be reduced in patients classified as high-risk for having NSTE-ACS by transferring these patients directly to a hospital with 24/7 PCI facilities.[13] Implementing

these novel prehospital pathways by using CRS for risk stratification could result in healthcare cost savings of hundreds of millions of euro's/dollars annually. [18,40]

Limitations

First, not all studies provided raw data on the different types of admission diagnoses. In some studies, only information on whether a patient had an AMI or ACS at hospital admission was available, without specific data on the type of ACS. Mortality status within 30 days of inclusion was available in all patients, however, the event rate was relatively low (1%). Secondly, different POC-analyzers and troponin assays were used across the studies, resulting in varying cut-off values for scoring the troponin component, which could have influenced the results. Using the available data, we attempted to standardize the scoring of the troponin component of the CRS across the included studies (sFigure 7). Furthermore, the troponin assays used were conventional and not high-sensitivity assays. At last, only HEART-derived CRS were used for our meta-analysis. As mentioned earlier, T-MACS is also available for risk stratification of suspect NSTE-ACS. Unfortunately, studies investigating this score were not eligible for inclusion in our analysis as the troponin component T-MACS was not evaluated by EMS paramedics in the prehospital setting.

## Conclusion



In well-trained EMS systems, where prompt and accurate follow-up of low-risk patients is possible, HEART-derived clinical risk scores effectively identify patients with a very low risk of 30-day mortality and MACE. However, implementation in other healthcare systems requires additional validation, given the variations in healthcare structure, risk stratification processes, and follow-up capabilities.

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# Chapter 8

## Prehospital assessment of Patients with Suspected Acute Coronary Syndrome: A Concise Clinical Summary for Prehospital Triage in the Netherlands

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*A concise document has been published as a "Leidraad" at the website of Zorgevaluatie & Gepast Gebruik (ZE&GG)*
*https://zorgevaluatiegepastgebruik.nl/implementatieagenda/rms-pht-001/prehospitale-triage-bij-pijn-op-de-borst*

## Abstract

This document describes risk stratification tools for patients with suspicion of acute coronary syndrome (ACS) in EMS (ambulance) and primary care (general practitioner (GP)) setting. Although validated clinical decision rules (e.g. modified HEART or preHEART score) are commonly used in EMS setting, they are not yet well-validated in GP setting. Clinical decision rules should preferably be based on high sensitivity point-of-care (POC) troponin, both in ambulance and primary care settings.

Patients identified as low risk may remain safely at home if close monitoring and dedicated follow-up is present. The ambulance professional may consider referral to the GP when appropriate, though, this is not required for all low-risk cases. Patients with an intermediate risk score should be considered for hospital referral. This decision should take into account overall clinical assessment, regional protocols, and (where applicable) shared decision-making in consultation with hospital physician. Implementation requires interdisciplinary collaboration, quality assurance, and further research to address remaining knowledge gaps.

## Introduction

The organization of prehospital care in the Netherlands has unique features that contribute to equal access of both prehospital and hospital care for all citizens. Depending on urgency of symptoms, patients may receive ambulance assessment, general practitioner (GP) or self-care advice. For those evaluated in person, further triage occurs at patient's bedside. Dutch ambulance personnel are able to perform and interpret an ECG, while GPs primarily rely on history taking and clinical judgement. Both professions follow established protocols and guidelines.[1,2] Patients with typical symptoms and a high a-priori risk are referred directly to (cardiac) emergency departments (ED). However, the majority present with less defined symptoms, increasing the risk of missing a serious (cardiac) diagnosis. To mitigate this risk, healthcare professionals often triage defensively, which contributes to overcrowding of EDs. ED overcrowding is a growing public health concern world-wide and negatively impacts affects access to urgent or emergent care.[3,4] In the Netherlands, several initiatives have explored how to leverage the strengths of the prehospital care system to improve risk stratification for patients with suspected acute coronary syndrome (ACS), many of whom would otherwise be transported directly to EDs.

This paper provides concise clinical guidance for current and future prehospital triage of patients with suspected ACS across the Netherlands.

## Rationale and Background of Prehospital Risk Assessment of Acute Chest Pain



*Scope of the problem*

In the Netherlands, approximately 1.5 million high-urgency ambulance transfers were carried out in 2023, of which nearly 240.000 were related to acute cardiac presentations.[5] In Dutch primary care, chest pain accounts for 1.3%, translating to approximately 850.000 consultations annually.[6,7] ED visits typically result in extensive diagnostic work-up and prolonged in-hospital stays. Ultimately, only about 10% of acute chest pain presentations are diagnosed with ACS, while the vast majority are classified as non-cardiac chest pain (NCCP).

*Health care challenge: balancing efficiency and safety*

Validation of risk assessment instruments that enable prehospital healthcare professionals to make adequate triage decisions – while maintain a balance between *efficiency* and *safety* - remains challenging. Current GP assessments are estimated to misclassify 10-20 % of ACS cases as NCCP.[7-10] A national survey among Dutch GPs reported an acceptable miss rate below 2%.[11] Based on these data, we recommend a minimum sensitivity of 98% for prehospital risk assessment tools in patients with suspected ACS. This aligns with international consensus

regarding acceptable miss rates for major adverse cardiac events (MACE), usually defined as all-cause death, ACS or unplanned revascularization within 30 days.[12]

Beyond safety, there is need to improve efficiency and consequently an adequate *specificity* of prehospital risk assessment. Simply, referring all patients with chest pain to EDs is unaffordable, both in terms of finances and personnel.

*Economic Potential of Prehospital Risk Stratification*
According to the ARTICA trial, the added value of its pre-hospital rule-out strategy could amount to an estimated €50 million per year in the Netherlands .[13,14] The POB HELP-study hypothesized that if a decision rule is implemented in 50% of general practices, and assuming a 10% reduction in referrals, this could potentially lead to an annual cost reduction of €31 million.[15]

Therefore, it is important to effectively and safely identify chest pain patients who are at low-risk for ACS in prehospital setting and prevent or at least diminish referral of NCCP to EDs, while maintaining a high level of safety.

## Decision rules for Acute Chest Pain in Prehospital Settings

Clinical decision rules, such as HEART (History, ECG, Age, Risk Factors, Troponin)[16], EDACS[17] , and T-MACS[18] are commonly used at EDs to risk stratify patients with chest pain. Evolution of point-of-care (POC) troponin tests has driven adaptation of these clinical decision rules from ED to *prehospital* scenery. These clinical decision rules also face specific challenges in the prehospital environment.[13,14,19-24] As such, new clinical decision tools have been developed specifically for *prehospital* use, in which EMS setting (ambulance) and primary care (GPs) are discussed separately in upcoming paragraphs.

## Decision rules in EMS setting

The modified HEART and preHEART (prehospital HEART) score, both derived from the original HEART score, are most frequently studied decision rules in EMS setting.[13,14,19-23] Differences between these scores are summarized in *Table 1*. Using the HEART score or modified HEART score, patients with 0-3 points are classified as low risk for MACE, 4-6 points as intermediate, and 7-10 points as high risk.[25] Currently, limited evidence is available regarding *direct* comparison between different prehospital decision rules in EMS, however both preHEART and HEART scores have better overall diagnostic performance compared to T-MACS and sole POC-troponin measurement.[20]

A recent meta-analysis of 15 studies highlighted the efficacy and added value of prehospital clinical decision rules with POC troponin testing, compared to relying solely on conventional POC-troponin measurement.[22] Even in patients with short duration of symptoms ("early presenters" with onset of chest pain within 2 hours before EMS contact), decision rules incorporating troponin have shown good diagnostic performance in EMS setting.[13,14,21] No safety concerns have been reported to date, although larger trials are currently underway.[26] Ongoing EMS studies will further evaluate prehospital risk stratification using newer, high sensitivity (hs)-POC troponin assays (Table 2).

Figure 1 illustrates the **current** consensus regarding prehospital risk assessment in patients presenting with chest pain. The first step in risk stratification is to exclude patients with NCCP and promptly identify those with very high-risk features of ACS, such as cardiogenic shock or ST segment elevation.[27] For these patients, immediate hospital transfer is indicated. In <u>all</u> other cases, clinical decision rules incorporating (hs)-POC troponin- such as modified HEART or preHEART- are recommended to stratify patients into low-risk or intermediate/high-risk categories.

Despite growing evidence supporting the safety of leaving <u>low-risk</u> patients at home, it is important to note that studies such as ARTICA and FamouS Triage were not primary powered to assess safety.[13,21] In other words, although initial data suggest that it may be safe to leave low-risk patients at home, such strategy requires a structured *implementation* approach. This includes *appropriate training of ambulance personnel and systematic monitoring* of patients who are not transported to hospital. A national-wide registry could play a pivotal role in collecting and structuring these data, enabling future quality controls and innovation. This strategy should be endorsed by all directly involved health care professionals. A more detailed guidance document for implementation and monitoring by Ambulancezorg Nederland, is currently available.[28] At present, both intermediate and high risk patients in the EMS setting should continue to be considered for hospital *transfer* to enable further diagnostic evaluation and potential treatment.



## Decision rules in <u>primary care</u>

Patients who present to their GP with chest pain differ from those seen by EMS in terms of symptom characteristics and overall risk for ACS. Therefore, risk stratification tools must be validated specifically for use in primary care setting. Several risk scores have been evaluated in this context[29], most notably the Marburg heart Score. Although this score demonstrates high negative predictive values, it does not meet the required safety standards in terms of accepted miss rate or false negative rate of <2%.[30] The HEART score has been assessed in a large cohort of patients presenting to urgent primary care. However, it did not outperform a standalone hs-troponin assay combined with clinical judgment in patients presenting

≥3 hours after symptom onset.[31,21] In Dutch primary care, only one study has evaluated a simplified version of the HEART score in which the troponin component was either omitted or replaced by GP's clinical intuition ("gut feeling"). These modified versions showed promise but require further validation.[33] With the introduction of POC troponin, two ongoing studies are currently evaluating strategies including a single hs-POC troponin measurement in daytime general practices (POB-HELP) and out-of-hours primary care settings (HEART-GP).[15,33]

## Cardiac Troponin for Risk Assessment of Chest Pain

Within aforementioned clinical decision rules, cardiac Troponin (cTn) plays an important role. CTn is a serum biomarker with high diagnostic accuracy for myocardial necrosis and hs-cTn is the cornerstone of the universal definition of myocardial infarction (MI).[34]

Two important analytical performance characteristics are:
- The limit of detection (LOD) for quantitative results.
- The 99th percentile in a normal reference population.

Hs-cTn tests detect values above the LOD in ≥50% of healthy individuals and measure the 99th percentile with coefficient of variation of ≤10%.[35] These tests are routinely used in hospitals (Table 3, supplementary material). Recently, POC (hs)-cTn tests (Table 4, supplementary material) have emerged, which do not require central laboratory infrastructure and significantly reduce time-to-diagnosis, enabling their use in (pre)hospital settings. Cullen et al. recently provided a comprehensive overview of potential applications of POC hs-cTn assays, including prehospital environment.[24] Table 5 summarizes available POC (hs)-cTn assays suitable in EMS setting. The introduction of POC hs-cTn testing in prehospital settings can improve safety (quickly ruling in MI) and efficiency (avoiding unnecessary referrals). Clinicians have faced a conflict between POC speed and central lab accuracy.[36] Combining them both in a POC hs-cTn assay is the next step to enhance prehospital risk assessment quality and safety.

There is growing evidence that conventional (non-hs) POC cTn T (Cobas h232) and I (iSTAT by Abbot) tests – when incorporated in a clinical risk tools – may help rule out MI in low-risk patients.[37-41] Current efforts evaluate various POC hs-cTn I devices (Siemens' Atellica VTLi, Quidel's TriageMeter Pro, LSI Medience's Pathfast, Abbott i-STAT), addressing logistical challenges in standardizing assays across single rule out strategies in prehospital care. Siemens' Atellica VTLi hs-cTnI using a whole blood cut-off value near the LOD of 4 ng/L, has already demonstrated safety and reliability for ruling out myocardial ischemia in ED settings.[42] Its application in prehospital care appears promising for ruling out ACS.[15,43]

Before implementing POC hs-cTn in prehospital settings, several requirements must be met: validated cut-off values, ISO15189-compliant laboratory support, competent handling by healthcare professionals, and standardized devices. Detailed information is provided in supplementary materials (S1).

Currently, regional differences in POC troponin analyzers are present across the Netherlands. Regions currently using non-high-sensitivity POC analyzers are encouraged to transition to hs-POC devices to align with best practices and improve diagnostic accuracy.

## Prehospital Clinical Context combined with Other Patient Data

Beyond clinical decision rules and POC troponin testing, prehospital risk assessment should centrally incorporate the patient's clinical context, symptom presentation and individual preferences. Shared decision-making plays a crucial role in this process, especially when hospital referral is not straightforward.

The HART-c study evaluated a prehospital triage strategy approach that combined patient data with remote cardiologist consultation. Compared to a historical control group, this approach showed a significantly increased proportion of patients who remained at home (11.8% vs. 5.9%) with a low MACE rate of <1%.[44]

Although this strategy may be beneficial for patient prehospital risk assessment, particularly in cases where hospital referral is not straight forward, such comprehensive risk assessment method requires several preconditions before it can be implemented. Most notably, the integration of shared data platforms and remote hospital consultation is still a future perspective and requires regional endorsement. Establishing a *regional triage network* among health care providers is essential to facilitate collaboration and ensure continuity of care. In addition, questions regarding professional responsibility and liability must be addressed- particularly in cases where patients are not referred to the hospital. In principle, all healthcare professionals involved in the risk assessment share responsibility for patient outcomes, with primary responsibility resting with the provider physically present at prehospital scene. Finally, structural reimbursement for remote hospital consultation must be formalized. The Dutch healthcare authority (NZa) recently introduced a nationwide reimbursement method ("Facultatieve prestatie") for remote consultations in prehospital (ambulance) settings.[45]

## Organization of Prehospital Risk Assessment of NSTE-ACS in Regional Networks

The aforementioned triage networks can only be established through close collaboration between EMS, GPs, ED's, clinical chemists, patient representatives, and cardiologists of *both PCI and non-PCI centers*. In the Netherlands, such collaborations already exist for ST elevation acute coronary syndrome (STEMI-ACS) patients.[46] Expanding existing networks should include patients presenting with chest pain and suspected NSTE-ACS.

The proposed extension of regional NSTE-ACS networks should include:

- Recommendations already supported by current guidelines:
  - Clearly defined geographic areas of responsibility.
  - Shared written protocols for prehospital risk assessment.
  - Remote technologies enabling prehospital ECG interpretation by dedicated physicians.
- New recommendations based on recent EMS studies:
  - Regional consensus and alignment of implementation of prehospital risk assessment, including:
    - Exclusion of patients with very high-risk ACS criteria or unstable vital signs (according to national ambulance and ESC protocols)
    - Inclusion of self-referrals or GP referrals (depending on regional arrangements).
    - Inclusion of "early presenters" (onset of chest pain / complaints within 2 hours) when using hs-cTn embedded in a clinical decision rule and followed by appropriate monitoring.
  - Same day and "closed-loop" communication between EMS and GP in cases were care is transferred to GP (e.g. very low-risk chest pain).
  - Monitoring the quality of prehospital risk assessment implementation, including:
    - EMS documentation of the algorithm used and corresponding results (troponin levels and risk score).
    - Quality control of patient outcome

## Current State and Future Perspectives

Beyond current ESC guidelines and LPA[2,27], this is the first document that explicitly recommend the use of *clinical decision rules* –such as the *modified HEART or preHEART score*- with *(high sensitivity) POC troponin testing* in patients with chest pain and suspicion of ACS in prehospital setting. These tools enable effective risk stratification by distinguishing between low risk and intermediate/high patients.

In addition to identify low risk individuals, the modified HEART and preHEART scores can also stratify patients with intermediate and high risk categories. Although, a recent study suggests that high risk patients should be transported directly to a PCI center to optimize patient routing[47], this document can only recommend that transfer decisions for intermediate or high risk patients be based on local arrangements between GPs, EMS and health care providers from *both PCI and non-PCI* centers.

Future perspective in primary care pathway

In patients with suspected ACS, GPs are expected to use hs-POC-troponin testing.[31] Embedding hs-POC troponin within clinical decision rules (e.g. modified HEART) is preferred, as this approach structurally integrates patient symptoms, cardiovascular risk factors and ECG findings into clinical judgements. However, routine ECG acquisition in general practice remains variable and depends on several factors, including practice setting, patient population and the level of training. In patients with a high clinical suspicion of ACS, troponin testing is encouraged, not for rule-out purposes, but to provide a baseline (T0) measurement. We anticipate that hs-cTn POC devices will be readily implemented in out-of-hours GP cooperatives and in large daytime practices, particularly those located in communities with high cardiovascular disease burden. In practices that opt not to use a hs-cTn POC device, we propose referral to the EMS pathway. Figure 2 provides a schematic overview of the proposed future primary care pathway.

Future perspective in EMS pathway

Figure 3 presents a proposed ***future*** risk assessment pathway for chest pain patients in **EMS** setting using a clinical decision rule in which hs-POC troponin testing is embedded. Initially, patients with very high-risk criteria or those with a clear NCCP should be identified and excluded for further risk stratification. For all other patients, prehospital triage should be supported by structured risk assessment. Within clinical decision rules – such as the modified HEART or preHEART score-, a hs POC troponin measurement can be performed. According to current guidelines[27] the use of hs-cTn is actually unavoidable in this context.

Patients with **low** risk score and negative hs-troponin may remain at home, provided EMS clinical judgment support a non-cardiac origin of chest pain and *no* other acute condition is present. In cases of uncertainty (predominantly **intermediate** risk patients), remote consultation with a hospital physician (HART-c study)[44], may be considered. This approach could significantly improve outcomes in this group, where MACE percentages range from 13% to 20%.

For **high** risk patients, the TRIAGE ACS study has evaluated the feasibility and cost-effectiveness of prehospital risk assessment and direct transfer to a PCI center in patients at

high risk for NSTE-ACS.[47] Ongoing research aims to further establish the evidence supporting the added value of this strategy.

For referred patients, the GP or ambulance personnel can collect the initial blood sample (T0), allowing only one additional hs-cTn test at the ED (T1), thereby reducing ED length of stay [48]. However, this strategy requires either the use of the same hs-cTn POC device in both EMS and hospital setting or analysis hs-cTn measurement of the T0-sample on the hospital's central lab analyzer.

## Reimbursement of Prehospital Risk Assessment

Multiple studies have demonstrated that prehospital risk assessment systems—designed to reduce unnecessary hospital transfers by ruling out ACS—can lead to substantial healthcare savings.[13,14,21,47] These systems result in fewer patients being transported to hospitals, thereby reducing the need for diagnostics procedures and treatment efforts.[48]

From 2026 onwards, prehospital risk assessments conducted by ambulance professionals will be structurally reimbursed.

## Implementation and Evaluation

Effective implementation of prehospital risk stratification using POC devices requires structured training of EMS and primary care personnel. This training should cover the use of clinical decision rules, patient assessment and interdisciplinary collaboration. Ongoing education and structured quality assurance- supported by registry-based monitoring- are essential to maintain diagnostic sensitivity and ensure consistent application of the pathway.

It is recommended to evaluate this proposed pathway on an annual basis per region. As part of the implementation strategy, both daytime GP visits and out-of-hours GP consultations should be monitored to assess impact and identify areas for improvement. Regional coordination bodies, such as the Acute Care Regions (AZOs) and the Regional Consultation on Acute Care (ROAZ), may serve a facilitating or coordinating role in this context.

## Knowledge Gaps

Prehospital risk assessment of patients with suspected ACS still faces several knowledge gaps. A direct comparison between existing clinical decision rules has not yet been conducted, and future studies are needed to determine which score is most suitable in prehospital setting. The definition of low risk (modified HEART or preHEART ≤ 3) requires further clarification. Increasing the threshold to a score of 4, when combined with an embedded hs-POC troponin

measurement, may allow more patients to be managed outside the hospital. To enhance the safety of ruling out ACS, one could consider implementing serial (second) troponin on site by EMS personnel.[21] However, diagnostic value of serial hs-POC troponin measurements in prehospital setting remains uncertain.[49] Additionally, integration of machine learning and artificial intelligence (AI) tools (telemedicine, AI recognition of ECG's at risk for NSTE ACS) may further improve the positive predictive value of prehospital risk assessment in patients with chest pain.[50]

## Summary

1. In EMS settings, validated clinical decision rules *including* handheld hs-cTn POC troponin are recommended for risk assessment and triage of chest pain patients with suspected ACS. The modified HEART and preHEART scores are most extensively studied in the literature.

2. In EMS settings, the use of modified HEART or preHEART score with high sensitivity POC troponin should be considered (expert opinion). Regions currently using non-high-sensitivity POC analyzers are encouraged to transition to hs-POC devices to align with best practices and improve diagnostic accuracy.
3. Withholding hospital referrals of patients at low risk (modified HEART or preHEART score ≤3) appears to be cost effective. Safety of this strategy has not yet proven in adequately powered clinical trials. A nationwide implementation strategy with monitoring of patients left at home is being initiated (literature and expert opinion).

