Ruling out acute myocardial infarction in emergency primary care

The OUT-ACS study

(**O**ne-ho**U**r **T**roponin in a low-prevalence population of **A**cute **C**oronary **S**yndrome)

Tonje Rambøll Johannessen

Department of General Practice, University of Oslo, Oslo, Norway

Department of Cardiology, Oslo University Hospital, Ullevaal, Oslo, Norway

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Preface

After receiving my medical degree in 2013, I worked as a GP registrar with additional out-of-hours rotation in a small Norwegian municipality. The following year, I was employed as a primary care physician at Oslo Accident and Emergency Outpatient Clinic (OAEOC). The contrast between the small out-of-hours clinic to the largest primary care emergency clinic in Norway was significant and inspiring. I have been at the clinic ever since.

With the large volume of patients with chest pain, I soon recognised the essential gatekeeper role of the OAEOC on urgent hospital admissions. The clinic has a unit for short-term observation, where low-risk patients with chest pain constitute one of four admissions. The chest pain routine comprises serial high-sensitivity troponin T (hs-cTnT) measurements sampled with a 4-hour interval with conclusive results within 8-10 hours.

In a random podcast episode during the 2015 Christmas holidays, the principal investigator, Dr Reichlin from Switzerland, spoke enthusiastically about a novel hs-cTnT algorithm ruling out acute myocardial infarction after one hour. The following week I presented the work by Dr Reichlin at the OAEOC, including thoughts on the potential benefits of applying such an algorithm at the OAEOC in the future. By chance, my current principal supervisor, Odd Martin Vallersnes, was in the audience and challenged me to write a short draft on how the algorithm could be validated in emergency primary care. Five months later, the study protocol for the OUT-ACS (One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome) study was completed.

Since 2016, the 0/1-hour algorithm for hs-cTnT has been thoroughly validated in hospital settings. The following thesis comprises a four-part synopsis of the OUT-ACS study, encompassing validation of the ESC 0/1-hour algorithm in a low-prevalence setting and a cost-evaluation of assessing low-risk patients with chest pain in emergency primary care.

Acknowledgements

This project had not been possible without the support from the Department of General Practice at the University of Oslo, the Department of Cardiology at Oslo University Hospital (OUS), Ullevaal, and the Department of Emergency General Practice at the Oslo Accident and Emergency Outpatient Clinic (OAEOC) of the City of Oslo Health Agency. The project was also supported by the Department of Medical Biochemistry at OUS, Ullevaal, analysing the 1-hour study samples.

First and foremost, I would like to express my sincere appreciation to my three supervisors, Dr Odd Martin Vallersnes, Professor Dan Atar, and Professor Sigrun Halvorsen, for their knowledge, continued encouragement, and support. I had not been able to complete this project without their valuable contributions. It was a privilege to proceed with this project under their guidance.

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I appreciate the patience and assistance from Ibrahimu Mdala, who taught a non-statistician some basic statistics and how to manoeuvre in SPSS and STATA. The last paper would not have been possible without the two co-authors Dr John Munkhaugen, for rapidly providing hospital data and his valuable feedback, and Professor Torbjørn Wisløff, contributing with knowledge and conducting the cost-effectiveness analyses.

The continuous support from the OAEOC superiors, Jon Ørstavik, Beate Nilsen, Fredrik R. Iversen, and Hege Therese R. Karlsen, has been overwhelming. I am humbled by the always supportive Dr Anne Kathrine Nore, her valuable inputs during the initial phase of the project, as a co-author, and for being invited to her home to celebrate the accomplished patient inclusion in 2018.

A special appreciation to the staff at the observation unit and Minja H. Yun Nygaard for allowing me to initiate the project at her busy department. Also grateful for the initial administrative assistance by Maud Rigalt Jørgensen and Adjoa Badu, Tone Klette, and Linda Andersen during the enrolment period.

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addition, I appreciate the valuable comments from Ralph Haarskamp and his research group for inspiring me to extend the research after completing my PhD.

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Finally, my completion of this project would not have been possible without the support from friends and family. My profound thanks to my supportive partner and father to our two children, Henrik Molnes. Your encouragement, patience, acceptance, and continuous moral support are highly appreciated! Thank you.