4. Patients at intermediate or high risk for ACS should be considered for transfer to a (cardiac) ED - either PCI or non-PCI center- depending on local arrangements (literature and expert opinion).

5. Studies are ongoing to determine whether the use of clinical decision rule and/or hs POC troponin testing in primary care adds value compared to GP clinical judgment alone (literature).

6. Dedicated regional risk assessment networks remain the cornerstone of safe and effective prehospital triage. Shared data and collaborative decision-making between prehospital and hospital professionals may further enhance the quality and safety of prehospital risk assessment (literature and expert opinion).

## Conclusions

Use of validated decision rules – such as modified HEART or preHEART- with POC troponin testing is recommended for risk stratification in patients with suspected ACS. Hs-POC troponin is the preferred biomarker in both EMS and primary care, although its clinical utility, as well as that of decision rules, remains under investigation. Withholding hospital referral for low-risk ACS patients may be cost-effective but should only be considered with proper monitoring and structured follow-up, given limited safety data available. Hospital transfer should continue to be considered for all patients at intermediate or high risk, either directly to PCI-center or to a non-PCI center depending on local arrangements.

## Acknowledgements

We acknowledge contribution of J.W. Schoones regarding appropriate reference managing.

## Supplementary Materials (S1)

### Preface

Safe and efficient prehospital risk assessment is crucial to ensure that our limited healthcare resources are adequately allocated to those that need our care most. The first multidisciplinary National Working Group for prehospital triage was established to address the growing urgency and importance of harmonising prehospital cardiac risk assessment in order to improve patient care and control increasing health care demand.

This document focuses on acute 'chest pain' or 'chest discomfort', as this is one of the most important reasons for patients to seek medical care. The holy grail herein lies in finding risk assessment tools that improve both efficiency *and* safety by identifying patients at low risk for acute cardiac events. This consensus document provides an overview of the status on prehospital risk assessment of chest pain with suspected ACS. The working group as well as the independent review committee consisted of medical professionals involved in risk assessment of cardiac patients.

The working group has accomplished a critical review of the current literature concerning prehospital risk assessment of chest pain patients with suspicion of ACS, particularly involving (validated) risk assessment decision rules, (high sensitivity) point-of-care troponin assays and triage networks. Beyond a review of the literature, expert opinions have been integrated in this consensus document. The document is reviewed by members of HartVaatHAG and experts from the National Society of Clinical Chemists (NVKC) at Zwolle and Leiden University Medical Centre.



### HEART score

The HEART score is an acronym of its components: History, ECG, Age, Risk factors and Troponin. Each of aforementioned parameters can be scored with a certain level of points (0-2), yielding a total amount of 10 points, wherein a higher score reflects a high risk for MACE. Modifications of the original HEART score have led to the development of the *modified* HEART and *pre*HEART scores.

### Literature Search

In cooperation with a trained librarian, a search strategy for PubMed was composed. Three queries were compiled. The first query consisted of the combination of two subjects: prehospital risk assessment and/or point-of-care troponin and chest pain. The second query consisted of the combination of two subjects: prehospital risk assessment or point-of-care

troponin and acute coronary syndrome and/or myocardial infarction - both subjects were searched as the main subject of the articles. The third query consisted of the combinations of three components: chest pain, diagnosis, and guidelines - alle three subjects are searched as being the main subject. Case reports and meeting abstract references were excluded. Only articles published from 2014 and onwards were selected.

For the different concepts, all relevant keyword variations were used, not only keyword variations in the controlled vocabularies of the various databases, but the free text word variations of these concepts as well. The first query of the search strategy was optimized for the three additionally consulted databases: Embase (OVID version), Web of Science (Core collection) and Cochrane Library. Three permutations of the search were created: a search for RCTs, a search for systematic reviews, and a search with no study type limit. The results were managed by EndNote. The search was executed on september 6, 2024.

## Cardiac Troponin

The optimal cut off value per POC hs-cTn device for rule out of low risk ACS patients in a prehospital setting has to be defined. Using a cut off value near the LOD (high diagnostic sensitivity) enhances safety, whereas efficiency is served by a slightly higher cut off value – that includes intermediate measurement uncertainty – in order to rule out myocardial ischemia in a substantial number of patients. Besides cut-off values, other factors affecting diagnostic performance are the a priori risk, the time interval between symptom onset and testing, and patient factors (age, sex).

Quality standards and analytical performance requirements for hs cTnT/I tests according to the International Federation of Clinical Chemistry (IFCC) guidelines are high. It is therefore recommended that the entire process of POC hs-cTn should be *supported by an ISO15189 accredited laboratory*. POC devices should preferably be firm and handheld. Furthermore, it's imperative to ascertain the robust diagnostic reliability of POC tests, taking into account the variability in measurement accuracy across devices and the necessity for stringent quality controls as per laboratory standards.

Operators of POC devices must be *competent* in correctly operating the devices, collecting patient material and ensuring the quality of the entire procedure. Recording of test results should preferably be automatic (electronic patient file) and traceable to the (certified) operator.

Application of (preferably uniform) POC devices throughout the acute prehospital care pathway would further improve risk assessment of patients with chest pain. The use of POC testing in and out of the hospital could lead to serial testing to detect an increase/decrease in cTn, potentially shortening the time to diagnosis and treatment.

**Table 1. Clinical Decision Rules**

| Variables of the different clinical risk scores and points awarded | | | |
|---|---|---|---|
| | **HEART** | **Modified HEART** | **preHEART** |
| **History** | Clinical suspicion (mildly suspicious = 0, moderately suspicious = 1, highly suspicious = 2) | | |
| **ECG** | ST-deviation[a] = 2<br>Non-specific repolarization abnormalities [b] = 1<br>Normal = 0 | | |
| **Age** | ≥ 65 years = 2<br>≥ 45 years and < 65 years = 1<br>< 45 years = 0 | | ≥ 70 years = 2<br>≥ 40 years and < 70 years = 1<br>< 40 years = 0 |
| **Risk factors** | ≥ 3 risk factors[c] or medical history of atherosclerotic disease = 2<br>1-2 risk factors = 1<br>0 risk factors = 0 | | Male gender = 2<br>Female gender = 0 |
| **Central laboratory Troponin** | ≤ Normal limit = 0<br>1– 3 x normal limit = 1<br>≥ 3 x normal limit = 2 | Depending on analyzer and study protocol | |
| **POC-troponin** | Depending on analyzer and study protocol | | |

Abbreviations: ECG; electrocardiogram, POC; point-of-care

[a] ST-deviation: ST depression or T-wave inversion in 2 consecutive leads

[b] Non-specific repolarization disturbances: left or right bundle branch block, pericarditis

[c] Risk Factors: diabetes mellitus, tobacco smoker, hypertension, hypercholesterolemia, obesity, family history of coronary artery disease

Risk categories (modified) HEART/preHEART: Low risk for MACE occurrence = ≤ 3, Intermediate risk for MACE = (modified) HEART score 4-6, preHEART score 4-7, High risk for MACE = (modified) HEART score 7-10, preHEART score 8-10

**Table 2.** Studies on prehospital decision rules for chest-pain (PMID: 35383078)

| Study | Study design | Setting | No. of patients | Decision Tool | Troponin assessment | Primary endpoint | Follow up |
|---|---|---|---|---|---|---|---|
| Famous II | Famous II Prospective observational cohort | EMS | 700 | HEART | POC troponin Cobas h232 | MACE: death, ACS, revascularization | 45 days |
| Famous III | Famous III Prospective implementational cohort | EMS | 536 | HEART | POC troponin Cobas h232 | MACE: death, ACS, revascularization | 45 days |
| ARTICA | ARTICA Randomized clinical multicenter trial | EMS | 866 | HEART | POC troponin Cobas h232 | Costs | 30 days and 1 year |
| preHEART1-2 | preHEART 1-2 prospective cohort, development and validation | EMS | 1208 & 435 | HEART Pre-HEART | Abbott i-Stat | MACE and Mortality at 3 days | 30 days |
| TRIAGE-ACS | TRIAGE-ACS Prospective, implementational cohort | EMS | 1069 | preHEART, HEART, T-MACS | Abbott i-Stat | ACS and MACE 30 days | 30 days and 1 year |
| preHEART3 | preHEART3 RCT (PROBE) | EMS | 5170 | preHEART | Abbott i-Stat | Combined: Mortality at 3/30dys, and ACS with CABG/ PCI to non-pci centre | 1 year |
| ACCESS study | ACCESS study Prospective cohort | EMS | 1054 | HEART | Samsung LABGEO POC TnI | MACE | 30 days |
| URGENT 2.0 | URGENT 2.0 RCT | EMS | 852 | HEART with hs-POC troponin | Atellica® VTLi | MACE | 30 days |
| POPular HEART | POPular HEART Prospective observational cohort | EMS | 650 | HEART | Abbott i-Stat | MACE | 30 days |
| IPD meta-analyse prehospital risk stratification | IPD meta-analyse prehospital risk stratification IPD meta analysis | EMS | > 10.000 | HEART preHEART | | ACS or MACE | 30 days |
| IMPRESS study | IMPRESS study Cross-sectional study | Primary care | 954 | Symptom based prediction model | - | ACS | 30 days |

| Study | Study design | Setting | No. of patients | Decision Tool | Troponin assessment | Primary endpoint | Follow up |
|---|---|---|---|---|---|---|---|
| HEART GP | HEART GP Diagnostic accuracy study | Primary care | 900 | H(E)ART, MHS, INTERCHEST | Atellica® VTLi | ACS | 6 weeks |
| POB-HELP | POB HELP RCT | Primary care | 1500 | MHS + hs-troponin I | Atellica® VTLi | ACS and MACE | 6 months |
| Safety First & TRACE | Safety First & TRACE Diagnostic accuracy | Primary care | 2000 + 1473 | NTS, MHS, INTERCHEST | | | 6 weeks |
| HARTc 2.0 study | HARTc 2.0 study RCT | EMS | 1368 | Modified HEART with hs-troponin | Atellica® VTLi | MACE (Death, ACS, unplanned revascularization), costs | 30 days and 1 year |

**Table 3.** Central Lab High Sensitivity cardiac Troponin (hs cTnT/I) tests on the EU market in 2023

| Company/ Platform / Assay | LoB (ng/L) | LoD (ng/L) | % CV at 99th Percentile | Conc at 20% CV (ng/L) | Conc at 10% CV (ng/L) | Reference Population N, Ages, Sex | 99th Percentile Overall M/F (ng/L) | Specimen Type | Percent Normals Measures ≥LoD Overall M/F |
|---|---|---|---|---|---|---|---|---|---|
| Abbott systems/ Alinity STAT High Sensitivity Troponin-I; commercial-OUS | 1.0 | 1.6 | Overall: 4.0%<br>F:5.3%<br>M:3.5% | 1.3 | 4.7 | Overall-n=153121-75y<br>F:n=76421-75y<br>M:n=76621-73y | Overall: 26.2<br>F:15.6<br>M:34.2 | Lithiumheparin (with/ without separator), K2 EDTA, K3 EDTA, serum (with/ without separator), serumwith thrombin-based clot activator | Overall:85%<br>F:78%<br>M:92% |
| Abbott/ ARCHITECT i systems/ ARCHITECT STAT High Sensitivity Troponin-I; commercial | 0.7 -1.3 | 1.1 | Overall: 4.0%<br>F:5.3%<br>M:3.5% | 1.3 | 4.7 | Overall-n=153121-75y<br>F:n=76421-75y<br>M:n=76621-73y | Overall: 26.2<br>F:15.6<br>M:34.2 | Lithiumheparin (with/ without separator), K2 EDTA, K3 EDTA, serum (with/ without separator), serumwith thrombin-based clot activator | Overall:85%<br>F:78%<br>M:92% |
| Beckman Coulter/ Access 2, DxI / Access hsTnI; commercial –OUS | 0.0 to1.7 | 1.0 to2.3 | Overall: 3.7%<br>F:4.2%<br>M:3.6% | 1.0to2.3 | 5.6 | Overall-n=108921-99y<br>F:n=595M:n=494 | Overall: 17.5<br>F:11.6<br>M:19.8 | Heparinplasma | >50% |
| bioMérieux VIDAS High Sensitive Troponin I; commercial | 1.9 | 3.2 | 7.0% | 4.9 | NP | Overalln=81541-80y<br>F:36841-80y<br>M:44741-80y | Overall:19<br>F:11<br>M:25 | Serum or heparin plasma | NP |

| Company/ Platform / Assay | LoB (ng/L) | LoD (ng/L) | % CV at 99th Percentile | Conc at 20% CV (ng/L) | Conc at 10% CV (ng/L) | Reference Population N, Ages, Sex | 99th Percentile Overall M/F (ng/L) | Specimen Type | Percent Normals Measures ≥LoD Overall M/F |
|---|---|---|---|---|---|---|---|---|---|
| Fujirebio Lumipulse G G1200and G600IIhsTnI | 1.2 | 2.1 | ≤4.6% | NP | 7.3 | Overall n=1018,18-90 years<br>F:428<br>M:590 | Overall: 28.6<br>F:22.4<br>M:32.9<br>Serum Overall: 26.9<br>F:21.4<br>M:29.4<br>Li-Hep plasma Overall: 29.6<br>F:27.8<br>M:32.8 | Redtopserum, serum separator tube, rapid clotting tubes; Disodium EDTA*, Dipotassium EDTA*,Lithium heparin, Sodiumheparin, SodiumCitrate, PST-with lithium heparin | Overall: 68.3%<br>Serum: 68.1%<br>Li-Heparin Plasma: 65.0% |
| LSI Medience PATHFAST cTnI; commercial | NP | 1 | <6% | 2 | 3.1 | Overalln=47418-86y<br>F:236<br>M:238 | Overall: 15.46<br>M:16.91<br>F:11.46 | Heparin-Na, heparin-Li or EDTA whole blood or plasma | Overall: 76.3% |
| LSI Medience PATHFAST hs-cTnI / PATHFAST cTnI-II | 1.23 | 2.33 | 6.1% | 4 | 15 | Overall n=734<br>Age>18<br>F:352<br>M:382 | Overall: 27.9<br>F:20.3<br>M:29.7 | Heparin-Na, heparin-Li or EDTA whole blood or plasma | Total:66.3%<br>F:52.8%<br>M:78.8% |
| Ortho/ VITROS/ hsTroponin I; commercial | 0.14 to0.51 | 0.39 to0.86 | <10% | 1.23 | 1.99 | Overall n=95222-91y<br>F:486<br>M:466 | Serum Overall:11<br>F:9<br>M:12<br>LiHep Plasma Overall:11<br>F:9<br>M:13 | Serum; Lithium Heparin; Plasma | >50% |

| Company/ Platform / Assay | LoB (ng/L) | LoD (ng/L) | % CV at 99th Percentile | Conc at 20% CV (ng/L) | Conc at 10% CV (ng/L) | Reference Population N, Ages, Sex | 99th Percentile Overall M/F (ng/L) | Specimen Type | Percent Normals Measures ≥LoD Overall M/F |
|---|---|---|---|---|---|---|---|---|---|
| Quidel / Alere TriageTrue hs-cTnI | 0.4 (plasma) 0.5-0.8 (whole blood) | 0.7–1.6 (plasma) 1.5-1.9 (whole blood) | 5.0–5.9% at21ng/L (plasma) 5.9–6.5% at 22 ng/L (whole blood) | 2.1–3.6 (plasma) 2.8 (whole blood) | 4.4–8.4 (plasma) 5.8–6.2 (whole blood) | Overall n=789 F:391 M:398 | Overall: 20.5 F:14.4 M:25.7 | EDTA whole blood or plasma | Overall: ≥50% |
| Roche/ cobase601, e602, e411/cTnT-hs18-min; commercial | 2.53; (1.58for e411) | 3.16; (2.54for e411) | <10% | 1.72 (4.01for e411) | 3.94 (7.45for e411) | Overall n=5332 0-71y F:49.7% | Overall:14 F: 9 M:17 | Serum,plasma: EDTA,heparin | Overall: 57.4% |
| Roche/ cobase601, e602, e411/cTnT-hsSTAT; commercial | 2.36; 2.14for e411 | 2.85; 3.25for e411 | <10% | 1.21 (2.88for e411) | 2.92 (6.74for e411) | Overall n=5332 0-71y F:49.7% | Overall:14 F:9 M:17 | Serum,plasma: EDTA,heparin | Overall: 57.4% |
| Roche/ cobas e801/ e402 cTnT-hs18-min and 9-min; commercial | 18min: 2.21 9min: 1.91 | 18min: 2.97 9min: 2.72 | <10% | 18min: 2.30 9min: 1.00 | 18min: 5.40 9min: 3.22 | Overall n=5332 0-71y F:49.7% | Overall:14 F:9 M:17 | Serum,plasma: EDTA,heparin | Overall: 57.4% |
| Siemens ATELLICA VTLihs-cTnI | 0.55 | 1.2 (plasma) 1.6 (whole blood) | 6.5% (plasma) 6.1% (whole blood) | 2.1 (plasma) 3.7 (whole blood) | 6.7 (plasma) 8.9 (whole blood) | Overall ln=694 18-91y F:331 M:363 | Overall: 22.9 F:18.5 M:27.1 | Li Hep whole blood and plasma, capillary; blood | Overall:84% F:80% M:87% |

**Table 4.** Point of Care (POC) non-high sensitivity and high sensitivity cardiac troponin devices on the EU marker in 2023

| Company/ Platform / Assay | LoB (ug/L) | LoD (ug/L) | % CV at 99th Percentile | Conc at 20% CV (ug/L) | Conc at 10% CV (ug/L) | Reference Population N, Ages, Sex | Specimen Type | 99th Percentile (ug/L unless noted) |
|---|---|---|---|---|---|---|---|---|
| Abbott- (non hs) i-STAT | 0.02 | NP | 16.5% | 0.07 | 0.1 | Overall, N=162 | Sodium and Lithium heparinized whole blood and plasma | Overall: 0.08 |
| Abbott- hs-TnI i-STAT | 0.57 ng/L (plasma) 0.78 ng/L (whole blood) | 1.05 ng/L (plasma) 1.61 ng/L (whole blood) | < 4.9% (plasma) ≤ 5.1% whole blood at 21 ng/L | 3.70 ng/L (plasma) 6.88 ng/L (whole blood) | | Overall N=895 F: 490 M: 404 | Li-Hep whole blood and plasma | Overall 21 ng/L F: 13 ng/L M 28 ng/L |
| Roche Cardiac POC (non hs) Troponin T – Roche Cobas 232 | NP | 0.04 | NP | 0.04-2.0 | 9.3% between 0.04-0.2 | Overall N = 302 | Heparinized whole blood | NP |
| LSI Medience Pathfast **hs-cTnI** / Pathfast cTnI-II | 1.23 ng/L | 2.33 ng/L | 6.1% | 4 ng/L | 15 ng/L | Overall n=734 F:352 M:382 | Heparin-Na, Heparin-Li or EDTA whole blood or plasma | Overall 66.3% F: 52.8% M: 78.8% |
| Quidell/ Alere Triage True **hs-cTnI** | 0.4 ng/L (plasma) 0.5-0.8 ng/L (whole blood) | 0.7-1.6 ng/L (plasma) 1.5-1.9 ng/L (whole blood) | 5-5.9% at 21 ng/L (plasma) 5.9-6.5^% at 22 ng/L (whole blood) | 2.1-3.6 ng/L (plasma) 5.8-6.2 ng/L ng/L (whole blood) | 4.4-8.4 ng/L (plasma) 5.8-6.2 ng/L (whole blood) | Overall N=789 F: 391 M: 398 | EDTA whole blood or plasma | Overall 20.5 ng/L F: 14.4 ng/L M: 25.7 ng/L |
| Siemens Atellica VTLi **hs-cTnI** | 0.55 ng/L | 1.2 ng/L (plasma) 1.6 ng/L (whole blood) | 6.5% (plasma) 6.1% whole blood at 22 ng/L | 2.1 ng/L (plasma) 3.7 ng/L (whole blood) | 6.7 ng/L (plasma) 8.9 ng/L (whole blood) | Overall N=694 F: 331 M:363 | Li-Hep whole blood and plasma, capillary blood | Overall 22.9 ng/L F: 18.5 ng/L M 27.1 ng/L |

**Table 5**. Overview of point-of-care non-high sensitivity and high sensitivity cardiac troponin devices for EMS, which are available on the EU market anno 2023. The first three analyzers are hand-held, whereas the Triage True analyze represents a small portable analyzer.

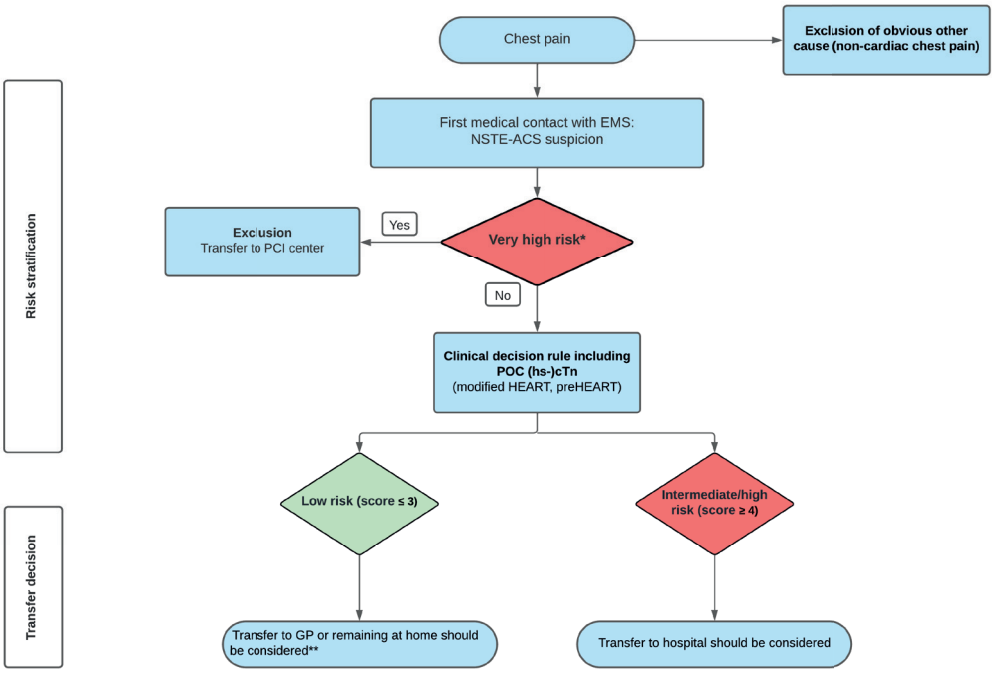
| Device | Manufacturer | Troponin | 99th URL | Measuring range | Time to result | Specimen collection |
|---|---|---|---|---|---|---|
| **Cobas h 232 POC system** | Roche Diagnostics | Troponin T | N/A | 40 – 2000 ng/L | 12 min | Heparinized venous whole blood |
| **Atellica® VTLi Patient-side Immunoassay Analyzer*** | Siemens Healthineers | High Sensitivity Troponin I | ● Overall 22.9 ng/L<br>● Male 27.1 ng/L<br>● Female 18.5 ng/L | LoD* – 1250 ng/L<br>*LoD plasma 1.2<br>*LoD Whole blood 1.6 | ~8 min | Whole blood (lithium heparin)<br>Venous (lithium heparin)<br>Capillary |
| **i-STAT™ non-hs-cTnI** | Abbott | Troponin I | ● 0.08 ng/ mL<br><br>Each institution should establish its own reference range using the i-STAT cTnI assay. | 0.00-50.00 ng / mL<br><br>Performance characteristics have not yet been established for cTnI values above 35.00 ng/mL | 10 min | Heparinized whole blood or plasma samples collected in syringes or evacuated tubes containing lithium heparin.<br>Non-heparinized whole blood samples tested within one minute of drawing from a patient into a plastic syringe or plastic evacuated tube containing no additives. |

| Device | Manufacturer | Troponin | 99th URL | Measuring range | Time to result | Specimen collection |
|---|---|---|---|---|---|---|
| **i-STAT™ hs-cTnI** | Abbott | Troponin I | ● Overall 21 ng/L<br>● Male 28 ng/L<br>● Female 13 ng/L | 2.9 – 1000.0 ng/L | | Heparinized whole blood or plasma samples collected in syringes or evacuated tubes containing lithium heparin. Non-heparinized whole blood samples tested within one minute of drawing from a patient into a plastic syringe or plastic evacuated tube containing no additives. |
| **Triage Meter Pro®** | Quidel | High Sensitivity Troponin I | ● Overall 20.5 ng/L<br>● Male 25.7 ng/L<br>● Female 14.4 ng/L | 1.0 – 1000 ng/L | <20 min | EDTA whole blood or plasma |

99th URL: the 99th percentile upper reference limit; LoD: Limit of detection; cTnI: cardiac troponin I; EDTA: ethylenediaminetetraacetic acid

* the latest software version of this IVD-POC device is under investigation by the Notified Bodies and checked for its compliance with the IVDR 2017/746

**Fig. 1** illustrates current (scientific) consensus for prehospital risk assessment by Emergency Medical Services (EMS) of chest pain patients suspected for acute coronary syndrome (ACS)




**Disclaimer: In all situations patient or EMS autonomy regarding preference for (non-)conveyance to ED should be respected**

*
**Very high risk criteria:** haemodynamic instability, cardiogenic shock, recurrent/refractory chest pain despite medical treatment, life-threatening arrhythmias, mechanical complications or myocardial infarction, acute heart failure clearly related to NSTE-ACS, ST-segment depression > 1 mm/ 6 leads plus ST-segment elevation aVR and/or V1

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As long as it complies with the national ambulance protocol (LPA) and/or regional protocols

**Fig 2** Flowchart of proposed future prehospital pathway for management of patients with chest pain and suspicion of acute coronary syndrome (ACS) presenting to general practitioners

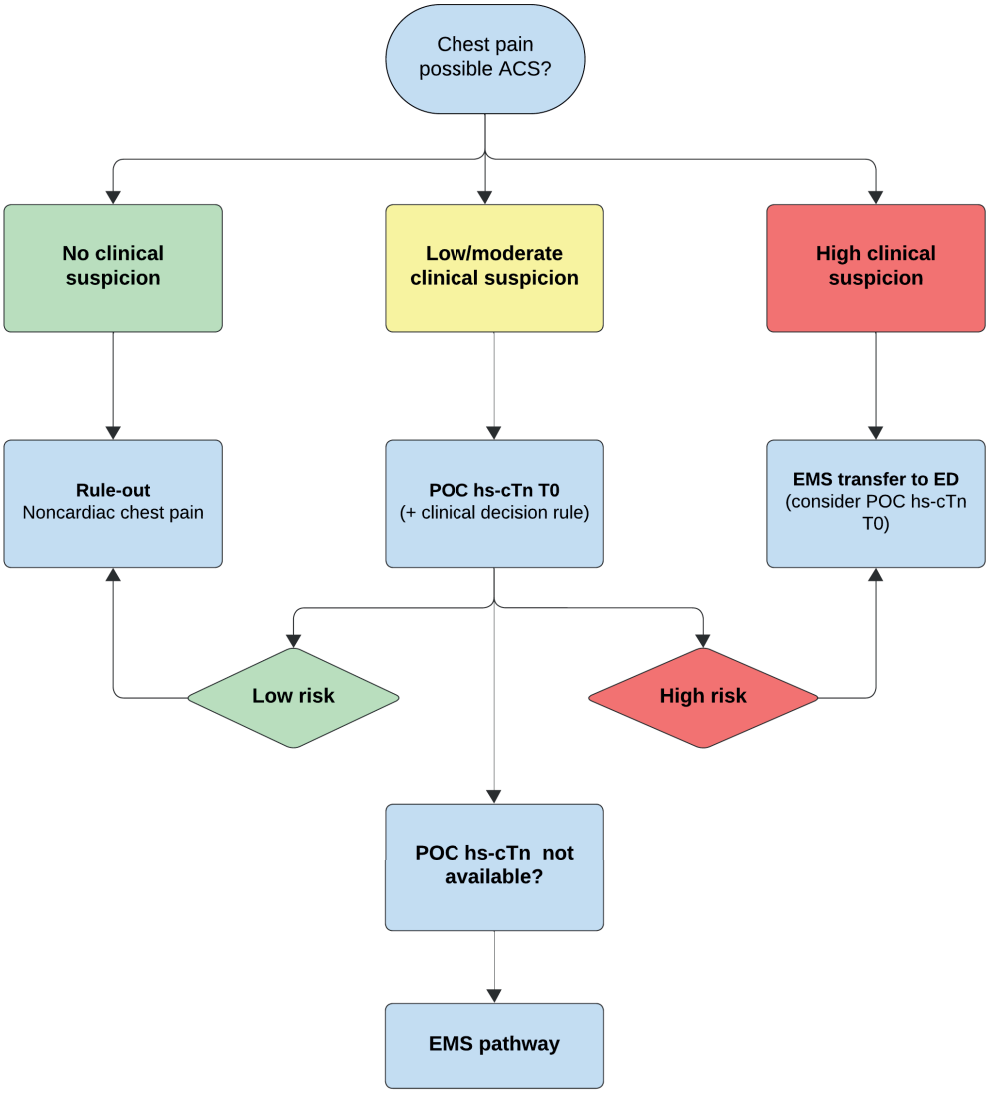
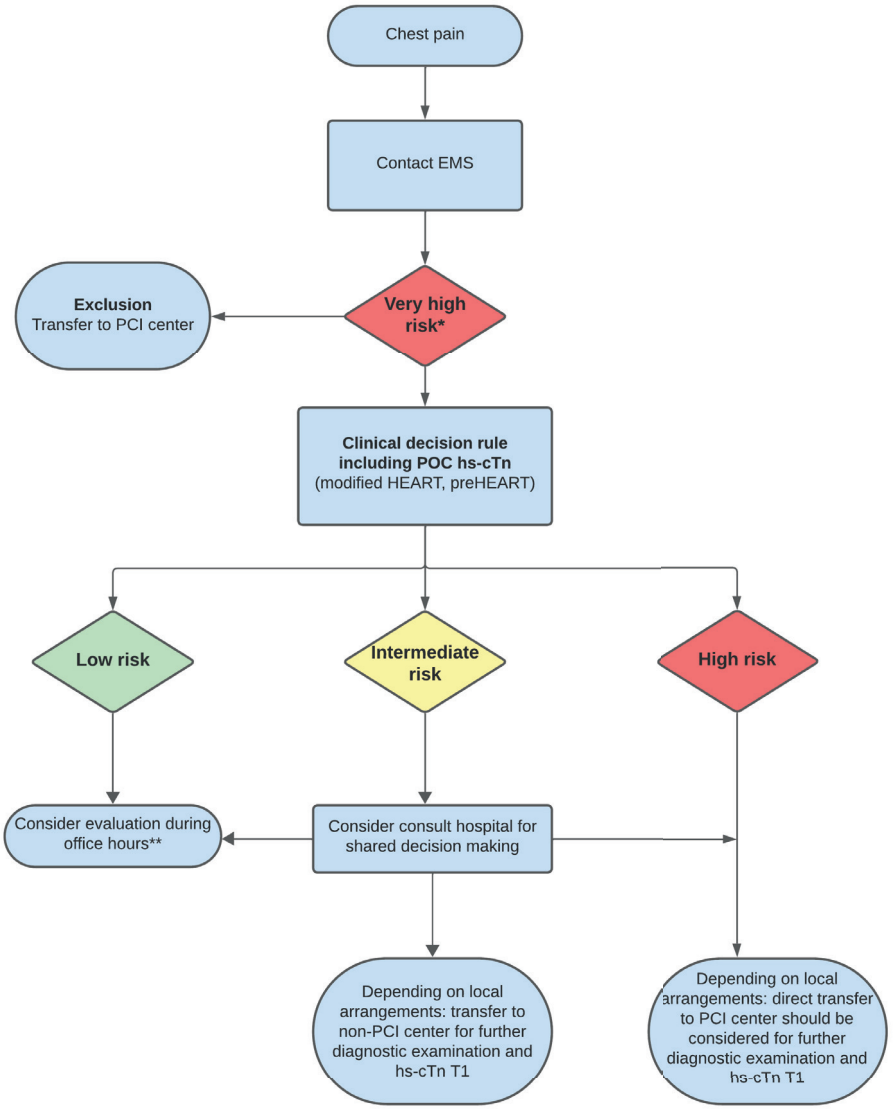


**Fig 3** Flowchart of proposed future pathway for management of patients with chest pain and suspicion of Acute Coronary Syndrome (ACS) for EMS services. As insufficient data is currently available, this is a suggested future track which cannot be implemented directly into practice




**Disclaimer: In all situations patient or EMS autonomy regarding preference for (non-)conveyance to ED should be respected**

*

**Very high risk criteria**: haemodynamic instability, cardiogenic shock, recurrent/refractory chest pain despite medical treatment, life-threatening arrhythmias, mechanical complications or myocardial infarction, acute heart failure cleary related to NSTE-ACS, ST-segment depression > 1mm/ 6 leads plus ST-segment elevation aVR and/or V1.

**

According to LPA.

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# Part Two

*Timing of (invasive) treatment in patients with NSTE ACS*

# Chapter 9

## Antithrombotic PreTreatment and Invasive Strategies in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome

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## Abstract

In the current era, the antithrombotic treatment of patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS) includes standard aspirin, and one of the potent $P2Y_{12}$ inhibitors ticagrelor or prasugrel. The optimal timing of ticagrelor has not been adequately studied, while prasugrel is only recommended after coronary angiography prior to PCI. The invasive strategy, including indication and timing of angiography, depends on risk stratification and a mortality benefit has been shown in selected high-risk NSTE-ACS undergoing early (<24 h) intervention.

**Keywords:** non-ST segment elevation acute coronary syndrome; antithrombotic treatment; routine invasive strategy; optimal timing

## 1. Introduction

The acute treatment of patients diagnosed with non-ST segment elevation acute coronary syndrome (NSTE-ACS), consists of pharmacological treatment and potential invasive coronary angiography with subsequent revascularization if necessary. Whereas, in ST-segment elevation myocardial infarction, characterized by an occluded epicardial coronary artery, primary percutaneous intervention (PCI) as soon as possible results in improved outcomes, the invasive treatment decision in NSTE-ACS is more complex. In NSTE-ACS typically angiographically significant stenosis is observed, while the epicardial flow is maintained. In this review, we focus on antithrombotic treatment strategies (before or at the time of coronary angiography) and the invasive management in NSTE-ACS.

## 2. Antithrombotic Pretreatment Strategies

Antithrombotic treatment (ATT) is the cornerstone in NSTE-ACS patients regardless of invasive management. The choice, combination, timing of initiation and treatment duration, all depend on patient characteristics, including the ischemic and bleeding risk, as well as on procedural aspects. Activation of platelet aggregation and the coagulation cascade plays a key role in the initial phase and evolution of NSTE-ACS. Therefore, platelet inhibition and anticoagulation are important, especially in those patients undergoing revascularization.

### *2.1. Oral Antiplatelet Therapy*

Aspirin or acetylsalicylic acid (ASA) is the basis of antiplatelet inhibition. The clopidogrel in unstable angina to prevent recurrent ischemic Events (CURE) trial showed that the addition of clopidogrel results in improved clinical outcomes.[1] Based on the results of the PLATO (platelet inhibition and patient outcomes) and TRITON-TIMI 38 (trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel–thrombolysis in myocardial infarction 38) trials, where the superiority of the novel $P2Y_{12}$ receptor inhibitors has been shown over clopidogrel, dual antiplatelet treatment (DAPT), including ASA and a potent $P2Y_{12}$ receptor inhibitor (ticagrelor or prasugrel), are recommended by current clinical guidelines.[2,3]

While ASA is started as soon as possible, the optimal timing of initiation of the $P2Y_{12}$ receptor inhibitor is a matter of debate. Pretreatment with $P2Y_{12}$ inhibition includes a variety of different scenarios. The $P2Y_{12}$ inhibitor can be given prehospital (ambulance), at the emergency department or even in the catheterization laboratory after coronary angiography (CAG), but before PCI. The rationale for pretreatment in NSTE-ACS is to achieve sufficient platelet inhibition at the time of PCI, avoiding ischemic complications, such as acute stent thrombosis. Disadvantages are a high bleeding risk in patients with extensive coronary artery disease with an indication for revascularization by urgent coronary artery bypass grafting

(CABG), or those who turn out to have another diagnosis, such as aortic dissection. The pretreatment with clopidogrel the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA)-5 PRELOAD study randomized 409 patients to receive 600 mg clopidogrel loading dose 4–8 h before PCI or a 600 mg loading dose in the catheterization laboratory after coronary angiography, but before PCI.[4] In this trial no significant difference in the 30-day incidence of major adverse cardiac events (MACE): A composite of cardiac death, myocardial infarction, or unplanned target vessel revascularization, between the pretreatment and no pretreatment groups (8.8% vs. 10.3%; *P* = 0.72). No increased risk of bleeding or vascular complications with pretreatment was observed either (5.4% vs. 7.8%; *P* = 0.42). The main limitation of this study is the small proportion of patients with NSTE-ACS (only 39% of the study population). Randomized pretreatment studies with ticagrelor in NSTE-ACS have not been performed. However, in the PLATO trial, 18,624 patients were pretreated with ticagrelor versus clopidogrel before undergoing coronary angiography. Ticagrelor reduced the risk of ischemic events as compared to clopidogrel (9.8 vs. 11.7%. hazard ratio (HR), 0.84; 95% confidence interval [CI], 0.77 to 0.92; *P* < 0.001).[2] Prasugrel has been investigated more frequently than ticagrelor. In the TRITON-TIIMI 38 trial, 13608 patients with moderate-to-high-risk acute coronary syndromes (ACS) were randomly allocated to prasugrel or clopidogrel. All patients randomly allocated to prasugrel were given 60 mg after coronary angiography, when the anatomy was known. This study showed significant reductions in the prasugrel group in the rates of myocardial infarction (9.7% for clopidogrel vs. 7.4% for prasugrel), urgent target vessel revascularization (3.7% vs. 2.5%) and stent thrombosis (2.4% vs. 1.1%). In the ACCOAST trial (ACCOAST—comparison of prasugrel at the time of percutaneous coronary intervention or as pretreatment at the time of diagnosis in patients with non-ST elevation myocardial infarction), patients were randomized to prasugrel pretreatment or a strategy comparable to TRITON-TIMI 38.[5] In the ACCOAST trial, 4033 patients with NSTE-ACS and a positive troponin level scheduled for CAG were randomized to prasugrel 30 mg before CAG (pretreatment group) or placebo (control group). When CAG was followed by PCI, an extra 30 mg of prasugrel was added in the pretreatment group at the time of PCI, while control patients receive the complete 60 mg of prasugrel. No reduction in the primary endpoint (composite of cardiovascular death, recurrent myocardial infarction, stroke, urgent revascularization or glycoprotein IIb/IIIa rescue therapy through day 7) was found with pretreatment of 30 mg prasugrel (HR with pretreatment 1.02; 95% CI, 0.84-1.25; *P* = 0.81). There was, however, a significant increase in thrombolysis in myocardial infarction (TIMI) major bleeding, whether or not related to CABG, at day 7 in the pretreatment group (2.6% vs. 1.4%. HR 1.90; 95% CI 1.19–3.02; *P* = 0.006). This trial was prematurely interrupted on recommendation from the data safety monitoring board when 398 of the 400 intended primary endpoint events had been collected, corresponding to 4033 of the approximately 4100 patients originally planned. The increase in TIMI major bleeding was irrespective whether the procedure was performed by radial or femoral access .[6] Therefore, there is inconclusive evidence regarding the optimal timing of $P2Y_{12}$ inhibition.

With regard to the optimal $P2Y_{12}$ inhibitor, the two potent $P2Y_{12}$ inhibitors ticagrelor and prasugrel were compared head-to-head in the ISAR-REACT 5 trial.[7] In this multicenter, randomized, open-label trial, 4018 patients with ACS (58.9% were NSTE-ACS) were randomly assigned to ticagrelor (180 mg loading dose before coronary angiography) or prasugrel (60 mg loading dose at the time of PCI). The primary endpoint (a composite of death, myocardial infarction, or stroke at one year) occurred in 184 of 2012 patients (9.3%) in the ticagrelor group and in 137 of 2006 patients (6.9%) in the prasugrel group (HR, 1.36; 95% CI, 1.09–1.70; *P* = 0.006. There was no significant difference in bleeding. The ISAR-REACT 5 trial results have to be interpreted with caution. Around a third of patients were not treated with the assigned drug. Furthermore, the incidence of the primary outcome in ticagrelor-treated patients in ISAR-REACT 5 and PLATO was similar at 9.3% and 9.8%. However, the comparison of the results of prasugrel-treated patients in ISAR-REACT 5 and TRITON-TIMI 38 study shows a large difference: The incidence of the primary outcome being 6.9% and 9.9%, respectively. Despite these limitations, this is the only randomised clinical trial comparing these drugs, and further data is necessary to determine whether prasugrel is the superior $P2Y_{12}$ inhibitor.

*2.2. Current Guideline Recommendation*

In the 2015 European Society of Cardiology (ESC) Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation no recommendation for or against pretreatment with these agents can be formulated.[8] Prasugrel in whom coronary anatomy is not known is not recommended.