Tonje R. Johannessen, Oslo, 29 March 2022

Summary

Background: Chest pain is a frequent symptom among patients presenting to primary care and hospital emergency departments. As Norway has referral-based access to the EDs, many patients with chest pain consult a primary care physician. Due to diagnostic uncertainty, the hospital referral rate of non-cardiac chest pain is high, leading to congested EDs and extensive use of health care expenditure of limited value.

Aims and Methods: The prospective, observational diagnostic OUT-ACS (***O****ne-ho****U****r* ***T****roponin in a low-prevalence population of* ***A****cute* ***C****oronary* ***S****yndrome*) study was conducted between 2016 to 2018 at a large emergency primary care clinic in Oslo, Norway. The study aimed to investigate the diagnostic and prognostic performance of the European Society of Cardiology (ESC) 0/1-hour algorithm for high-sensitivity cardiac troponin T (hs-cTnT) in patients with a low pre-test probability of acute coronary syndrome (ACS). Patients with non-specific, non-traumatic chest pain admitted for serial hs-cTnT measurements at the clinic were eligible. Patients with a highly suspected ACS were directly hospitalised, hence not available for enrolment. Hs-cTnT was measured after 0-, 1-, and 4-hours from all participants. The patients were assigned to *rule-out, rule-in,* or further *observation* by applying the algorithm.

Two retrospective sub-analyses were performed. The first aimed to validate the novel criteria for patients in the observation group. In the second, the diagnostic performance of a single hs-cTnT measurement was compared with the HEART (History, ECG, Age, Risk factors and Troponin) score. The primary outcome measure in Papers I–III was the rule-out performance of the adjudicated diagnosis of AMI at index, using the 0/4-hour hs-cTnTs in accordance with the *Third Universal Definition of Myocardial Infarction*. The secondary prognostic outcome was the combined incidence of all-cause mortality and AMI in the following 90 days, obtained through linkage with the *Norwegian Cardiovascular Disease Registry*.

The cost-effectiveness of assessing low-risk patients with chest pain in emergency primary care was estimated and compared to routine hospital management. The primary outcome measure was the costs per quality-adjusted life-years of assessing low-risk patients outside of hospital. The secondary outcomes were the estimated reductions in costs and length of stay in the two settings. Cost estimates from the OUT-ACS cohort were compared with anonymous extracted 2018 data on low-risk patients at a large general hospital in Drammen, Norway.

Results: The median age among 1711 included patients was 56 years, and 52 % were males. AMI was the final diagnosis in 3.6 % (n=61) of the cohort. By applying the ESC 0/1-hour algorithm, 76.6 % were assigned to the rule-out group. High rule-out performance was demonstrated (negative predictive value 99.9 %, sensitivity 98.4 %, and a 90-day incidence of combined AMI and all-cause mortality of 0.3 %). Only 66 patients were assigned towards rule-in where a moderate rule-in accuracy was demonstrated (positive predictive value 68.2 % and specificity 98.7 %).

For the remaining patients in the observation group, 38 % were assigned to a safe AMI rule-out using the novel observation group criteria, increasing the overall efficacy of the ESC 0/1-hour algorithm from 80.5 % to 90 %. In the case of a single hs-cTnT measurement, the ESC 0-hour criterion was superior to the HEART score (sensitivity 100 % and 91.8 %, respectively). The low-risk sensitivity was improved to 98.4 % with the modified HEART score using lower hs-cTnT criteria but at the expense of increased false-positive cases.

The estimated cost reduction per low-risk patient assessed in emergency primary care was calculated to €1794 with a mean decrease in length of stay of 18.9 hours and an average per-person QALY gain of 0.0005. With decreased costs and increased QALY, the primary care approach is considered cost-effective in Norway.

Conclusions: In the observational OUT-ACS study, the ESC 0/1-hour algorithm appears to be safe, efficient, applicable, and cost-effective for the assessment of low-risk patients with chest pain in emergency primary care.

Norsk sammendrag

Bakgrunn: Brystsmerter er en stadig økende kontaktårsak både i og utenfor sykehus i Norge og internasjonalt. Da pasienter ikke har direkte tilgang til norske akuttmottak uten henvisning, oppsøker en stor andel av pasientene fastlege eller legevakt. Grunnet diagnostisk usikkerhet overføres mange med ikke-kardiale brystsmerter til sykehus for å utelukke akutt hjerteinfarkt. Dette medfører opphopning av pasienter i akuttmottakene og omfattende bruk av helseressurser av begrenset nytteverdi.