*2.3. Intravenous Antiplatelet Therapy*

The $P2Y_{12}$ inhibitor cangrelor, an i.v. adenosine triphosphate (ATP) analogue that binds reversibly and with high affinity to the $P2Y_{12}$ receptor and has a fast onset and fast offset of action. This might provide a desirable combination of protection from ischemia without an excessive risk of bleeding. In the placebo-controlled CHAMPION-PLATFORM (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trial, 5362 patients with NSTE-ACS were randomly assigned to cangrelor or placebo at the time of PCI, followed by 600 mg clopidogrel.[9] No reduction in the primary endpoint (a composite of death, myocardial infarction, or ischemia-driven revascularization at 48 h) was found in the cangrelor group, as compared with the placebo group (odds ratio (OR) in the cangrelor group, 0.87; 95% CI, 0.71–1.07; *P* = 0.17). In CHAMPION-PHOENIX, 11,145 patients who were undergoing either urgent or elective PCI and were randomized to a bolus and infusion of cangrelor or to receive a loading dose of 600 mg or 300 mg of clopidogrel. The rate of the primary efficacy endpoint (a composite of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 h) was 4.7% in the cangrelor group and 5.9% in the clopidogrel group (*P* = 0.005). Stent thrombosis occurred in 0.8% of the patients receiving cangrelor and in 1.4% in the clopidogrel group (OR, 0.62; 95% CI, 0.43–0.90;

*P* = 0.01). There was no significant increase in bleeding. With its ability to reduce ischemic complications of PCI, cangrelor can be implemented in situations in which ADP-receptor blockade is needed, but a short-acting intravenous agent would be preferred, such as patients waiting to undergo CABG.

The use of Intravenous glycoprotein (GP) IIb/IIIa inhibitors as pretreatment have been extensively studied, and attention should be given to the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) timing trial [10]. In this trial, 9207 patients with moderate to high-risk ACS were randomly assigned to routine GPIIb/IIIa inhibitor treatment (eptifibatide or abciximab) before PCI or deferred selective use. The primary endpoint (a composite of death, myocardial infarction or unplanned revascularisation for ischemia) at 30 days occurred in 7.1% in the routine group and 7.9% in the deferred group (relative risk, 1.12; 95% CI, 0.97–1.20; *P* = 0.044 for noninferiority; *P* = 0.13 for superiority). There was less major bleeding in the deferred group compared to routine administration at 30 days (4.9% vs. 6.1%; *P* < 0.001 for non-inferiority; *P* = 0.009 for superiority). Eptifibatide was also studied in the EARLY ACS (Early versus Delayed, Provisional Eptifibatide in Acute Coronary Syndromes) trial [11]. Early administration of this GPIIb/IIIa inhibitor leads to an increased risk of major bleeding, while ischemic events did not meet statistical significance.

*2.4. Current Guideline Recommendation*

Based on these trials, the current ESC guideline states that it is not recommended to administer GPIIb/IIIa inhibitors in patients in whom coronary anatomy is not known. The use of GPIIb/IIIa is reserved for the bailout setting with thrombotic complications.

*2.5. Anticoagulants During the Acute Phase*

In addition to antiplatelet therapy, anticoagulants are proven to be effective in reducing ischemic events in NSTE-ACS. With regards to the acute phase, the use of anticoagulant therapy is an essential adjunct to antiplatelet therapy in the acute treatment of ACS and is limited to treatment during initial hospitalization and revascularization. In a meta-analysis of 12 trials involving over 17.000 patients, short-term unfractionated heparin, or low molecular weight heparin halved the risk of myocardial infarction or death up to 7 days.[12] Based on these trials, in which therapy was started within a few hours after diagnosis, it is recommended that this therapy is started early. No trials have been performed investigating the exact timing of anticoagulants. Anticoagulants are generally given until revascularization or discharge.

*2.6. Unfractioned Heparin (UFH) and Low Molecular Weight Heparin (LMWH).*

As described above, the use of UFH or LMWH in addition to aspirin has been shown to be associated with lower short-term ischemic events. UFH is usually weight-adjusted, and monitored using activated clotting times. LMWH, the most widely used being enoxaparin, is

dosed based on the weight. Based on a more dose-effect relationship that is more predictable, no monitoring is necessary. UFH has been compared with LMWH, and meta-analyses have shown less ischemic and bleeding outcomes with the use of LMWH.[13,14] However, although these meta-analyses include patients with NSTE-ACS, dedicated NSTE-ACS trials are lacking.

*2.7. Fondaparinux*

Fondaparinux is a synthetic pentasaccharide that reversibly binds to antithrombin. Dosing is not based on weight, and monitoring is not necessary, and fondaparinux does not lead to heparin-induced thrombocytopenia. In the (Organisation to Assess Strategies in Acute Ischemic Syndromes) OASIS-5 trial, fondaparinux and enoxaparin were compared. Fondaparinux was non-inferior to enoxaparin, but halved in hospital major bleeds at follow-up at nine days.[15] Furthermore, there was a significant mortality benefit at six-month follow-up. This mortality benefit was not reproduced in a large Swedish registry .[16] Despite the superior safety profile, fondaparinux was associated with more catheter thrombosis than enoxaparin, requiring the additional administration of UFH at the time of PCI.

*2.8. Bivalirudin*

Bivalirudin directly binds to thrombin. Bivalirudin has been compared to UFH in the ACUITY trial.[17] Patients were randomized to UFH/LMWH plus GPIIb/IIIa inhibition, bivalirudin plus GPIIb/IIIa inhibition or bivalirudin with bailout use GPIIb/IIIa inhibition. In this trial, while ischemic outcomes were comparable, bivalirudin with bailout use GPIIb/IIIa inhibition resulted in significantly less bleeding. However, the reduction in bleeding seems to be explained by concomitant GPIIb/IIIa inhibition. In the MATRIX (minimizing adverse hemorrhagic events by transradial access site and systemic implementation of angiox) trial, with a more selective GPIIb/IIIa inhibitor use in the UFH arm, no difference in a combination of ischemic and bleeding outcomes was observed.[18] With regards to individual outcomes, stent thrombosis was increased, and bleeding risk decreased with bivalirudin. In VALIDATE-SWEDEHEART (Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies) trial, UFH use was compared with bivalirudin with limited use of GPIIb/IIIa inhibitors.[19] The investigators showed comparable risks for both ischemia and bleeding when comparing the two drugs.



*2.9. Anticoagulant and Treatment Strategy*

Based on the above, in invasively managed patients, UFH is the standard of choice. Bivalirudin can be used as an alternative to UFH. In conservatively managed patients, fondaparinux is the first, choice. In case of cross-over from a conservative to an invasive strategy, additional UFH or bivalirudin is necessary for PCI.

*2.10. Current Guideline Recommendation*

In the 2015 ESC guideline, UFH and bivalirudin are recommended in NSTE-ACS undergoing

PCI, while fondaparinux (with additional UFH during PCI) is recommended regardless of the treatment strategy. Enoxaparin is recommended if fondaparinux is not available.

## 3. Invasive Coronary Angiography and Revascularization

CAG has an important role in NSTE-ACS. It can confirm or rule out (obstructive) coronary artery disease, and as a consequence, guide antithrombotic therapy. Second, the culprit and non-culprit lesion(s) can be identified; establishing the indication for coronary revascularization by either PCI or CABG. Finally, it can assist in prognostication by assessing the patient's risk on the basis of coronary anatomy.

Comparable to STEMI, revascularization in selected NSTE-ACS patients improves 1-year survival [20]. However, different treatment strategies have emerged over the last two decades. They differ with regard to the decision for invasive management and the timing of invasive management. The decision for an invasive strategy should carefully weigh the patient risk profile and coronary angiography/revascularisation-related risk. These include numerous factors, such as clinical presentation, comorbidities, risk scores, the occurrence of high-risk characteristics specific for either CABG or PCI, frailty, cognitive status, estimated life expectancy and the complexity of coronary anatomy.

### *3.1. Invasive Versus Conservative Treatment*

In general, patients admitted with NSTE-ACS undergo either scheduled for routine CAG and revascularization or a selective (conservative) approach. The routine invasive strategy consists of early CAG within 24 to 72 h after admission and subsequent PCI or CABG, where appropriate. The selective invasive or conservative strategy consists of initial pharmacological therapy and only CAG with additional PCI or CABG if the pharmacological therapy fails and/or (recurrent) ischemia is detected. Multiple clinical trials have been performed comparing these two treatment strategies, and current guideline recommendations are mainly based on the following three trials with long-term follow-up.

In the ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes) trial 1200 patients with NSTE-ACS, including an elevated cardiac troponin T, were randomly assigned to an early invasive strategy or to a more conservative (selectively invasive) strategy. No benefit was seen for the early invasive strategy in terms of death, non-fatal myocardial infarction, or rehospitalization for anginal symptoms within one year after randomization.[21] The FRISC-II (Fragmin and Fast Revascularization during Instability in Coronary Artery Disease) investigates 2457 patients with NSTE-ACS who were randomly allocated to invasive or non-invasive treatment.[22] The composite of death or myocardial infarction occurred in 127 (10.4%) versus 174 (14.1%) patients (risk ratio (RR) 0.74 [0.60–0.92], $p = 0.005$). There were also reductions in readmission (451 [37%] vs. 704 [57%]; RR 0.67 [0.62–0.72], $p < 0.001$), and

revascularization after the initial admission (92 [7.5%] vs. 383 [31%]; RR 0.24 [0.20–0.30], $p < 0.001$). Moreover, the RITA-3 (randomized trial of a conservative treatment strategy versus an interventional treatment strategy in patients with unstable angina) randomized 1810 patients with NSTE-ACS to early intervention or conservative treatment.[23] In this study, an invasive approach was a better strategy, but the difference was mainly driven by a reduction in refractory angina pectoris. The primary endpoint (a combined rate of death, non-fatal myocardial infarction, or refractory angina at four months; and a combined rate of death or non-fatal myocardial infarction at one year) was met in 86 (9.6%) of 895 patients in the intervention group, compared with 133 (14.5%) of 915 patients in the conservative group (RR 0.66, 95% CI 0.51–0.85, $p = 0.001$). While the early benefit of a routine invasive strategy has, thus, been shown, long-term results are varying. Therefore, Fox et al. performed a pooled analysis of all randomized studies (FRISC-II, ICTUS and RITA-3) with 5-year outcomes.[24] Over five years, 14.7% (389 of 2,721) of patients randomly allocated to a routine invasive (RI) approach reach the endpoints cardiovascular death or non-fatal MI versus 17.9% (475 of 2,746) in the selective invasive (SI), more conservative strategy (HR: 0.81, 95% CI: 0.71–0.93; $p = 0.002$). The most marked treatment effect was on myocardial infarction (10.0% RI strategy vs. 12.9% SI strategy), and there were consistent trends for cardiovascular deaths (HR: 0.83, 95% CI: 0.68–1.01; $p = 0.068$) and all deaths (HR: 0.90, 95% CI: 0.77–1.05).

There were 2.0% to 3.8% absolute reductions in cardiovascular death or MI in the low- and intermediate-risk groups and an 11.1% absolute risk reduction in highest-risk patients.

Important in the interpretation of the trials is the revascularization rate in the conservative or selective invasive treatment arms. In the ICTUS trial, in the early invasive strategy as per protocol, 97% of patients underwent coronary angiography within 48 h and 98% during hospitalization. Coronary angiography during hospitalization was 96% in both early invasive groups of RITA-3 and FRISC-II, and by design, was to be performed <72 h from randomization and <7 days from admission for the index event, respectively. More importantly, coronary angiography during hospitalization in the non-invasive groups of FRISC-II and RITA-3 was only 7% and 16%, respectively, compared with 53% of patients in the selective invasive group in ICTUS. Therefore, selective invasive treatment might be an alternative strategy as long as ischemia detection is performed with a low threshold. This might explain the results of the ICTUS trial, in which the selective invasive treatment included ischemia detection before discharge. Furthermore, in the Netherlands, there is a high density of PCI and non-PCI angiography performing centers facilitating the transfer of unstable patients or patients with a positive ischemia detection test.

In summary, a routine invasive strategy has benefit consisting of a reduction in recurrent myocardial infarction or death, with a larger benefit in higher-risk patients.

*3.2. Timing of Invasive Treatment*

The second decision involves the optimal timing of angiography following the routine invasive strategy. Different time windows are defined as immediate (within 2 h), early invasive (within 24 h) or delayed invasive (after 24 h but within 72 h). In the immediate strategy group no randomized clinical trials have been performed because of very-high-risk criteria identifying patients who need an urgent invasive approach. These criteria consist of: Hemodynamic instability or cardiogenic shock, refractory angina pectoris despite medical treatment, cardiac arrest or life-threatening arrhythmias, acute heart failure and recurrent dynamic ST- or T-wave changes.

In patients with an out-of-hospital cardiac arrest (OHCA), but without ST-segment elevation on electrocardiography (ECG), the right timing of coronary angiography especially is still unknown [25,26]. Whether these patients should undergo immediate coronary angiography or delayed invasive treatment after neurological recovery was addressed in the Coronary Angiography after Cardiac Arrest (COACT) trial. In this multicenter randomized investigator-initiated trial 552 patients with NSTE-ACS and OHCA were randomly assigned to immediate angiography and delayed angiography.[27] The primary endpoint was survival at 90 days. At 90 days, no difference was seen in both groups (64.5% vs. 67.2%; OR, 0.89; 95% CI, 0.62–1.27; $P = 0.51$)

While a routine invasive approach in NSTE-ACS is recommended by clinical guidelines, the optimal timing of invasive strategy is still under debate. Multiple trials have compared immediate, early and delayed invasive treatment strategies, with discrepant results, and all were statistically underpowered to detect a mortality benefit. This issue was addressed in a meta-analysis of Jobs et al. which includes all randomized controlled trials comparing an early versus delayed invasive strategy and reporting all-cause mortality at least 30 days after in-hospital randomization.[28] The authors find that in eight trials (a total of 5324 patients) with a median follow-up of 180 days, no significant mortality reduction was seen in the early invasive group compared with the delayed invasive group (HR 0.81; 95% CI 0.64–1.03; $p = 0.088$). However, in a prespecified analysis of patients with elevated troponin, present diabetes, a GRACE risk score > 140 and older age (>75 years), lower mortality was seen with an early invasive strategy. Tests for interaction effects were inconclusive. We note that these meta-analyses are dominated by the largest TIMACS trial, providing the majority of patients for the meta-analysis. Furthermore, there is a large variety in the definition of early or delayed invasive strategy between the different trials.

With regard to the GRACE risk score > 140, the randomized clinical TIMACS trial should be noted.[29] In this landmark trial, the largest RCT to date, 3031 patients with NSTE-ACS were randomly allocated to early invasive (within 24 h after randomization) or delayed intervention (≥36 h after randomization). At six months, no difference was seen in the primary outcome

(a composite of death, myocardial infarction, or stroke) in the early-intervention group (9.6%) as compared to the delayed-intervention group (11.3%), HR in the early-intervention group, 0.85; 95% CI, 0.68–1.06; *P* = 0.15). The median time to angiography was 14 h in the early invasive strategy and 50 h in the delayed invasive group. Prespecified analysis of high-risk patients showed that early intervention improved the primary outcome in the third of patients who were at highest risk (i.e., GRACE risk score >140; HR, 0.65; 95% CI, 0.48–0.89). Albeit a positive subgroup in an overall negative trial, this finding was recently reproduced. In the VERDICT trial (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography) 2147 patients with a clinical suspicion of NSTE-ACS were 1:1 randomized to very early invasive coronary angiography (within 12 h of diagnosis) or standard invasive (within 48–72 h) [30]. The primary endpoint was a combination of all-cause death, non-fatal recurrent myocardial infarction, hospital admission for refractory myocardial ischemia, or hospital admission for heart failure. With a median follow-up time of 4.3 years, no difference was seen in the primary endpoint in the very early group (27.5%) versus the standard group (29.5%), (HR, 0.92; 95% CI, 0.78–1.08. However, the benefit of an early invasive treatment strategy for predefined high-risk patients (GRACE risk score > 140) was also confirmed in this trial (HR, 0.81; 95% CI, 0.67–1.01; *P* value for interaction = 0.023).

*3.3. Current Guideline Recommendations*

As outlined in Table 1, the ESC recommends CAG within two hours in patients with very-high-risk criteria. In patients with a rise and/or fall in cardiac troponin, dynamic ST-or T-wave changes and a GRACE risk score > 140, the guidelines recommend an early invasive strategy. Intermediate risk criteria mandate a delayed invasive approach (within 72 h).

**Table 1.** Risk criteria mandating invasive strategy in non-ST segment elevation acute coronary syndrome (NSTE-ACS). Adapted from the European Society of Cardiology (ESC) guidelines [8].

| **Very-high-risk criteria** |
|---|
| Hemodynamic instability or cardiogenic shock |
| Recurrent or ongoing chest pain refractory to medical treatment |
| Life-threatening arrhythmias or cardiac arrest |
| Mechanical complications of MI |
| Acute heart failure |
| Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation |
| **High-risk criteria** |
| Rise or fall in cardiac troponin compatible with MI |
| Dynamic ST-or T-wave changes (symptomatic or silent) |
| GRACE score >140 |
| **Intermediate-risk criteria** |
| Diabetes mellitus |
| Renal insufficiency (eGFR < 60 mL/min/1.73m$^2$ |
| LVEF <40% or congestive heart failure |
| Early post-infarction angina |
| Prior PCI |
| Prior CABG |
| GRACE risk score >109and < 140 |
| **Low-risk criteria** |
| Any characteristics not mentioned above |

CABG = coronary artery bypass graft ; eGFR = estimated glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events ; LVEF = left ventricular ejection fraction; PCI= percutaneous coronary intervention; MI = myocardial infarction

*3.4. Summary and Clinical Perspective*

In Table 2, the key points in antithrombotic treatment and invasive approach in NSTE-ACS patients are outlined.

**Table 2.** key points in antithrombotic pretreatment and invasive strategies in NSTE-ACS.

| **Key points in antiplatelet therapy** |
|---|
| Aspirin still remains the cornerstone |
| DAPT with a potent $P2Y_{12}$ inhibitor is recommended |
| Pretreatment with $P2Y_{12}$ inhibitors have no benefits on MACE |
| **Key points in anticoagulant therapy** |
| Anticoagulation should be started at diagnosis |
| UFH is the first-line therapy |
| Fondaparinux is the first-line therapy with a selective invasive or conservative management |
| **Key points in invasive coronary angiography and revascularization** |
| Routine invasive strategy is recommended by clinical guidelines |
| An early invasive strategy in patients with high-risk criteria is recommended |

DAPT = dual antiplatelet therapy; MACE = major adverse cardiovascular events (a composite endpoint of cardiovascular death, recurrent myocardial infarction, stroke, urgent revascularization) ; UFH = unfractionated heparin



With the introduction of clopidogrel and the potent $P2Y_{12}$ inhibitors ticagrelor and prasugrel, patients benefit from significant reductions in cardiovascular mortality and recurrent myocardial infarction when added to aspirin, the cornerstone of ACS treatment. Strategies in combining antithrombotic treatments will be the focus in future research where ischemic benefit should outweigh the risk of (major) bleeding. While waiting for these trials, an invasive evaluation of coronary anatomy should be a mandatory part of the treatment strategy in high-risk patients presenting with NSTE-ACS.

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# Chapter 10

## Timing of invasive strategy in patients with non-ST segment elevation acute myocardial infarction: A nationwide retrospective cohort analysis

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## Abstract

*Background*

The Dutch ACS working group endorses a delayed invasive approach for non-ST segment elevation myocardial infarction (NSTEMI) patients as safe and acceptable. We analysed the timing of invasive coronary angiography (ICA) and percutaneous coronary intervention (PCI) for all patients admitted with NSTEMI.

*Methods*

For this retrospective observational cohort study initiated by the Netherlands Heart Registration, we extracted Dutch medical claims and diagnosis codes for all NSTEMI patients who underwent PCI. Primary outcome was the time from hospital admission to ICA and PCI in patients admitted to PCI and non-PCI centres. Secondary analyses included the time from ICA to PCI and variation among individual PCI centres.

*Results*

A total of 36,573 NSTEMI patients (median age 68 years, 30% female) were included in the analysis. 24,857 patients (68%) were admitted to a hospital with PCI facilities (*n*= 30) and 11,716 patients (32%) to a hospital without PCI on site (*n*= 42). ICA was performed < 3 days (72 hours) in 33,476 patients (92%). For patients admitted in PCI centres ICA was performed < 3 days in 94% (*n*=23,328), median 0 days (IQR 0-1) vs 87% (*n*= 10,148), median 1 day (IQR 1-2) in non-PCI centres. The longest delay (median 3 days; IQR 2-5) between ICA and PCI occurred in patients first admitted to non-PCI centres and transferred after local ICA.

*Conclusions*

ICA within three days is achieved in a very high percentage of patients in both PCI and non-PCI centres. A clearly larger percentage receives PCI within three days when directly admitted to a PCI centre.

**Key words:** non-ST segment elevation myocardial infarction, invasive coronary angiography; percutaneous coronary intervention; national claims data, time to ICA; time to PCI, length of stay; ACS guidelines

## Abstract (Dutch)

*Achtergrond*

De Nederlandse ACS werkgroep onderschrijft een laat invasieve coronair angiografie (ICA) voor patiënten met een non-ST-segment elevatie myocardinfarct (NSTEMI) als zowel veilig en acceptabel. In deze studie werd de timing van ICA en percutane coronaire interventie (PCI) geanalyseerd voor alle patiënten die met NSTEMI werden opgenomen.

*Methoden*

Retrospectieve observationele cohortstudie geïnitieerd vanuit de PCI-registratiecommissie van de Nederlandse Hart Registratie (NHR). Nederlandse medische verzekeringsgegevens en nationale diagnosecodes van alle patiënten met NSTEMI die een PCI hebben ondergaan zijn verzameld. De primaire uitkomstmaat was de verblijfsduur tot ICA en PCI voor patiënten die werden opgenomen in PCI- en niet-PCI centra. Secundaire analyses omvatten de tijd van ICA tot PCI en de variatie tussen individuele PCI centra.

*Resultaten*

36.573 NSTEMI-patiënten (mediane leeftijd 68 jaar, 30% vrouw) werden geïncludeerd. Hiervan werd 24.857 (68%) opgenomen in ziekenhuizen met PCI faciliteiten (n=30), terwijl 11.716 patiënten (32%) werden opgenomen in ziekenhuizen zonder PCI faciliteiten (n=42). ICA werd bij 33.476 patiënten (92%) uitgevoerd binnen 3 dagen (72 uur). Bij patiënten die initieel in een PCI centrum werden opgenomen, werd bij 94% de ICA binnen 3 dagen uitgevoerd (mediaan 0 dagen, IQR 0-1), vergeleken met 87% in niet-PCI centra (mediaan 1 dag, IQR 1-2). Een delay van mediaan 3 dagen (IQR 2-5) tussen ICA en PCI werd vastgesteld bij patiënten initieel opgenomen in niet-PCI centra en transfer ná lokale ICA.

*Conclusies*

Invasieve coronair angiografie binnen drie dagen werd bereikt bij een zeer hoog percentage patiënten in zowel PCI- als niet-PCI centra. Een duidelijk groter percentage ondergaat PCI binnen drie dagen wanneer zij initieel worden opgenomen in een PCI centrum.

## Introduction

The most recent 2023 guidelines for the management of acute coronary syndromes (ACS) recommend an early invasive strategy, defined as invasive coronary angiography (ICA) within 24 hours of presentation, for high-risk patients with non-ST-segment elevation ACS (NSTE-ACS). This approach is supported by a class IIa recommendation with level A evidence for patients with established non-ST-segment elevation myocardial infarction (NSTEMI), dynamic ST- or T-wave changes, transient ST-segment elevation, or a Global Registry of Acute Coronary Events (GRACE) risk score greater than 140`.[1] However, with regard to composite clinical endpoints, in 11 randomised clinical trials invasive coronary angiography and/or percutaneous coronary intervention (PCI) have no superiority over a delayed invasive strategy (< 72 hours).[1] There was, however an observed survival benefit with an early invasive strategy in patients with a GRACE risk score > 140.[2,3] Recognising variability in clinical practice, the Dutch ACS Working Group provided a schematic overview of key topics to address discrepancies in the management of high-risk NSTE-ACS patients in the Netherlands.[4] Their recommendations suggest that, for patients admitted directly to PCI-capable centres, ICA should ideally be performed within 24 hours, but no later than 72 hours in cases where logistical challenges arise. For patients initially admitted to non-PCI centres, transfer to a hospital with on-site PCI should be considered to ensure ICA is performed within 24 hours, with a 72-hour window as a maximum permissible delay. A Dutch prospective single-centre registry demonstrated that only 59% of high-risk NSTE-ACS patients were treated in accordance with 2015 NSTE ACS guidelines.[5] Furthermore, a retrospective analysis of claims data from 9,641 patients covered by one of the largest health insurance companies in the Netherlands found that direct admission to PCI-capable centres for NSTE-ACS was associated with shorter hospital stays, faster time to revascularisation, fewer interhospital transfers, and reduced overall healthcare costs compared to patients initially presenting to non-PCI centres.[6] Data on adherence to the latest 2023 guidelines for NSTEMI patients are currently lacking. Therefore, we aim to evaluate the timing of ICA and PCI of NSTEMI patients treated with PCI in a nationwide retrospective cohort.

## Methods

This study is part of a quality project initiated by the Netherlands Heart Registration (NHR), in close collaboration with the Dutch Association of Health Insurers (Zorgverzekeraars Nederland) and the Dutch Health Care Information Centre (Vektis). The aim of the project was to investigate the feasibility of using claims data for quality improvement purposes and to create, without extra registration burden, relevant new insights for the monitoring and further improvement of the quality of care. A pilot project was initiated with the PCI registration committee of the NHR.

Within the NHR, cardiologists and cardiothoracic surgeons register baseline, procedural and outcome data for all invasive cardiac interventional, electrophysiological and surgical procedures. Through public reporting, the NHR supports cardiac patients, healthcare providers, and policymakers by making outcome data transparent.[7] The platform for the interpretation of the registered data is primarily embedded in registration committees, in which mandated cardiologists and cardiothoracic surgeons represent their hospitals. In cases of relevant outcome variation, healthcare delivery processes are discussed, and best practices are shared. In addition, quality improvement projects, including the presented study, are initiated. The PCI registration committee agreed to full transparency of the data in these quality projects.

## Study design

*National claims database*

For this retrospective, observational cohort study, data were extracted from a national medical claims database (Vektis). Dutch residents (excluding military personnel and prisoners) who are (obliged) insured for health care costs are registered in a central database. These data consist of registered claims data of all health insurance companies in the Netherlands. All Dutch hospitals register diagnoses and procedures in the diagnosis-treatment combination (DBC), which is the current reimbursement system in the Netherlands. This system is comparable to the diagnosis-related group (DRG) system in other countries.[8] Eventually, the reimbursements are processed by insurance companies. These nationwide claims data are validated for quality assessments in the Netherlands. Baseline characteristics, diagnoses, and individual medication were highly accurate between the claims database and the patient records.[9]

*Study population*

The study population consisted of adult patients diagnosed with NSTEMI and treated with a PCI between 1 January 2018 and 31 December 2021. When multiple PCI's were performed in the same patient within 365 days, we only included the first PCI in the analysis. As NSTEMI patients can be admitted to PCI centres as well as to non-PCI centres, both were included.



*Outcome measures*

The primary outcome measures were the duration of hospitalisation prior to ICA and PCI. The length of stay was defined as the number of consecutive days between the date of the index admission and the date of the first ICA or PCI procedure. Length of stay was calculated for the total cohort, as well as for the separate years. Also the variation among individual centres was assessed. The secondary outcome was the time from ICA to PCI, defined as the number of days between the index ICA and the date of the PCI procedure (acute PCI, one-vessel PCI, multivessel PCI, or PCI with FFR guidance). In cases where PCI was performed

without a separately registered ICA, it ICA was assumed that ICA occurred simultaneously (in the same procedure) with the index PCI. The length of stay from ICA to PCI was obtained for all patients admitted to PCI and non-PCI centres. For patients admitted to non-PCI centres, the time interval between the date of local ICA and referral to a hospital with PCI facilities were also extracted.

*Statistical and data analysis*

Continuous data were summarised as mean and standard deviation (SD) if normally distributed. In cases of non-normal distribution, medians with 25$^{th}$ and 75$^{th}$ percentiles were presented. Categorical data were summarised as frequencies and percentages. All analyses were performed for the total PCI group, and separately for patients primarily admitted to PCI centres and patients who were primarily admitted to a non-PCI centre. Data analyses were performed using SAS software version 9.4, SAS Institute Inc. (NC, United States) .

## Results

A total of 36,573 patients with NSTEMI followed by PCI were included in the analysis. The median age was 68 years (IQR 59 - 76) and 30% of the cohort were female. A total of 24,857 patients (68%) were directly admitted to a hospital with PCI facilities on-site (*n*= 30), whereas 11,716 patients (32%) were initially sent to hospitals without PCI on-site PCI (*n*= 42). Baseline characteristics are presented in Tab. 1.

**Table 1. Patient characteristics 2018-2021**

| | *Total cohort (n= 36,573)* | *Patients admitted to PCI centre (n= 24,857)* | *Patients admitted to non-PCI centre (n= 11,716)* |
|---|---|---|---|
| Age (years), median (IQR) | 68 (59-76) | 68 (58-76) | 69 (60-77) |
| Female sex, *N* (%) | 10,871 (30) | 7,276 (29) | 3,595 (31) |

*IQR* = interquartile range; *PCI = percutaneous coronary intervention*

*Primary outcome measures*

For the total cohort, ICA was performed  3 days (< 72 hours) in 33,476 patients (92%). The median time to ICA was 1 day (IQR 0-2). Among patients admitted to a PCI centre, ICA was performed within 3 days in 94% (*n*= 23,328), with a median time from admission of 0 days (IQR 0-1). In patients admitted to a non-PCI centre, ICA was performed within 3 days in 87% (*n*= 10,148), with a median time from admission of 1 day (IQR 1-2). (Infographic: Fig.1). Fig. 2 and Tab. 2 present the analysis of time to ICA. For the total cohort, 77% (*n*= 28,209) underwent PCI within 3 days. The median time to PCI was 1 day (IQR 0-3) and this was consistent throughout the years 2018-2021. PCI within 3 days was achieved in 90% of patients (*n*= 22,295) admitted to a PCI centre (median 0 days; IQR 0-2), compared to 50% of patients (*n*= 5,914) in a non-PCI centre (median3 days; IQR 2-6). Fig. 3 and Tab. 2 present the analysis of time to PCI.

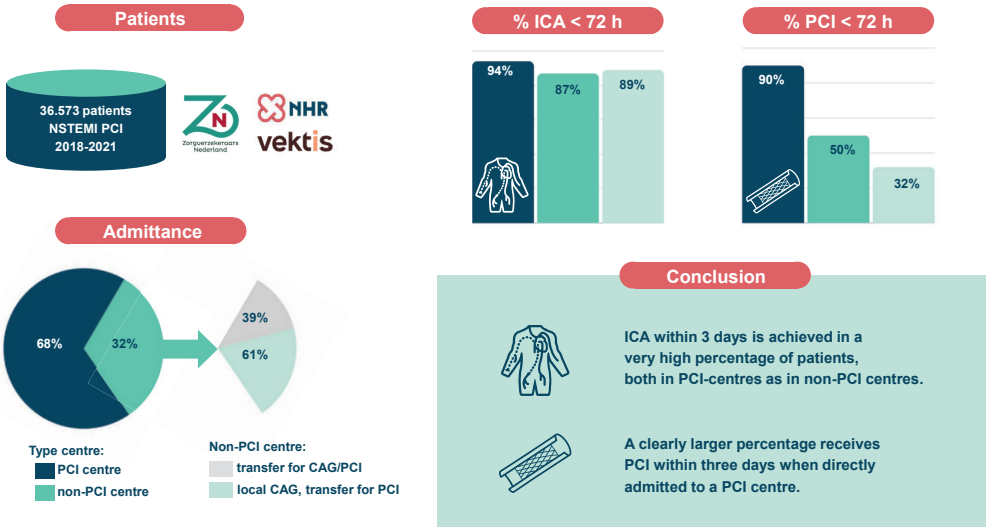



**Figure 1. Infographic**

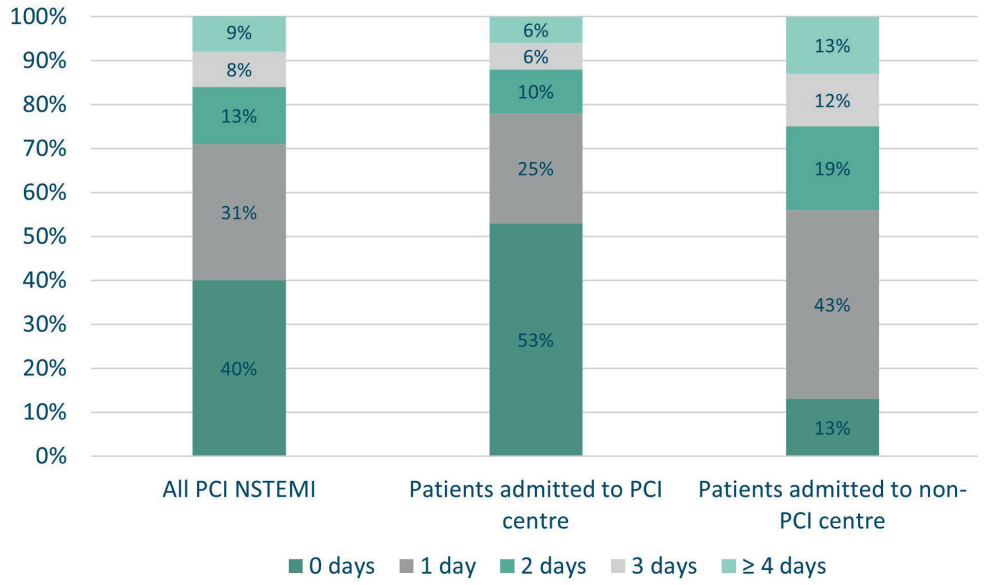



**Figure 2. Time from admission to ICA.** ICA= invasive coronary angiography; NSTEMI=non-ST segment elevation myocardial infarction ; PCI=percutaneous coronary intervention

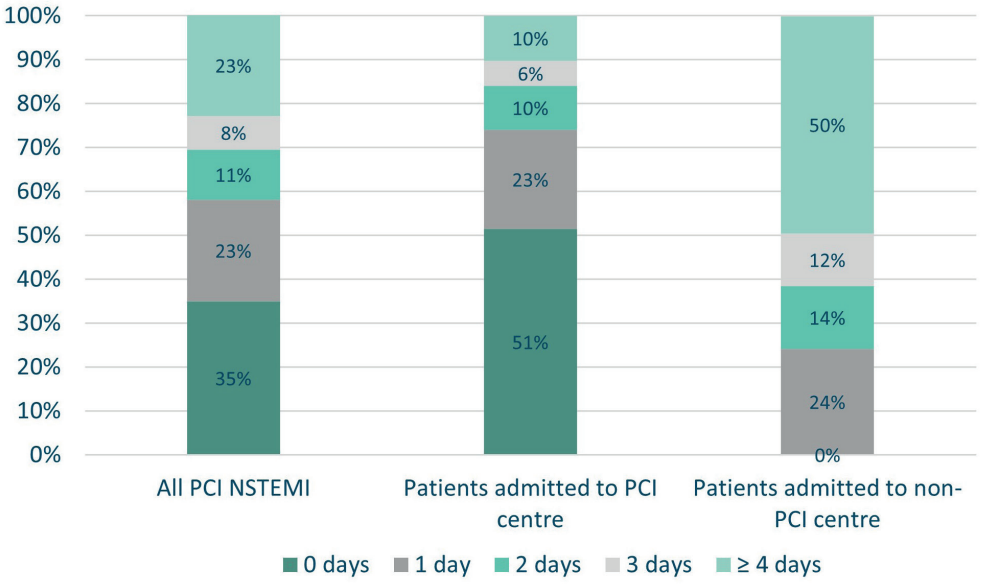



**Figure 3. Time from admission to PCI**

PCI=percutaneous coronary intervention; NSTEMI=non-ST segment elevation myocardial infarction

*Secondary analyses*

For the total cohort, median time form ICA to PCI was 0 days (IQR 0-0) as demonstrated in Tab. 2. The time window between ICA and PCI was median 0 days (IQR 0-0) in patients admitted in PCI-centres compared to 1 day (IQR 0-4) for the patients initially admitted in in non-PCI centres. 61% of patients (*n*= 7,124) admitted to a non-PCI centre underwent ICA before referral to a centre with PCI on-site. In these patients, ICA was performed within 3 days in 89% (*n*= 6,331) and PCI within 3 days in 32% (*n*= 2,260). The waiting time in these *n* = 7,124 patients between ICA and PCI was 3 days (IQR 2-5*).* Fig. 4 illustrates the heterogeneity in waiting times for PCI across different centres.

**Table 2: Timing of invasive strategy: PCI vs non-PCI centre (2018-2021)**

| | *Total cohort (n= 36,573)* | *Patients admitted to PCI centre (n= 24,857)* | *Patients admitted to non-PCI centre (n= 11,716)* | *Patients admitted to non-PCI centre with local ICA (n= 7,124)* |
|---|---|---|---|---|
| Time from admission to ICA, median (IQR) | 1 (0-2) | 0 (0-1) | 1 (1-2) | 1 (1-2) |
| 0 days *n* (%) | 14,726 (40.3%) | 13,248 (53,3%) | 1,478 (12,6%) | 1,401 (19,7%) |
| 1 days *n* (%) | 11,159 (30,5%) | 6,123 (24,6%) | 5,036 (43,0%) | 2,665 (37,4%) |
| 2 days *n* (%) | 4,844 (13,2%) | 2,566 (10,3%) | 2,278 (19,4%) | 1,394 (19,6%) |
| 3 days *n* (%) | 2,747 (7,5%) | 1,391 (5,6%) | 1,356 (11,6%) | 871 (12,2%) |
| ≥ 4 days *n* (%) | 3,097 (8,5%) | 1,529 (6,2%) | 1,568 (13,4%) | 793 (11,1%) |
| Time from ICA to PCI, median (IQR) | 0 (0-0) | 0 (0-0) | 1 (0-4) | 3 (2-5) |
| 0 days *n* (%) | 27,784 (76,0%) | 23,061 (92,8%) | 4,723 (40,3%) | 436 (6%) |
| 1 days *n* (%) | 1,537 (4,2%) | 266 (1,1%) | 1,271 (10,8%) | 1,219 (17%) |
| 2 days *n* (%) | 1,708 (4,7%) | 331 (1,3%) | 1,377 (11,8%) | 1,314 (18%) |
| 3 days *n* (%) | 1,307 (3,6%) | 241 (1,0%) | 1,066 (9,1%) | 1,017 (14%) |
| ≥ 4 days *n* (%) | 4,237 (11,6%) | 958 (3,9%) | 3,279 (28,0%) | 3,138 (44%) |
| Time from admission to PCI, median (IQR) | 1 (0-3) | 0 (0-2) | 3 (2-6) | 5 (3-7) |
| 0 days *n* (%) | 12,769 (34,9%) | 12,769 (51,4%) | 0 (0,0%) | 0 |
| 1 days *n* (%) | 8,447 (23,1%) | 5,623 (22,6%) | 2,824 (24,1%) | 543 (7,6%) |
| 2 days *n* (%) | 4,165 (11,4%) | 2,486 (10,0%) | 1,679 (14,3%) | 807 (11,3%) |
| 3 days *n* (%) | 2,828 (7,7%) | 1,417 (5,7%) | 1,411 (12,0%) | 910 (12,8%) |
| ≥ 4 days *n* (% | 8,364 (22,9%) | 2,562 (10,3%) | 5,802 (49,5%) | 4,864 (68,3%) |

*ICA* = invasive coronary angiography; *IQR* = interquartile range; *PCI* = percutaneous coronary intervention