Formål og metode: OUT-ACS (***O**ne-ho**U**r **T**roponin in a low-prevalence population of **A**cute **C**oronary **S**yndrome*) studien er en prospektiv, diagnostisk observasjonsstudie gjennomført over to år (2016-2018) ved Allmennlegevakten på Legevakten i Oslo. Studien hadde som formål å validere de diagnostiske og prognostiske egenskapene til ESCs (*European Society of Cardiology*) 0/1-times algoritme for høysensitiv hjertespesifikk troponin T (hs-cTnT) i en lavprevalenspopulasjon for akutt koronarsyndrom (AKS). Pasienter med uspesifikke, ikke-traumatiske brystsmerter innlagt på legevaktens observasjonspost for troponinprøver oppfylte kriteriene for inklusjon, mens pasienter med mistenkt AKS ble direkte innlagt på sykehus og var av den grunn ikke tilgjengelige for inklusjon. Hs-cTnT ble målt etter 0, 1 og 4 timer, hvor pasientene senere ble triagert til *rule-out, rule-in* eller *observasjonsgruppen* basert på 0/1-times kriteriene i ESC algoritmen.

En retrospektiv subanalyse ble gjennomført for å validere egne kriterier for pasienter i observasjonsgruppen, mens en annen subanalyse hadde som mål å sammenligne den diagnostiske ytelsen av én enkel hs-cTnT-måling med HEART (Historie/anamnese, EKG, Alder, Risikofaktorer og Troponin) risikoskår. Det primære utfallsmålet i de tre første publikasjonene var algoritmens evne til å utelukke hjerteinfarkt på legevakt. Diagnosen hjerteinfarkt ble validert av en endepunkts-komité hvor 0- og 4-timers prøvene ble tolket i samsvar med den *Tredje internasjonale definisjonen for akutt hjerteinfarkt*. Det sekundære prognostiske utfallsmålet var samlet forekomst av dødsfall og hjerteinfarkt de etterfølgende 90 dagene, innsamlet via kobling med *Norsk hjerte- og karregister*.

Kostnad-effektverdi av å benytte 0/1-times algoritmen for avklaring av lavrisikopasienter med brystsmerter på legevakt fremfor innleggelse på sykehus ble deretter evaluert. Ressursbruk og kostnader fra OUT-ACS-kohorten ble sammenlignet med anonyme, administrative 2018-data fra Drammen sykehus. Det primære utfallsmålet var kostnader per kvalitetsjusterte leveår (QALY), mens sekundære utfallsmål var estimert reduksjon i kostnader og liggetid per lav-risikopasient i de to ulike settingene.

Resultat: Totalt 1750 pasienter samtykket til studiedeltagelse, hvor 1711 av disse ble inkludert i de endelige analysene. Snittalder var 56 år og 52 % var menn. Akutt hjerteinfarkt ble diagnostisert hos 61 (3,6 %) pasienter. Ved å tolke 0- og 1-times prøven i henhold til algoritmen, fikk 76,6 % utelukket hjerteinfarkt *(rule-out)* med høy sikkerhet (negativ prediktiv verdi 99,9 %, sensitivitet 98,4 % og en lav samlet forekomst av infarkt og død etter 90 dager (0,3 %)). Kun 66 pasienter havnet i *rule-in* gruppen, som oppnådde moderat nøyaktighet for akutt hjerteinfarkt (positiv prediktiv verdi 68,2 % og spesifisitet 98,7 %). For pasienter gjenværende i den intermediære observasjonsgruppen fikk 38 % utelukket infarkt med sensitivitet på 100 % ved å ta i bruk de nye kriteriene for observasjonsgruppen. Total effektivitet av algoritmen, som tilsvarer andel rule-in og rule-out, økte fra 80,5 % til 90 % ved å kombinere 0/1-times algoritmen med de nye observasjonskriteriene. Dersom kun én troponinmåling benyttes, vil 0-timeskriteriet fra algoritmen være tryggere enn HEART risikoskår (sensitivitet på henholdsvis 100 % og 91,8 %). Sensitiviteten ble styrket til 98,4 % ved å ta i bruk en modifisert versjon av HEART-skår med lavere troponinkriterier, men på bekostning av en betydelig økning i falske positive tilfeller. Estimerte kostnader og liggedøgn ble redusert med 19.250 NOK og 18,9 timer per lav-risikopasient håndtert på legevakt fremfor sykehus, samt en økning i QALY på 0.0005 per pasient. Med lavere kostnader og økt QALY, anses det derfor som svært kostnadseffektivt å ta i bruk 0/1-timesalgoritmen utenfor sykehus.