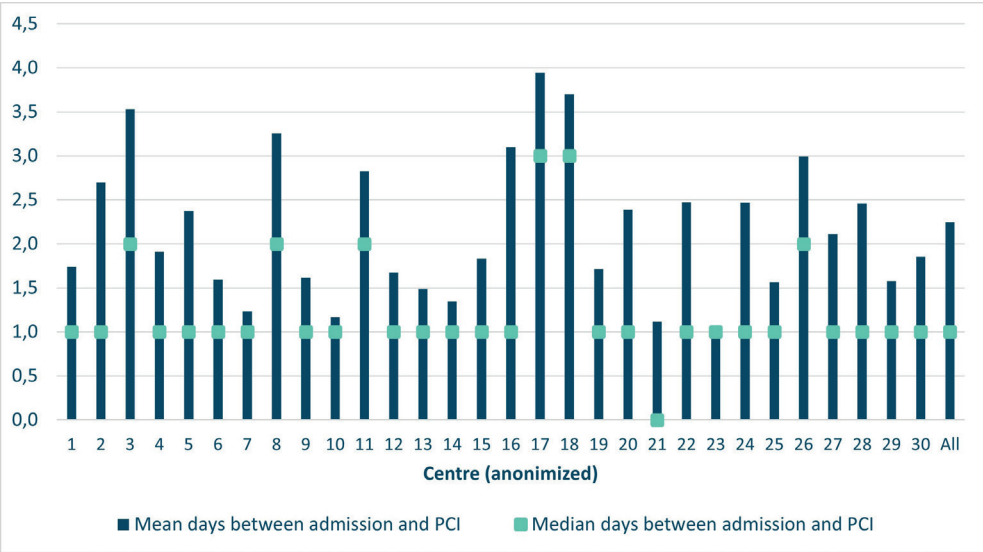



**Figure 4. Time from admission to PCI, per individual PCI centre (2018-2021)**
PCI=percutaneous coronary intervention

## Discussion

The key finding of this nationwide retrospective cohort study was that in patients diagnosed with NSTEMI followed by PCI, an invasive evaluation (ICA) within 3 days (72 hours) is achieved in a very high percentage of patients, both in PCI-centres (94%) as in non-PCI centres (87%). For the total cohort, 92% underwent ICA within 3 days, which is the time window as recommended by the Dutch ACS working group. However, when considering the latest European NSTE-ACS guidelines, the adherence rate of an early (< 24 h) invasive strategy in the Netherlands is below the class IIa recommendation of the ESC. Is should be noted that ICA within 24 hours for stable NSTEMI patients (without very high-risk criteria) was downgraded from a class I to a class IIa recommendation, and therefore should be merely considered, as there is no superiority in death or non-fatal myocardial infarction in several large meta-analysis.[1] Overall adherence to the ESC guidelines showed conflicting results. In a national registry from Germany, university and academic hospitals showed the highest rate of guideline adherence, with almost 99% of the hospitals reporting immediate invasive management within 24 hours in patients with NSTE-ACS [10]. Outside Europe, a nationwide registry study in China showed that hospitals had much less guideline adherence, with PCI performed within 72 hours after admission in only 31% of patients with NSTE-ACS. One third of the patients with intermediate to very high risk did not undergo invasive evaluation or treatment at all.[11]

Overall adherence to perform invasive coronary angiography meets the Dutch standards, although there is a variation in waiting time to PCI between the 30 Dutch PCI centres. The Dutch ACS Working Group endorses a delayed invasive strategy for NSTEMI patients, considering it both safe and acceptable.[4] Further reductions in waiting times could be achieved by sharing best practices (such as about in-hospital logistics, improvement of transfer and waiting times), which can encourage hospitals to shorten the time from diagnosis to ICA and subsequent PCI. Implementing best practices can further enhance the quality of care (i.e. patient satisfaction) for NSTEMI patients in the Netherlands. Our secondary analysis showed that 19% of the total cohort (*n*=7,124) underwent ICA in a non-PCI centre before being transported to a hospital with PCI facilities. Although guideline adherence is high even among patients who underwent local ICA in non-PCI centres (89%), this approach leads to a delay in PCI treatment. The longer waiting time in these patients is recognisable in real world. In a sub-analysis from the EARLY-ACS trial, timely angiography and revascularisation were often not achieved in transferred patients versus patients presented at hospitals with direct PCI capabilities.[12] However, it is still unknown if an early invasive strategy leads to better clinical outcomes.[13,14]. In a prospective multicentre two cohort study, the prehospital identification of patients eligible for direct transfer to PCI centres has proven feasible, leading to a reduction in hospital length of stay and healthcare costs.[15] Though transporting all NSTEMI patients to PCI centres would present significant logistical challenges for both ambulance services and catheterisation laboratories. Evidence from a prospective single-centre registry in the Netherlands indicates that only 59% of NSTEMI patients underwent PCI treatment.[5] In this registry, 23% received conservative treatment, while 18% required a CABG, suggesting a significant number of these transfers to PCI centres may have been unnecessary. Therefore, advice of a preferred admittance or a direct transfer of diagnosed NSTEMI patients to PCI centres remains a subject of ongoing debate. Currently, no randomised clinical trials have evaluated the strategy of initial ICA at PCI versus non-PCI centres with respect to healthcare resources and costs. Reducing ambulance transports and the number of ICAs in non-PCI centres can enhance the efficiency of healthcare. Future studies have to address this issue.



*Strengths and limitations*

An important strength of this study is the national coverage: national claim data of all health insurance companies in the Netherlands were analysed. Data from NSTEMI patients who underwent PCI were included. The validity of the use of medical claims data for quality purposes has been assessed by Van Eindhoven et al. by means of retrospective records reviews in patients with acute myocardial infarction. Baseline characteristics, diagnosis and individual medication were comparable between the national claims data and the medical records in four representative hospitals.[9] A limitation of this study is the inability to include patients' clinical baseline characteristics, as this information was not available in the claims database. As a result, we were unable to identify NSTEMI patients who might benefit from

early invasive coronary evaluation, such as those with high-risk criteria. In future, linking medical claims data with clinical data (e.g. from the Netherlands Heart Registration with Dutch Hospital Data) could provide valuable insights for identifying patients who would benefit most from early ICA and/or PCI.[7] Finally, time intervals were recorded in days, as the claims database did not provide time stamps with hour-level precision.

## Conclusion

In patients with NSTEMI treated with PCI, ICA within 3 days (72 hours) is achieved in a very high percentage of patients, both in PCI-centres (94%) as in non-PCI centres (87%). A clearly larger percentage of patients receive PCI within three days when first admitted to a PCI centre.

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# Chapter 11

## Costs analysis from a randomized comparison of immediate versus delayed angiography in patients successfully resuscitated after out-of-hospital cardiac arrest

### health economic implications of the COACT trial

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## ABSTRACT

**Background**

In out-of-hospital cardiac arrest (OHCA) patients without ST-segment elevation, immediate coronary angiography did not improve clinical outcomes when compared to delayed angiography in the Coronary Angiography after Cardiac Arrest (COACT) trial. Whether one of the two strategies has benefits in terms of healthcare resource use and costs is currently unknown.

**Methods**

538 patients were included in the COACT trial and randomized to either a strategy of immediate or delayed coronary angiography. A cost consequence analysis was performed. Detailed healthcare resource use and cost-prices were collected from the initial hospital episode and compared between both groups. A generalized model with a log link function and a gamma distribution was performed. Generic quality of life was measured with the RAND36 and collected at 12 months follow-up.

**Results**

Overall costs until discharge did not show a statistically significant difference (EUR 33575 vs EUR 33880, P = 0.86). For the immediate angiography group, mean procedural costs (CAG and/or PCI, coronary artery bypass graft) were higher when compared to the delayed angiography group (EUR 4384 vs EUR 3028 (P<0.001). Costs concerning Intensive Care Unit and ward stay did not differ between groups. At 12 months, the median for the RAND-36 questionnaire physical component score was 49.2 in the immediate angiography group and 50.4 in the delayed group p=0.57.

**Conclusions**

The mean total costs between OHCA patients randomized to an immediate angiography or a delayed invasive strategy were similar. With respect to the higher invasive procedure costs in the immediate group, a strategy awaiting neurological recovery followed by coronary angiography and planned revascularization can be considered.

Clinical trial registration number: NTR 4973 (NL4857)

## Introduction

The outcome of patients with out-of-hospital cardiac arrest (OHCA) remains poor with survival to hospital discharge ranging between 10-30%.[1] Even after the return of spontaneous circulation has been achieved, mortality is still around 40%.[2] The leading cause of in-hospital mortality is poor neurologic outcome, which cannot be predicted in the very early phase after cardiac arrest.[3] While international guidelines recommend emergency coronary angiography (CAG) and percutaneous coronary intervention (PCI) in selected patients after OHCA[3,4], the right timing of intervention is still under debate.[5,6] However, emergency angiography in patients without a coronary or ischemic cause of the OHCA can further delay evidence-based interventions on survival like targeted temperature management and hemodynamic support. The Coronary Angiography after Cardiac Arrest (COACT) trial was designed to address this issue. In this investigator-initiated, randomized, open-label, multicenter trial, a strategy of immediate coronary angiography was compared with a strategy of delayed angiography in patients who had been successfully resuscitated after cardiac arrest and did not have ST-segment elevation on electrocardiography (ECG).[7] With respect to 90 days survival no significant difference was seen between the two groups.[8] Also no improvement in 1-year clinical outcome was observed.[9] A recent meta-analysis of 3581 patients (11 studies) also found no significant difference in 30-day mortality, neurological outcome and PCI rate between early versus non-early CAG in OHCA without ST-segment elevation.[10] In case of equivalence with regard to health outcomes it is important to assess the costs related to either strategy. Significant differences in costs between the two modalities can provide information for policymaking and help in final decision-making about the implementation of either an immediate or delayed angiography strategy in patients with OHCA. Total costs related to managing patients with OHCA are mainly driven by in-hospital costs and length of stay at the Intensive Care Unit (ICU) during the initial hospitalization (11,12). We performed a pre-specified cost-consequence analysis at discharge and collected RAND-36 quality of life scores at 12 months.

### Methods

Details of the COACT trial have been published previously.[7-9]In summary, the COACT was a multicenter, randomized, controlled open-label trial involving 19 hospitals in the Netherlands. Between January 2015 and July 2018, a total of 552 comatose OHCA patients with an initial shockable rhythm and without ST-segment elevation on the ECG were randomized in a 1:1 ratio to undergo immediate or delayed coronary angiography. Antithrombotic and revascularization strategies were left to the discretion of the treating physicians and followed prevailing guideline recommendations.[4] Unstable coronary lesions, including a stenosis of at least 70%, were recommended to treat by the study protocol. Post-resuscitation care, including targeted temperature management, was in line with current

resuscitation guidelines.[3] Patients were followed up by telephone interview conducted 90 days and one year after randomization.

*Health care resource use and cost-prices*
Resource use data were collected for all patients included. Data from the following important cost-intensive procedures during admittance were collected: coronary angiography (immediate or delayed), coronary revascularization by percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) and implantable cardioverter defibrillator (ICD) implants. PCI was categorized as immediate (acute), elective and staged.

Healthcare costs were evaluated from the perspective of the Dutch healthcare system. The cost-prices of ICU, CCU and ward admission were determined per day according to the 2018 reference list of the Dutch National Healthcare Institute.[13] Hospital procedure costs are based on standard 2018 list prices and the Diagnosis treatment combination to transparency (DOT), the current reimbursement system in the Netherlands. This DOT is comparable with the diagnosis-related group (DRG) system in other countries. See supplementary table 1 for a detailed description of the average prices of ICU, CCU and ward days and the list prices for health care activities and procedures.

*Subgroup analysis*
Resource use and costs were compared between the immediate and delayed angiography groups for the following subgroups: age ≥ 70 years and < 70 years, male, female, known diabetes mellitus, prior myocardial infarction, prior CABG, patients who survived to discharge and patients who did not survive.

*Statistical analysis*
Continuous data were summarized as mean and standard deviation (SD). Categorical data were summarized by frequencies and percentages. For the cost analysis, mean differences and 95% confidence intervals (CI) for differences were calculated (univariable analysis).

Cost is usually a parameter with a skewed distribution. To take this into account as well as possible heteroscedasticity, an additional cost analysis was performed using a generalized linear model (GLM) with a log link function relating the conditional mean to independent variables and using a gamma distribution specifying the relationship between the variance and the mean.

All data analyses were performed using SPSS statistics version 25 (IBM, New York, United States)

*Quality of* life

Generic quality of life was measured with the RAND-36 and collected at 12 months follow-up. The following domains were measured: physical functioning, social functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, energy/fatigue, and general health perceptions.

## Results

After exclusion of patients without available written consent, 538 patients were eligible for inclusion in the COACT trial. In total, 17 patients were excluded (8 in the immediate and 9 in the delayed angiography group) due to missing data (no hospital admission and/or ICU data). Thus, data from 521 patients was available for cost analysis: 265 patients in the immediate angiography group and 256 patients in the delayed group. Baseline characteristics are shown in table 1. Both groups showed no difference with respect to demographic and clinical characteristics. In most patients, the cardiac arrest was witnessed by bystanders and the median time to basic life support was within five minutes. Patients were predominantly male.

**Table 1. Baseline characteristics**

| | **Immediate angiography group (N=265)** | **Delayed angiography group (N=256)** | **P-value** |
|---|---|---|---|
| Age (yrs) | 68 (58-75) | 66 (57-74) | 0.199 |
| Male sex | 216 (82) | 184 (76) | 0.110 |
| Hypertension | 129 (49) | 122 (48) | 0.719 |
| Previous myocardial infarction | 69 (26) | 74 (29) | 0.463 |
| Previous CABG | 40 (15) | 23 (9) | 0.031 |
| Previous PCI | 43 (16) | 59 (23) | 0.052 |
| Previous coronary artery disease | 94 (36) | 93 (36) | 0.839 |
| Previous cerebrovascular accident | 19 (7) | 15 (6) | 0.537 |
| Diabetes Mellitus | 54 (21) | 41 (16) | 0.190 |
| Current Smoker | 49 (20) | 66 (27) | 0.066 |
| Hypercholesterolemia | 70 (27) | 76 (30) | 0.420 |
| Peripheral artery disease | 16 (6) | 23 (9) | 0.206 |
| Arrest witnessed | 212 (80) | 195 (76) | 0.291 |
| Median time from arrest to basic life support (min) | 2 (1-5) | 2 (1-5) | 0.983 |
| Median time from arrest to return of spontaneous circulation (min) | 15 (8-20) | 15 (8-20) | 0.677 |
| APACHE IV score | 108 ± 27 | 106 ± 31 | 0.395 |

The procedures are outlined in table 2. Revascularization was mainly performed by PCI, but most patients were treated conservatively. No significant difference was observed with respect to survival at 90 days and survival until hospital discharge.

**Table 2. Procedures**

| | **Immediate angiography group (N=265)** | **Delayed angiography group (N=256)** | **P-value** |
|---|---|---|---|
| CAG performed, N (%) | 258 (97) | 166 (65) | <0.001 |
| Time from arrest to CAG (hrs), median (IQR) | 2.3 (1.8-3.0) | 123.7 (52.0-200.1) | <0.001 |
| Time from randomization to CAG (hrs), median (IQR) | 0.8 (0.5-1.2) | 122.2 (48.2-209.7) | <0.001 |
| Revascularization, N (%)<br>PCI<br>CABG<br>Conservative treatment | <br>89 (34)<br>17 (6)<br>161 (61) | <br>62 (24)<br>22 (9)<br>173 (68) | <br>0.02<br>0.35<br>0.11 |
| **Survival, N (%)** | | | |
| Survival at 90 days | 171 (65) | 172 (67) | 0.52 |
| Survival until hospital discharge | 173 (65) | 176 (69) | 0.40 |

CAG=coronary angiography, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft

*Health care resource use*

Table 3 shows the healthcare resource use in each group. Similar length of stay in both groups was seen in the duration of intensive care unit hospitalization (both median 5 days). More than one-third (35%) of the participants did not undergo angiography in the delayed group versus 3% in the immediate group. PCI (acute or staged) was performed in a significantly higher proportion of patients in the immediate angiography group ( 33 % vs. 24 %; P = 0.02). On the other hand, CABG was more often performed in the delayed group (6.4% vs. 8.6%; P = 0.35). No statistically significant difference was observed in the rates of ICD implantation and renal support therapy.

**Table 3. Health Care Resource Use**

| | Immediate angiography group (N=265) | Delayed angiography group (N=256) | P-value |
|---|---|---|---|
| **Invasive coronary procedures, N (%)** | | | |
| None | 7 (3) | 89 (35) | <0.001 |
| Immediate CAG only | 154 (58) | 11 (4) | <0.001 |
| Immediate CAG with acute PCI | 61 (23) | 19 (7) | <0.001 |
| Immediate CAG with staged PCI | 20 (8) | 1 (0.4) | <0.001 |
| Immediate CAG with acute PCI and staged PCI | 6 (2) | 0 (0) | <0.001 |
| Immediate CAG with acute PCI and CABG | 2 (0.8) | 1 (0.4) | 1.000 |
| Immediate CAG with planned CABG | 15 (6) | 3 (1.2) | 0.005 |
| Delayed CAG only | 0 (0) | 73 (29) | <0.001 |
| Delayed CAG with direct PCI | 0 (0) | 29 (11.3) | <0.001 |
| Delayed CAG with staged PCI | 0 (0) | 12 (5) | <0.001 |
| Delayed CAG with planned CABG | 0 (0) | 18 (7) | <0.001 |
| **Hospitalization days, median (IQR)** | | | |
| Intensive care unit | 5 (3-7) | 5 (3-7) | 0.62 |
| Ward | 7 (0-16) | 9 (0-17) | 0.30 |
| Total length of stay | 13 (7-22) | 15 (8-23) | 0.16 |
| **Other procedures, N (%)** | | | |
| ICD implantation | 104 (39) | 103 (40) | 0.82 |
| Renal support therapy | 7 (3) | 11 (4) | 0.30 |

*Costs*

The cost drivers at discharge are depicted in table 4 and shown in figure 1. Overall total costs were similar between groups (immediate angiography group EUR 33575 ± 19612 vs delayed angiography group EUR 33880 ± 21044, P = 0.86). Applying the pre-specified GLM for overall costs showed similar results (β 0.991 (95% CI 0.894 – 1.099), p=0.86). Subgroup analysis also showed no difference in costs for any of the subgroups (table 5).

**Table 4. Health Care Costs: Mean Total Costs (SD) in EURO**

| | Immediate angiography group (N=265) | Delayed angiography group (N=256) | P-value | Mean difference in total cost (95% CI) |
|---|---|---|---|---|
| Total costs | 33575 ± 19612 | 33880 ± 21044 | 0.86 | -305 (-3804 to 3195) |
| Costs invasive coronary procedures | 4384 ± 3447 | 3028 ± 4220 | <0.001 | 1356 (694 to 2018) |
| Costs intensive care unit length of stay | 16167 ± 13308 | 16683 ± 13643 | 0.66 | -517 (-2836 to 1803) |
| Costs ward days | 5000 ± 5888 | 5942 ± 8200 | 0.13 | -941 (-2167 to 284) |
| Costs ICD implantations | 8024 ± 10002 | 8226 ± 10046 | 0.82 | -202 (-1928 to 1523) |

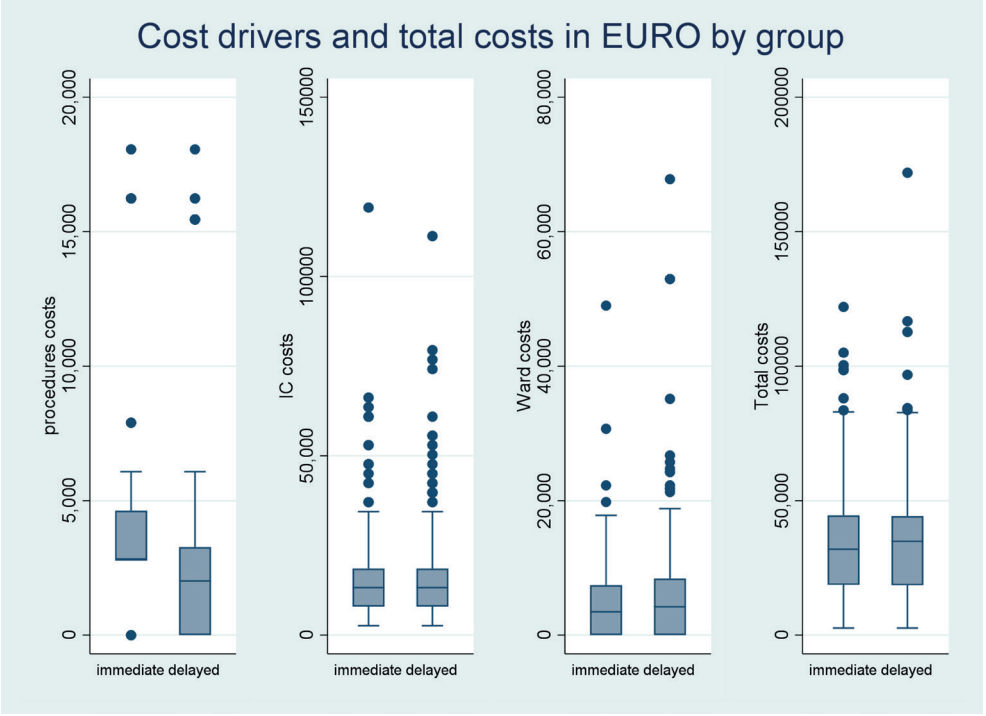



**Figure 1. Cost drivers and total costs in EURO by group**

Box plots of procedure costs, intensive care unit costs, ward costs, and total costs between the immediate and delayed angiography group. IC = intensive care

**Table 5. Subgroups: Mean Total Costs (SD) in EURO**

| | Immediate angiography group | Delayed angiography group | P-value | Mean difference in total cost (95% CI) |
|---|---|---|---|---|
| Age < 70 years (N=312) | 34956 ± 20162 N=150 | 37816 ± 20836 N=162 | 0.22 | -2860 (-7434 to 1714) |
| Age ≥ 70 years (N=209) | 31774 ± 18804 N=115 | 27096 ± 19730 N=94 | 0.08 | 4678 (-592 to 9949) |
| Female (n=111) | 30270 ± 18310 N=49 | 31444 ± 19219 N=62 | 0.75 | -1174 (-8306 to 5957) |
| Male (n=410) | 34325 ± 19859 N=216 | 34658 ± 21584 N=194 | 0.87 | -333 (-4357 to 3691) |
| Diabetes mellitus (N=95) | 27027 ± 19846 N=54 | 30120 ± 21243 N=41 | 0.47 | -3094 (-11509 to 5322) |
| Previous MI (n=143) | 34127 ± 20083 N=69 | 34330 ± 23285 N=74 | 0.96 | -203 (-7415 to 7009) |
| Previous CABG (n=63) | 32864 ± 18410 N=40 | 26704 ± 14325 N=23 | 0.17 | 6160 (-2762 to 15081) |
| Patients who survived at 90 days (N=343) | 40857 ± 18914 N=171 | 40856 ± 20119 N=172 | 1.00 | 0 (-4147 to 4148) |
| Patients who did not survive (N=172) | 20329 ± 12768 N=94 | 19594 ± 14811 N=84 | 0.72 | 734 (-3346 to 4814) |

The costs for individual components differed. The mean costs of invasive coronary procedures (CAG, PCI and/or CABG) were higher in the immediate group (EUR 4384 ± 3447 vs EUR 3028 ± 4220, P<0.001). Costs of hospitalization were EUR 16167 ± 13308 vs EUR 16683 ± 13643, P=0.66 for ICU admission and EUR 5000 ± 5888 vs EUR 5942 ±8200, P=0.13 for the ward days. Total length of stay was median 13 days in the immediate group vs median 15 days in the delayed group, P=0.16).