Konklusjon: Med den observasjonelle OUT-ACS studien fremstår ESCs 0/1-times algoritme for hs-cTnT som trygg, effektiv, egnet og kostnadseffektiv å ta i bruk for vurdering av brystsmertepasienter med lav risiko for akutt hjerteinfarkt på legevakt.

List of abbreviations

ACS	acute coronary syndrome
AMI	acute myocardial infarction
AUC	area under the (ROC) curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards statement
CAD	coronary artery disease
CI	confidence interval
cTn	cardiac troponin
CV	coefficient of variation
ECG	electrocardiogram
ED	emergency department
eGFR	estimated glomerular filtration rate
EMS	emergency medical services
ESC	European Society of Cardiology
GP	general practitioner
HEART	History, Electrocardiogram, Age, Risk factors, and Troponin
hs-cTnT/I	high-sensitivity cardiac troponin T/I
ICD-10	International Statistical Classification of Diseases and Related Health Problems - 10th Revision
ICPC-2	International Classification of Primary Care - 2nd Edition
IQR	interquartile range
LoD	limit of detection

LOS	length of stay
LR	likelihood ratio
MACE	major adverse cardiac event
NPV	negative predictive value
NSTE-ACS	non-ST-segment elevation acute coronary syndrome
NSTEMI	non-ST-segment elevation myocardial infarction
OAEOC	Oslo Accident and Emergency Outpatient Clinic
OOH	out-of-hours
OUT-ACS	One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome
POC-Tn	point-of-care troponin
PPV	positive predictive value
QALY	quality-adjusted life-years
RCT	randomised controlled trial
ROC	receiving operating characteristic
STARD	Standards for Reporting Diagnostic Accuracy Studies
STEMI	ST-segment elevation myocardial infarction
UA	unstable angina
UDMI	Universal Definition of Myocardial Infarction
WHO	World Health Organization

List of papers

This thesis is based on three original research articles and one research letter. These four papers are referred to by their Roman numerals (Paper I-IV):

I: Pre-hospital One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome: OUT-ACS Study

Johannessen TR, Vallersnes OM, Halvorsen S, Larstorp ACK, Mdala I, Atar D. Open Heart. 2020;7:e001296. doi: 10.1136/openhrt-2020-001296

II: Performance of the novel observation group criteria of the ESC 0/1-hour algorithm in a low-risk population (Research letter)

Johannessen TR, Halvorsen S, Atar D, Vallersnes OM.
Journal of the American Heart Association. 2022;0(0):e024927. doi: 10.1161/JAHA.121.024927

III: Comparison of a single high-sensitivity cardiac Troponin T measurement with the HEART score for rapid rule-out of acute myocardial infarction in a primary care emergency setting: a cohort study

Johannessen TR, Atar D, Vallersnes OM, Larstorp ACK, Mdala I, Halvorsen S. BMJ Open. 2021;11(2):e046024. doi: 10.1136/bmjopen-2020-046024

IV: Cost-effectiveness of a rule-out algorithm of acute myocardial infarction in low-risk patients: Emergency primary care versus hospital setting

Johannessen TR, Halvorsen S, Atar D, Munkhaugen J, Nore AK, Wisløff T, Vallersnes OM.
Submitted to BMC Health Services Research, January 2022

1. Introduction

1.1 Chest pain

Chest pain is one of the most frequent symptoms among patients presenting to the emergency services.[1, 2] In Switzerland, 6 % of all emergency medical services (EMS) calls concerned chest pain.[3] Chest pain also constituted 22 % of the EMS red response assignments in Norway,[4] and was the most frequent cause (61 %) for having an ambulance dispatched in the Netherlands.[5] It is also frequent in hospital emergency departments (EDs), contributing to extensive crowding and high use of medical resources.[2, 6-9] In 2002, acute chest pain was considered a health care burden in England and Wales, with an estimated 700 000 ED (6 %) presentations per year.[6] In the United States, 4.7 % of ED attendances are due to chest pain, the second most frequent cause after acute injuries.[2] The ED prevalence is higher in Norway (11-13 %),[7, 10] probably due to referral-based ED access. Acute non-specific chest pain is the second most common cause for hospital referral and somatic emergency admissions in Norway,[11-13] while acute myocardial infarction is the fifth.[11, 12]