*Quality of life*

Quality of life values were obtained in 235 of the 329 patients who survived until 1 year. No difference was found between the two treatment groups at one year. The median for the RAND-36 questionnaire physical component score was 49.2 (IQR 42.2-55.3) in the immediate angiography group and 50.4 (IQR 44.9-55.2) in the delayed group (P=0.57). The mental component of the RAND36 reveals a median of 51.3 (IQR 42.4-56.4) in the immediate angiography group and 50.0 (IQR 42.8-56.2) in the delayed group (P=0.55).

## Discussion

Our key finding is that at discharge, mean total costs are similar for strategies of either immediate or delayed coronary angiography and subsequent PCI in patients with OHCA without ST-segment elevation. However, the immediate strategy resulted in higher invasive procedure costs associated with higher rates of coronary angiography, additional PCI and staged PCI. A total of 35% of the patients in the delayed group did not receive coronary angiography compared to 3% in the immediate angiography group. This difference could be explained by early death rates before angiography could take place in the delayed group on the one hand. On the other hand, CAG in this group was often withheld due to an alternative non cardiac diagnosis. Patients who did survive and did not undergo angiography were those with neurological sequelae, co-morbidities and the use of non-invasive imaging. Also, more PCI procedures were observed in the immediate group, which can be explained by the urge of the intervention team to treat a possible culprit lesion. In the end, the higher costs in the immediate strategy group were balanced by the higher duration of total length of stay and a higher (non-significant) cost of ICD implantations in the delayed angiography group. This would explain the equivalence of mean total costs in both groups.

Costs might be saved when evaluating only those patients with good neurological recovery. From the doctor's perspective, work during out-of-office hours should be taken into consideration. During these circumstances, staffing is limited and each coronary intervention is labor-intensive, which eventually leads to more costs. There is no harm in terms of mortality when patients are scheduled in a controlled environment during daily office hours. Also the duration of hospital admittance can be reduced hypothetically by better up-front diagnosis at the emergency department. Standard total body CT-scan before ICU admittance might help in the early identification of a non-cardiac cause of the cardiac arrest.

In patients with non-ST segment elevation acute coronary syndrome (NSTE-ACS), cost-effectiveness trials without a setting of prehospital cardiac arrest reveal conflicting results. The Treat Angina with Aggrestat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) – thrombolysis in Myocardial INfarction (TIMI) 18 trial randomized 2220 patients with unstable angina pectoris and/or non-ST segment elevation myocardial infarction (NSTEMI) to an early invasive strategy or conservative management. Early CAG was preferred in terms of cost per year of life gained ($ 12739, range $8371 - $25769) compared to a conservative strategy.[14] In a cost-effectiveness analysis in patients with NSTE-ACS included in the third Randomised Intervention Trial of unstable Angina (RITA-3), mean incremental cost per QALY gained was most likely to benefit intermediate and high-risk patients.[15] However in The Fast Revascularisation during InStability in Coronary artery disease (FRISC) II trial an early interventional strategy was not cost-effective in the short-term.[16] In a more recent economic analysis, a strategy of

early invasive CAG versus medical management showed no benefit in elderly patients (> 75 years) diagnosed with NSTEMI in terms of cost-effectiveness and quality-adjusted life-year (QALY) gained .[17] Exploratory subgroup analyses suggested that sex did not affect mean total costs. In a previous analysis, this subgroup did not affect the clinical outcome as well.[18] Several ongoing trials should be mentioned. Their results will add further knowledge regarding the timing of coronary angiography in patients with an OHCA. The Direct or Subacute Coronary Angiography in Out-of-Hospital Cardiac Arrest study (DISCO), is an international multicenter trial recruiting 1006 patients with OHCA randomized to CAG as soon as possible versus delayed/selective CAG.[19] The TOMAHAWK[20] and ARREST[21] are trials with a similar design and patient population. We are eagerly awaiting the results of these trials and a costs-analysis. Also health economic implication might add additional evidence.

*Limitations*

Our cost analyses include patient-level resource consumption only from admittance until discharge. However, the highest impact on survival in both groups was seen within 15 days since randomization which approximates the median hospital duration in both arms. Moreover, neurological status at discharge (cerebral performance score, Glasgow coma scale) did not differ between the treatment arms, leading to a similar rehabilitation process and subsequent similar work disability. No quality of life scores were obtained at 90 days. However, RAND-36 quality of life scores were available at 12 months. As a result, we opted for a cost-consequence analysis instead of a cost-effectiveness analysis. In the latter case, it is essential that costs and effects are evaluated over the same timeframe. Moreover, we chose only to show results based on empirical data from our research and therefore not to make assumptions about costs or effect behavior which are not supported by empirical data (for example, extrapolation of cost to reach a 12-month time frame, or shrink QALY scores to a 90 days' timeframe).

## Conclusion

No significant difference in total health care costs is observed between the immediate and delayed coronary angiography strategy group in patients successfully resuscitated after OHCA with an initial shockable rhythm, but without ST-segment elevation. With respect to the higher invasive procedure costs in the immediate group, a strategy awaiting neurological recovery followed by coronary angiography and planned revascularization can be considered.

## Supplementary materials

**Supplementary table 1** - the 2018 reference list of the Dutch National Healthcare Institute

| **Healthcare resource use costs (EUR)** | |
|---|---|
| ICU per day | 2649.44 |
| Ward/CCU per day (weighted average) | 495 |
| **Invasive procedures costs (EUR)** | |
| Immediate CAG only | 2799.69 |
| Immediate CAG with direct PCI | 4623.94 |
| Immediate CAG with staged PCI | 6074.08 |
| Immediate CAG with acute PCI and staged PCI | 7898.33 |
| Immediate CAG with direct PCI and subsequent CABG | 18061.48 |
| Immediate CAG with subsequent CABG | 16237.23 |
| Delayed CAG only | 2015.66 |
| Delayed CAG with direct PCI | 3274.39 |
| Delayed CAG with staged PCI | 5290.05 |
| Delayed CAG with subsequent CABG | 15453.2 |
| ICD implantation | 20445.64 |

ICU = intensive care unit, CCU = cardiac care unit, CAG = coronary angiography, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, ICD = implantable cardioverter defibrillator

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# Chapter 12

## General discussion

As healthcare expenditures continue to rise, the need for accessible cost-saving strategies is becoming increasingly important. In this context, patients at low-risk of developing acute coronary syndrome (ACS) may be an appropriate target group, as the occurrence of non–ST-elevation ACS (NSTE ACS) or ST-elevation myocardial infarction (STEMI) in this population is rare. Ambulance staff and clinicians can effectively differentiate between low- and high-risk. Although we know that these low-risk patients are very unlikely to experience major adverse cardiac events (MACE), randomized clinical trials are still needed because clinicians rely on results of these studies with high level of evidence. This is also because changing established standards of medical care can be challenging, as they are embedded within routine clinical workflows and supported by standardized protocols that guide how healthcare professionals work. The ARTICA (Acute Rule-out of Non–ST-Segment Elevation Acute Coronary Syndrome in the (Pre)Hospital Setting by HEART Score Assessment and a Single Point-of-Care Troponin) study was therefore designed to demonstrate cost-saving superiority while ensuring that MACE outcomes are not compromised.

When NSTE ACS has been diagnosed, efficiency can be found in the optimal timing of antithrombotic therapy and the right timing of invasive coronary angiography (CAG). Antithrombotic pretreatment carries important implications for patients, requiring a careful balance between bleeding risk and the potential for (early) reduction of ischemic events. A standard early CAG strategy affects healthcare logistics, such as the need to transfer patients from non-PCI to PCI centers within a mandatory time window.

Below, we elaborate on the results and conclusions of the studies presented in Chapter 2 – 11 of this thesis.

PART ONE - Healthcare costs and pre-hospital assessment in patients at risk for NSTE ACS: the ARTICA randomized trial (Chapters 2 – 8)

In **Chapter 2**, the design of the ARTICA study is outlined in detail. The ARTICA trial was a randomized, multicenter clinical study conducted across six ambulance regions and focused on patients at low-risk of developing a NSTE ACS. A low-risk profile was defined by a modified HEART ([history–ECG–age–risk factors–troponin]) score ≤3, including a non-elevated point-of-care troponin (POC) measurement. Patients meeting these criteria were randomized either to standard hospital evaluation for ruling out ACS or to a pre-hospital strategy in which low-risk status was identified by ambulance staff and subsequent transport to the (cardiac) emergency department (ED) was withheld. The 30-day and 12-month study endpoints focused on healthcare expenditures and the incidence of MACE, including myocardial infarction, death, or unplanned revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). **Chapters 3 and 4** present the 30-day and final 12-month results, respectively. These findings demonstrate a substantial

reduction in healthcare costs among patients identified as low-risk in the prehospital setting (mean cost differences of EUR 611 at 30 days and EUR 717 at 12 months), favoring the group allowed to remain at home. No differences were observed between groups in the incidence of MACE or in quality-of-life. These results indicate that this pre-hospital strategy is cost-effective and provides strong evidence on safety, supporting its implementation in clinical practice.

**Chapter 5** examines the agreement between ambulance paramedics and physicians in assessing the HEAR score. This prespecified sub analysis showed that ambulance staff achieved agreement with hospital physicians in the majority of cases (88.9%) when classifying patients as low-risk (HEAR score ≤3) for NSTE ACS. However, continuous training in history-taking and electrocardiogram (ECG) interpretation is strongly recommended to further optimize the pre-hospital application of the HEAR score.

In **Chapter 6**, a response is provided concerning the use of non–high sensitivity POC assays in the ARTICA study. It was concluded that the ARTICA algorithm—combining the HEAR score with POC troponin—effectively compensates for the limited sensitivity of a single troponin measurement when used in the broader population of patients presenting with chest pain. This underscores the value of combining a biomarker-based strategy with clinical decision rules, that allow for a comprehensive estimation of the pre-test probability.

**Chapter 7** reports the results of a collaborative project with the Department of Cardiology of the Catharina Hospital in Eindhoven. An individual patient-level meta-analysis was conducted, incorporating studies utilizing HEART-based risk stratification algorithms. HEART-derived clinical risk scores were shown to reliably identify patients at very low-risk of 30-day mortality and MACE. Nonetheless, it should be emphasized that implementation in healthcare systems outside the Netherlands requires additional validation due to heterogeneity in healthcare structure, risk stratification processes, and follow-up capacities.

The first part of the thesis concludes with **Chapter 8**, which provides nationwide recommendations for the pre-hospital triage of patients with suspected ACS. Clinical decision rules incorporating HEART or PREHEART with high-sensitivity POC troponin analyzers should be considered. A nationwide implementation strategy initiated by the national ambulance organization (Ambulancezorg NL) with monitoring of patients left at home is currently being initiated.



PART TWO – Timing of (invasive) treatment in patients with NSTE ACS (Chapters 9 – 11).

**Chapter 9** presents a review of current evidence regarding antithrombotic therapy in patients with NSTE ACS. This literature review highlights that the optimal timing of ticagrelor

administration has not been adequately studied, whereas prasugrel is recommended only after coronary angiography preceding PCI. The indication and timing of an invasive strategy depend on risk stratification, and a mortality benefit has been demonstrated in selected high-risk NSTE ACS patients undergoing early (<24 hours) intervention.

In **Chapter 10**, a retrospective cohort study was conducted involving 36573 NSTEMI patients who underwent PCI between 2018 and 2021. The Dutch Acute Coronary Syndrome (ACS) Working Group considers deferred CAG —up to 72 hours after admission—safe and acceptable for NSTEMI patients. Although European guidelines recommend an invasive approach within 24 hours (class IIa recommendation), evidence supporting improved outcomes with this strategy remains lacking. This study evaluates the timing of invasive angiography and PCI in NSTEMI patients in the Netherlands, stratified by hospital type (PCI versus non-PCI centers). CAG within three days was achieved in a very high percentage of patients (92%) across both PCI centers and non-PCI centers (94% and 87%, respectively). A larger proportion of patients underwent PCI within three days when directly admitted to a PCI center (87% versus 50%). An important strength of this study is the national coverage: national claim data of all health insurance companies in the Netherlands were analyzed. Data from NSTEMI patients who underwent PCI were included. Because clinical baseline characteristics were unavailable, high-risk NSTEMI patients eligible for early invasive evaluation could not be identified.

Part 2 concludes with **Chapter 11**, which reports on a cost analysis involving out-of-hospital cardiac arrest patients without ST-segment elevation on the ECG enrolled in the COACT trial. Patients were randomized to early (within two hours) invasive coronary angiography versus delayed angiography after neurological recovery. The mean total hospital costs during the index admission were similar between the early and delayed strategy groups. Given the higher procedural costs associated with early angiography, a strategy in which neurological recovery is awaited prior to performing invasive coronary angiography—and subsequent (planned) revascularization when indicated—appears justifiable.

## Conclusion

By integrating cost-effectiveness analyses with hard clinical endpoints, clinical trials can offer a more comprehensive and meaningful scientific perspective. This was also seen after the results of the randomized ARTICA trial. Even though observational studies as early as 2013 already suggested that low-risk patients can be identified in the ambulance using a clinical decision rule, real momentum for implementing this strategy only emerged ten years later after the ARTICA trial showed that it could also lead to substantial cost savings. The debate remains open as to whether innovations that generate substantial cost savings can be implemented when non-inferiority for MACE has not been formally demonstrated.

## Future (research) perspectives on the ARTICA

*Prevention*

In addition to the focus on cost savings by withholding referral to cardiac ED's, there is also need to focus on prevention on the long-term. After successful triage, an ACS may be excluded at that particular moment. However, a considerable proportion of patients will have a medium to high long-term cardiovascular risk. Patients in the ARTICA study were low-risk of developing ACS, but a considerable proportion of the population did have an elevated long-term cardiovascular risk profile. Almost 20% of the population in the study had obesitas (BMI > 30 kg/m2), almost 20% had hypertension and more than 25% of the participants was an active smoker. An advantage of hospital evaluation is that it can create an opportunity to give extra attention to primary prevention, which is not entirely possible for patients left home. For the future, continuous lifestyle and cardiovascular risk factor management after prehospital evaluation may be a valuable opportunity.

*Artificial intelligence*

Artificial intelligence (AI) is developing rapidly, and algorithms to support prehospital evaluation may become feasible in the future. AI-driven ECG analysis could assist ambulance staff in more accurately identifying high-risk ECG signs in NSTE ACS (e.g. occlusive myocardial infarction). By combining AI ECG analysis with embedded clinical decision rules including high-sensitivity POC troponin testing, patients can be referred more efficiently to PCI-capable centers when necessary.

*Gender differences*

In the ARTICA trial more women than men were included so no underrepresentation was found. The HEART score appears to be applicable to low-risk women as well, even though history taking was based on the more traditional male presentation and classical risk factors. The role of gender specific symptoms, as well as female-specific cardiovascular risk factors (e.g. early menarche or menopause, polycystic ovary syndrome, breast cancer, and adverse pregnancy outcomes) should also be considered in future studies.

*Intermediate and high risk patients*

The evaluation of patients in the intermediate risk category is very challenging. The role of early non-invasive coronary CT angiography, and which patients may benefit most from this strategy, remains unclear. In addition, the direct transport of high-risk ACS patients to PCI centers has not yet been adequately investigated, particularly in randomized studies. These are key aspects that will be addressed in the upcoming ARTICA-2 trial[1]

[1] https://projecten.zonmw.nl/nl/project/pehospitale-triage-van-patienten-met-intermediair-en-hoog-risico-op-acs-de-artica-2-trial

## Future research perspectives on timing of medical and invasive treatment in NSTEMI

The rationale for pretreating patients with $P2Y_{12}$ inhibitors stems from evidence that periprocedural PCI risk is linked to the degree of platelet inhibition achieved at the time of intervention. Current evidence suggests that pretreatment should be considered only when early invasive coronary angiography (within 48 hours) is not feasible—for example in non-PCI centers where transfer may be delayed—and only when the patient is high-risk, the diagnosis is certain, and the likelihood of requiring surgery is low. In practice, these factors can be difficult to assess. In the past, we have always been cautious about reducing platelet inhibition in NSTEMI because of the thrombotic risk. However, with the latest-generation drug-eluting stents, we are seeing fewer thrombotic complications. This is also reflected in the numerous dual antiplatelet therapy (DAPT) strategy trials, exploring shorter DAPT durations, stopping aspirin early, and the use of mono therapy with a potent $P2Y_{12}$ inhibitor instead of aspirin after PCI. Future research should identify which patients benefit most from pretreatment with $P2Y_{12}$ inhibitors. Prehospital risk assessment using a clinical decision rule combined with high-sensitivity POC troponin may help guide this decision.

The timing of invasive coronary evaluation has consequences for our healthcare logistics in the Netherlands. The Dutch ACS working group recommends a CAG within 72 hours (delayed invasive strategy). Considering the latest European NSTE ACS guidelines, the adherence of an early (< 24 h) invasive strategy in the Netherlands is not in line with the class 2a recommendation of the ESC. It should be noted that CAG within 24 hours for stable NSTEMI patients (without very high-risk criteria) was downgraded in the latest ESC guidelines from a class I to a class IIa recommendation, and therefore should be merely considered, as there is no superiority in death or non-fatal myocardial infarction in several large meta-analysis. Overall adherence to perform CAG meets the Dutch standards, although there is a variation in waiting time to PCI between the 30 Dutch PCI centers. Further reductions in waiting times could be achieved by sharing best practices (such as about in-hospital logistics, improvement of transfer and waiting times), which can encourage hospitals to shorten the time from diagnosis to CAG and subsequent PCI. Implementing best practices can further enhance the quality of care (i.e. patient satisfaction) for NSTEMI patients in the Netherlands.



# Appendices

Nederlandse Samenvatting

Research data management

PhD portfolio

List of publications

Curriculum vitae

Dankwoord

## Nederlandse samenvatting

Pijn op de borst is de meest voorkomende reden voor verwijzing naar een spoedeisende hulp (SEH) of eerste hart hulp (EHH) in Nederland. Pijn op de borst kan wijzen op een hartinfarct of acuut coronair syndroom (ACS) en het uitsluiten hiervan vereist een intensief diagnostisch traject in het ziekenhuis dat gepaard gaat met een hoge belasting van beschikbare zorgmiddelen en daarmee hoge zorgkosten. De ARTICA-studie (acute rule-out of non-ST-segment elevation acute coronary syndrome in the (pre)hospital setting by HEART score assessment and a single point-of-care troponin) vormt het eerste deel van dit proefschrift (**hoofdstukken 2 t/m 8**). De ARTICA trial heeft gekeken naar de doelmatigheid en kosteneffectiviteit van een triagestrategie op de ambulance, waarbij laagrisicopatiënten met een vermoeden op een non-ST-segment elevatie acuut coronair syndroom (NSTE-ACS) al in de ambulance worden geïdentificeerd om af te zien van transport naar het ziekenhuis.
In het tweede deel (**hoofdstukken 9 t/m 11**) wordt nader ingegaan op patiënten met de diagnose NSTE ACS, waarbij de focus ligt op twee belangrijke strategieën om de zorg voor deze patiënten groep te verbeteren: de antitrombotische behandeling en de timing van invasieve coronaire angiografie (CAG). Hiervoor werd een omvangrijk landelijk cohort onderzocht, waarbij gebruik werd gemaakt van gegevens uit de Nederlandse Hartregistratie (NHR) en declaratiedata van alle zorgverzekerden in Nederland (VEKTIS-database). Ten slotte werden de zorgkosten geanalyseerd van buiten het ziekenhuis gereanimeerde patiënten met een non-ST-segment-elevatie myocardinfarct (NSTEMI) die een vroeg invasieve CAG ondergingen (COACT-trial data).