Acute chest pain accounts for 1-3 % of all consultations in primary care.[14-17] The complaints will have a benign, non-cardiac origin in most cases, such as chest wall syndrome, gastritis, upper respiratory infections, anxiety, or panic disorder.[15-19] The prevalence of ACS is relatively low, reported in the range of 1.5-6.5 %.[15-17, 19] Still, the fear of missing an AMI, combined with limited diagnostic options to provide a safe AMI rule-out, results in defensive medicine.[8, 17, 20, 21] Between 40-50 % of patients with chest pain are referred to a hospital ED for further assessment,[8, 17, 20] where the proportion of hospitalised patients ending up with an acute cardiovascular event as the final diagnosis is below 15 %.[8, 14, 16, 17, 22] The diagnostic challenges were recently illustrated by Vester et al., reporting that non-cardiac chest pain was found in 82 % of patients referred to hospital with cardiac-suspected origin.[8] This high incidence of false-positive admissions contributes to crowding and extensive use of resources in the hospital EDs.[8, 22]

The term *chest pain* encompasses more than having *pain in the chest*. According to the recent *2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain,* the term comprises "pain, pressure, tightness, or discomfort in the chest, shoulders, arms, neck, back, upper abdomen, or jaw, as well as shortness of breath and fatigue, which should all be considered anginal equivalents".[2] This definition will apply whenever *chest pain* is mentioned in the following thesis.

1.2 Acute coronary syndrome

It is crucial to consider an acute coronary syndrome (ACS) in patients presenting with acute chest pain.[1, 2, 23, 24] The broad term ACS includes several acute variants of ischemic heart disease, including unstable angina (UA) and AMI with or without ST-segment elevations (STEMI and Non-STEMI) on the initial ECG.[23, 24] The clinical diagnosis of STEMI is usually rapidly suspected on the ECG in case of a significant ST-segment elevation or a newly developed left bundle branch block.[23, 24] Other ischaemic changes without ST-segment elevations (e.g., newly developed ST-segment depressions, T-wave inversions, or development of pathological Q-waves) might be indicative of an NSTEMI.[24] As UA and NSTEMI both present with ischaemic symptoms, they are commonly referred to as non-ST-segment elevation acute coronary syndrome (NSTE-ACS).[24]

The *2020 European Society of Cardiology (ESC) Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation* highlight that the initial assessment of a suspected NSTE-ACS should include clinical examination, a 12-lead electrocardiogram (ECG), and a specific biomarker of myocardial injury, preferably a high-sensitivity cardiac troponin (hs-cTn).[24] According to the *4th Universal Definition of Myocardial Infarction (UDMI),* both acute myocardial injury (i.e., dynamic levels of cTn in the circulation with at least one measurement exceeding the 99th percentile of the upper reference limit (URL)) *and* clinical features of acute myocardial ischaemia (i.e.,

suspected ischaemic presenting symptoms, ischaemic findings at the initial ECG or supplementary imaging procedures, or identification of a coronary thrombus) need to be present for the diagnosis of AMI.[23] In case of myocardial ischaemia without myocardial injury, UA might be suspected.[23, 24]

1.3 Cardiac troponin

The protein complex of troponins was first discovered in 1965,[25] integrated within the contractile system of the myocardium.[26] The cardiac troponin complex comprises three isoforms; types T, C and I (Figure 1). The complex is attached to tropomyosin by troponin T, and troponin C has binding sites for calcium. An influx of calcium releases the inhibitory Troponin I binding to actin, exposing new binding sites for myosin heads.[26, 27] As the isoforms T and I are cardiac-specific, cardiac troponin T (cTnT) and I (cTnI) are ideal biomarkers for cardiac injury.[26] During injury of the cardiomyocytes, cTnT/I leaks into the circulation and can be detected by cTn-specific assays.