In **hoofdstuk 2** wordt de opzet van de ARTICA studie toegelicht. De ARTICA studie was een gerandomiseerde klinische multicenter studie in zes ambulance regio's bij patiënten met een laag risico op het ontwikkelen van een NSTE ACS. Een laag risico profiel wordt gekenmerkt door een gemodificeerde HEART [history-ecg-age-risk-troponin] score ≤ 3 inclusief een niet verhoogde point-of-care troponine. Deze patiëntengroep werd gerandomiseerd naar evaluatie en uitsluiten van het ACS in het ziekenhuis (standaard zorg) versus pre-hospitaal identificatie van laag risico en afzien van vervoer naar de SEH of EHH. De uitkomsten op 30 dagen en 12 maanden richtten zich op de zorgkosten en het optreden van majeure cardiale events (MACE), waaronder het optreden van een myocardinfarct, overlijden of niet-geplande revascularisatie via percutane coronaire interventie (PCI) dan wel coronaire bypasschirurgie (CABG).

In **hoofdstuk 3** en **hoofdstuk 4** worden respectievelijk de 30-dagen en de 12 maanden resultaten van de ARTICA studie beschreven. Hieruit blijkt dat bij patiënten met een laag risicoprofiel zoals door de ambulance geïdentificeerd, er duidelijke afname is van zorgkosten (gemiddeld verschil van EUR 611 per patiënt op 30 dagen en EUR 717 op 12 maanden) ten faveure voor de groep die thuis kon blijven. Tussen beide groepen werd geen verschil

waargenomen in het optreden van MACE, evenmin als in kwaliteit van leven. Op basis van deze resultaten kan worden geconcludeerd dat deze pre-hospitale strategie kosteneffectief is en ook sterke aanwijzingen biedt voor een veilige implementatie in de klinische praktijk.

In **hoofdstuk 5** werd gekeken naar de overeenkomsten tussen ambulanceverpleegkundigen en artsen in de beoordeling van de HEAR-score. Deze studie toonde aan dat ambulanceverpleegkundigen in het merendeel van de gevallen (88,9%) overeenstemming bereikten met ziekenhuisartsen bij de classificatie van patiënten als laag risico (HEAR-score ≤3) voor NSTE ACS. Voortdurende training in anamnese-afname (history) en ECG-beoordelingen wordt sterk aanbevolen om deze resultaten van het pre-hospitale gebruik van de HEAR-score verder in stand te houden en mogelijk te verbeteren.

In **hoofdstuk 6** wordt een reactie gegeven op de ARTICA studie over het gebruik van niet hoog sensitieve point-of-care troponine bepalingen. De conclusie is dat het ARTICA-algoritme (de combinatie van HEAR score én point-of-care troponine) in staat is het gebrek aan sensitiviteit van alleen een enkele troponinebepaling te compenseren in de totale populatie van patiënten die zich presenteren met pijn op de borst. Dat betekent dat elke biomarker dient te worden gecombineerd met aanvullende klinische beslisregels, om zo tot een zorgvuldige klinische pre-test waarschijnlijkheid te komen. Dit is belangrijk in de uiteindelijk besluitvorming om patiënten thuis te laten.

**Hoofdstuk 7** is het resultaat van een samenwerking met de afdeling Cardiologie van het Catharina Ziekenhuis in Eindhoven. In deze studie werd een individuele patiënt data meta analyse verricht. Diverse studies die gebruik maken van de HEART score algoritme zijn meegenomen in deze analyse. HEART-afgeleide klinische risicoscores identificeren effectief patiënten met een zeer laag risico op 30-dagen mortaliteit en MACE. Wel dient opgemerkt te worden dat implementatie in zorgstelsels buiten Nederland aanvullende validatie vereisen gezien de diversiteit in de structuur van gezondheidszorgsystemen, risicostratificatie en mogelijkheden voor follow-up.

Het eerste deel wordt afgesloten met **hoofdstuk 8** waarin op landelijk niveau aanbevelingen worden gegeven voor de prehospitale triage van patiënten met verdenking op een ACS. Hierin spelen de klinische beslisregels (HEART en PREHEART) een belangrijke rol naast het gebruik van hoog-sensitieve handheld troponine systemen.

**Hoofdstuk 9** beschrijft een review van de huidige stand van zaken in de antitrombotische behandeling van patiënten met een NSTE-ACS. Uit deze literatuuranalyse blijkt dat de optimale timing van ticagrelor niet adequaat is onderzocht, terwijl prasugrel pas wordt aanbevolen na invasieve CAG voorafgaand aan PCI. De invasieve strategie, inclusief de

indicatiestelling en timing van CAG, hangt af van het risicoprofiel van de patiënt. Een mortaliteitsvoordeel is alleen aangetoond bij geselecteerde hoog risico NSTE ACS patiënten die een vroege (<24 uur) interventie ondergaan.

In **hoofdstuk 10** wordt een retrospectieve cohort studie beschreven van 36 573 patiënten met een NSTEMI die een PCI hebben ondergaan tussen 2018 en 2021. De Nederlandse ACS werkgroep beschouwt een uitgestelde invasieve CAG tot 72 uur bij patiënten met NSTEMI als veilig en acceptabel. Europese richtlijnen adviseren echter een invasieve strategie binnen 24 uur, maar bewijs voor betere uitkomsten bij deze aanpak ontbreekt. Deze studie evalueert hoe snel een invasieve CAG en PCI worden uitgevoerd bij NSTEMI-patiënten in Nederland, afhankelijk van het type ziekenhuis van opname: met of zonder PCI-faciliteiten. Invasieve CAG binnen drie dagen wordt bij een zeer hoog percentage patiënten gerealiseerd (92%) in zowel in PCI- als non-PCI-centra (94% respectievelijk 87%). Een duidelijk groter deel van de patiënten ondergaat binnen drie dagen een PCI bij directe opname in een PCI-centrum 87% respectievelijk 50%.

Deel 2 wordt afgesloten met **hoofdstuk 11** waarin een studie werd uitgevoerd naar de ziekenhuiskosten in gereanimeerde patiënten buiten het ziekenhuis met een NSTEMI die in het kader van de COACT trial werden gerandomiseerd naar vroeg (binnen 2 uur) invasieve CAG versus invasieve CAG na herstel van neurologie. De gemiddelde totale kosten bij patiënten met een buiten het ziekenhuis opgetreden circulatiestilstand, die gerandomiseerd werden naar vroege invasieve CAG of een uitgestelde invasieve strategie, bleken tijdens de initiële ziekenhuisopname vergelijkbaar. In het licht van de hogere kosten van invasieve procedures in de vroeg invasieve CAG groep, is een strategie te verdedigen waarbij eerst neurologisch herstel wordt afgewacht, gevolgd door invasieve CAG en zo nodig aanvullende (geplande) revascularisatie.

## Research datamanagement

The research data presented in this thesis were collected during my PhD training at the Department of Cardiology, Center for cardiovascular care, Radboud university medical center Nijmegen, The Netherlands

## Ethics and privacy

This thesis is based on the results of research studies involving human participants, which were conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct and Radboudumc policy. The recognized Medical Ethics Review Committee 'METC Oost-Nederland' has given approval to conduct the ARTICA trial (**Chapters 2 – 5**). File number: NL66755.091.18). The institutional ethical review committee CMO Radboudumc, Nijmegen, the Netherlands has given approval to conduct the ARTICA trial (CMO Radboudumc dossier number: 2018-4674). Chapter 7 is an individual patient data meta-analysis and this study was reviewed and approved by the regional and local Medical Ethics Committees of the participating medical centres (MEC-U dossier number W23.140). **Chapter 11** is a prespecified substudy using data from the COACT trial (NL49015.029.14). The COACT trial received ethical approval from the METC VUmc under dossier number 2014.273.

According to Dutch legislation, data collection from electronic patient files was performed by personnel with a treatment relationship with the patient AND/OR by the researcher(s) upon consent by the study participant. The privacy of the participants in these studies was warranted by the use of pseudonymization. The pseudonymization key was stored on a secured network drive that was only accessible to members of the project who needed access to it because of their role

Informed consent was obtained from participants to collect and process their data for this research project. Consent was also obtained for the sharing and reuse of the pseudonymized data for future research, as applied in the individual patient data meta-analysis presented in Chapter 7.

## Data collection and storage

Data for **Chapter 3 – 5** was obtained by using Castor EDC for secured online questionnaires. Data for **Chapters 3 – 5** and **Chapter 11** was collected through electronic Case Report Forms (eCRF) of a prospective data collection in Castor EDC. Data were converged from (electronic) health records or Castor EDC to SPSS (SPSS Inc., Chicago, Illinois, USA).

Processed data and documentation (research protocol, experimental setup, codebook, software versions and a readme file) are archived in a data Repository*

Data from **Chapter 3 – 5** was stored and analyzed on the department research server (Q:\ Cardio_Opslag) and in Castor EDC and are only accessible by project members (C. Camaro, G.W.A. Aarts) working at the Radboudumc. These secure storage options safeguard the availability, integrity and confidentiality of the data. Paper (hardcopy) data is stored in secured cabinets within the Cardiology research department.

## Data sharing according to the fair principles

**Chapters 2 – 7 and Chapters 9 – 11** are published open access. Chapters 8 has been submitted for publication and is currently under review.
**Chapter 7** is based on existing data and available for reuse from the original authors of six published articles (DOI: 10.1093/eurheartj/ehad056, DOI: 10.1136/emermed-2020-210212, DOI: 10.1371/journal.pone.0239460, DOI: 10.1093/ehjacc/zuab109, DOI: 10.1136/heartjnl-2023-323346, DOI: 10.1016/j.annemergmed.2021.01.012).

**Chapter 10** is based on extracted data from a national medical claims database (Vektis). Dutch inhabitants (excluding military personnel and prisoners) who are (obliged) insured for health care costs are registered in a central database. These data consist of registered claims data of all health insurance companies in the Netherlands. All Dutch hospitals register diagnoses and procedures in the diagnosis-treatment combination, which is the current reimbursement system in the Netherlands.

**Chapter 11** is based on existing data and available for reuse from the original authors of the published article (DOI: 10.1056/NEJMoa1816897).

The dataset from **Chapters 2 – 5** has been published with open access in DANS Data Station Life, Health and Medical Sciences (https://doi.org/10.17026/dans-xd2-3zpg).

The data of **Chapter 7** are owned by the department of Cardiology Catharina Ziekenhuis Hospital Eindhoven, The Netherlands. These data are not stored in the Radboud Data Repository. Data can be made available 1 year after publication upon reasonable request from the corresponding author.

The data of **Chapter 10** are owned by the Netherlands Heart Registration (NHR). These data are not stored in the Radboud Data Repository.

**The table below details where the data and research documentation for each chapter can be found. All archived data remain available for at least 15 years after termination of the studies.*

| ***Chapter*** | ***DOI*** | ***NAME DATA REPOSITORY*** | ***License or Data Use Agreement*** |
|---|---|---|---|
| *3* | *DOI: 10.17026/DANS-XD2-3ZPG* | DANS station Life Sciences | *DANS license https://dans.knaw.nl/wp-content/uploads/2022/01/DANS_Licence_EN.pdf* |

## PhD portfolio of C. Camaro

Department: **Cardiology**

PhD period: **01/07/2016 – 31/12/2025**

PhD Supervisor(s): **Prof.dr N. van Royen en Prof.dr R.J.M. van Geuns**

PhD Co-supervisor(s): **Dr M.A. Brouwer, Dr P Damman**

| Training activities | Hours |
|---|---|
| **Courses** | |
| - eBROK re-registration (2017, 2021, 2024) | 15.00 |
| - eBROK ICH GCP E6(R3) (2025) | 1.00 |
| - Radboudumc - Scientific integrity course (2025) | 20.00 |
| **Seminars** | |
| - Research Integrity Rounds (2024) | 1.50 |
| - Monthly journal club cardiology Radboudumc (2016-2025) | 50.00 |
| **Conferences** | |
| - Venticare live, oral presentations (2017, 2018, 2021) | 12.00 |
| - CarVasZ symposium, oral presentations (2017, 2022) | 10.00 |
| - Cath lab symposium Nijkerk, oral presentations (2017, 2023) | 12.00 |
| - Dutch Society Cardiology congress (NVVC), oral presentation (2023) | 8.00 |
| - American Heart Association (AHA) Philadelphia, oral presentation (2023) | 16.00 |
| - Netherlands Heart Institute (NLHI) scientific council Utrecht, oral presentation (2024) | 6.00 |
| - Dutch cardiovascular alliance (DCVA) Utrecht, oral presentation (2024) | 6.00 |
| - EuroPCR Paris 2025, oral presentation (2025) | 12.00 |
| **Other** | |
| - Manuscript review activities Neth Heart J (2017 - 2025) | 30.00 |
| - Manuscript review activity PLOS One (2020) | 3.00 |
| - Manuscript review activity Heart (2021) | 3.00 |
| - Manuscript review activity Eur Heart J Qual Care Clin Outcomes (2024) | 3.00 |
| - Manuscript review activity N Engl J Med (2025) | 3.00 |
| - Manuscript review activity BMJ (2025) | 3.00 |

| Teaching activities | Hours |
|---|---|
| **Lecturing** | |
| - Summer school Cardiology module heart catheterization (2019) | 2.00 |
| - Prehospital triage lecture working visit Dutch healthcare institute (2023) | 2.00 |
| - Regional education days for internal medicine (RODIN) (2023) | 8.00 |
| - CVOI course leadership, organization and financing in Cardiology (2021- 2023) | 15.00 |
| - Point Lecture ARTICA results for University of Hamburg Germany (2024) | 2.00 |
| - Medical statement and the General Data Protection Regulation (2024) | 8.00 |
| - Ambulance Masterclass (2020, 2025) | 20.00 |
| - Teaching activities medical curriculum Radboud University (2016-2025) | 36.00 |
| **Supervision** | |
| - Supervision G.W.A. Aarts, PhD candidate (2019-2023) | 360.00 |
| - Supervision S.C. van Uden, master Docent Hoger Gezondheidszorg Onderwijs (2024-2025) | 25.00 |
| Total | 692.50 |

## List of publications

This thesis:

Aarts GWA, **Camaro C**, van Geuns RJ, Cramer E, van Kimmenade RRJ, Damman P, van Grunsven PM, Adang E, Giesen P, Rutten M, Ouwendijk O, Gomes MER, van Royen N. Acute rule-out of non-ST-segment elevation acute coronary syndrome in the (pre)hospital setting by HEART score assessment and a single point-of-care troponin: rationale and design of the ARTICA randomised trial. **BMJ Open**. 2020 Feb 17;10:e034403. doi: 10.1136/bmjopen-2019-034403

**Camaro C***, Aarts GWA*, Adang EMM, van Hout R, Brok G, Hoare A, Rodwell L, de Pooter F, de Wit W, Cramer GE, van Kimmenade RRJ, Damman P, Ouwendijk E, Rutten M, Zegers E, van Geuns RM, Gomes MER, van Royen N. Rule-out of non-ST-segment elevation acute coronary syndrome by single, pre-hospital troponin measurement: a randomized trial**. Eur Heart J.** 2023;19:1705-1714. doi: 10.1093/eurheartj/ehad056.

Aarts GWA*, **Camaro C***, Adang EMM, Rodwell L, van Hout R, Brok G, Hoare A, de Pooter F, de Wit W, Cramer GE, van Kimmenade RRJ, Ouwendijk E, Rutten MH, Zegers E, van Geuns RM, Gomes MER, Damman P, van Royen N. Pre-hospital rule-out of non-ST-segment elevation acute coronary syndrome by a single troponin: final one-year outcomes of the ARTICA randomised trial. **Eur Heart J Qual Care Clin Outcomes**. 2024 Aug 8;10:411-420. doi: 10.1093/ehjqcco/qcae004.

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Rutten M, Cobbaert CM, Arslan F, Rahel B, Van 't Hof A, Boogers JM. Prehospital assessment of Patients with Suspected Acute Coronary Syndrome: A Concise Clinical Summary for Prehospital Triage in the Netherlands. **In preparation**

**Camaro C,** Damman P. Antithrombotic PreTreatment and Invasive Strategies in Patients with Non-ST-Segment Elevation Acute Coronary Syndrome. **J Clin Med.** 2020;9:2578. doi: 10.3390/jcm9082578.

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*Authors contributed equally to this manuscript

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Aarts GWA, **Camaro C,** van Royen N. Ready for rapid rule-out of acute myocardial infarction. **Eur Heart J**. 2023;44:3889-3891. doi: 10.1093/eurheartj/ehad519

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**Camaro C**, Haanskorf M, van Oel H. Vraag en Antwoord: ECG in perspectief. Jubileumuitgave van de Nederlandse Vereniging voor Hart en Vaat Verpleegkundigen. 1e druk november 2014. ISBN 978-94-6228-559-0

For full list of other publications see: http://www.researcherid.com/rid/L-4241-2015

## Curriculum Vitae

Cyril Camaro werd geboren op 18 augustus 1978 in het St Radboud Ziekenhuis te Nijmegen.

In 1996 werd gestart met de studie geneeskunde aan de Katholieke Universiteit Nijmegen welke werd afgerond in 2002. Omdat hij voor zijn artsexamen nog niet precies wist welke richting hij op wilde, liep hij tijdens zijn geneeskundeopleiding extra stages op de afdelingen anesthesiologie (Radboudumc), reumatologie (Radboudumc), kindergeneeskunde (Interdisciplinair Kinderneurologisch Centrum) en fysiologie (Kuopio University Hospital, Finland). Nadien heeft hij nog twee jaar als basisarts ervaring opgedaan op de afdelingen Cardiologie van het Canisius Wilhelmina Ziekenhuis en het Radboudumc. Bij de cardiologie werd het enthousiasme voor het vak echt aangewakkerd en in 2005 kon gestart worden met de opleiding tot cardioloog (opleiders: prof.dr F.W.A. Verheugt en later prof.dr J.L.R.M. Smeets). De vooropleiding interne geneeskunde deed hij in het Jeroen Bosch Ziekenhuis te 's-Hertogenbosch (opleider: dr. P.M. Netten). Zijn B-jaar Cardiologie werd in 2008 doorlopen in het Rijnstate Ziekenhuis Arnhem (opleider: dr. H.A. Bosker).

1-1-2011 werd hij als cardioloog ingeschreven in het specialistenregister van de Registratiecommissie Geneeskundig Specialisten. Op 1-2-2011 kreeg de afdeling Cardiologie een zelfstandige Eerste Hart Hulp, waarbij Cyril vanaf de eerste dag werd aangesteld als medisch coördinator en stage begeleider. In 2012 werd gestart met zijn fellowship interventiecardiologie onder supervisie van prof.dr M.J de Boer en prof.dr H. Suryapranata welke in 2014 werd afgerond. Sindsdien is hij ook als staflid cardioloog / interventiecardioloog verbonden aan het centrum voor hart- en vaten, afdeling Cardiologie van het Radboudumc te Nijmegen.

In 2016 werd zijn promotietraject gestart (1$^{e}$ promotor: prof.dr N. van Royen, 2$^{e}$ promotor: prof.dr R.J.M. van Geuns) welke steeds meer vorm kreeg richting de prehospitale triage van patiënten met pijn op de borst. In 2018 ontving hij een subsidie binnen het doelmatigheidsprogramma van ZonMw voor de ARTICA trial waar hij tot op heden als principal investigator verantwoordelijk is. De ARTICA-1 studie ontving in 2025 de wetenschapsprijs van de Federatie medisch specialisten. In 2025 werd een nieuwe ZonMw subsidie toegekend voor het mogelijk maken van de ARTICA-2 studie.

Cyril heeft veel presentaties en scholingen verzorgd voor verpleegkundigen en voor zijn jarenlange bijdrage aan ECG-onderwijs voor de Nederlandse vereniging voor hart en vaat verpleegkundigen (NVHVV) werd hij in 2018 tot erelid benoemd.

Naast het uitvoeren van het prachtige vak interventiecardiologie is Cyril ook medisch zorgpadleider van het zorgpad acuut coronair syndroom (ACS) / STEMI. Daarnaast heeft

Cyril een grote belangstelling voor vraagstukken rondom het doelmatiger organiseren en financieren van de zorg. Daarom zet hij zich, naast zijn werkzaamheden in het ziekenhuis, actief in als voorzitter van de Beroepsbelangencommissie (BBC) van de Nederlandse vereniging voor Cardiologie (NVVC) en is co-voorzitter van de landelijke projectgroep pre-hospitale triage pijn op de borst/ACS van de NVVC en de Netherlands Heart Institute (NLHI).

Cyril woont samen met Lenneke en samen hebben ze twee zonen (Wout en Thijmen).

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