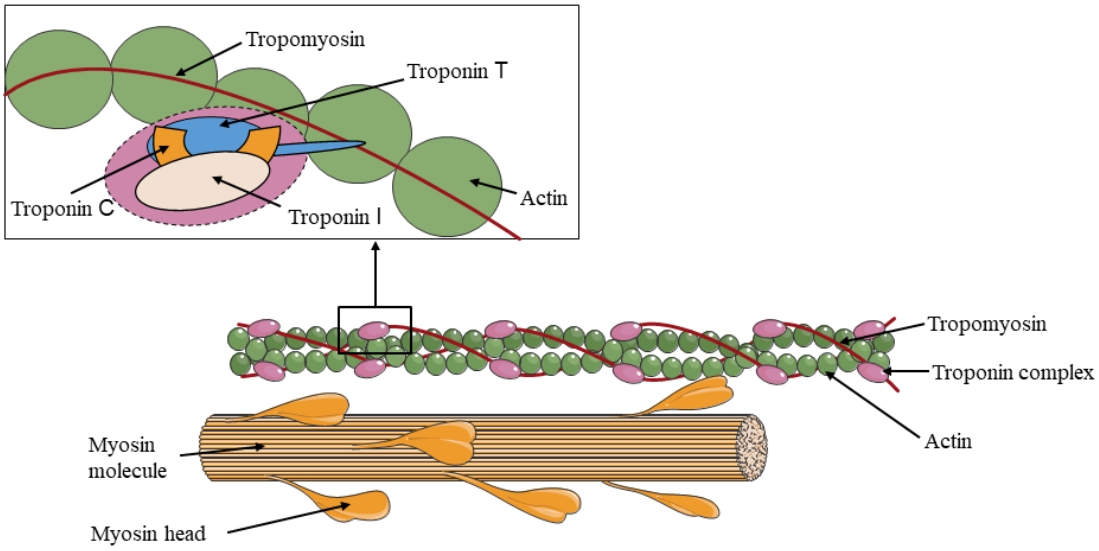

Figure 1 The troponin complex of the myocardium

Illustration by *Servier Medical Art (smart.servier.com)*, modified with the upper left square by TRJ.

The first generation cTnT assay was described by Hugo Katus and colleagues more than three decades ago.[28] During the 1990s, the performance was improved with 2nd and 3rd generation cTnT assays.[29-32] In parallel with cTnT, the cTnI assay was developed and validated.[33-36] The prognostic value of cTnT/I was also documented, as patients with elevated cTn levels had a significantly increased risk of AMI and death.[37, 38] In 1999, cTnT and cTnI were included in the updated AMI guidelines from the *American College of Cardiology (ACC)/American Heart Association*.[39] Troponin was then listed as the preferred biomarker of myocardial injury in the *2000 Joint ESC/ACC Re-definition of AMI*,[40] before being integrated as a diagnostic criterion in the first *UDMI* in 2007.[41]

Irrespective of the precision of the assay, the assay-specific 99th percentile URL was used as the threshold for AMI.[40-43] To be considered as valid, the 99th percentile URL of the chosen biomarker had to be measured with high precision (i.e., a coefficient of variation (CV) ≤ 10 %).[40, 41, 44] Such precision was not achievable across available contemporary cTn assays in 2007.[44] Consequently, the 10 % CV (=30 ng/L) was chosen as the AMI decision limit for the 4th generation of cTnT rather than the 99th percentile URL (14 ng/L).[42, 43, 45] For cTnI, there were multiple assays, each with separate 99th percentile URLs and decision limits.[43, 46, 47]

Further development and improvements of the assays were driven by the *UDMI* criterion and guidelines.[41, 44] In a validation/implementation study, lowering the decision limit for AMI with an improved cTnI assay demonstrated increased AMI detection and improved outcomes.[48] Optimal precision was achieved with the hs-cTn assays.[49-51] To be considered as high-sensitivity, the assay must be able to measure the 99th percentile URL with high precision (CV ≤ 10 %), in addition, to detect the cTn levels above the assay's limit of detection (LoD) in at least 50 % of healthy individuals.[52] As a result, hs-cTn assays are able to measure earlier and minor changes in troponin levels, also below the 99th percentile URL.[24]

1.4 AMI assessment in primary care

According to international guidelines, clinical assessment, a 12-lead ECG, and high-sensitivity cardiac troponins constitute the three mandatory next steps when diagnosing patients with a potential NSTE-ACS.[23, 24] Most primary care settings do not provide routine serial hs-cTn measurements or imaging modalities, and the initial assessment often comprises less sensitive diagnostic decision aids.

1.4.1 Clinical assessment

Based on the presenting signs and symptoms, the initial clinical assessment comprises taking a relevant medical history, exploring risk factors, and a focused clinical examination. Potential differential diagnoses, such as pulmonary embolism, pleuritis, pneumothorax, gastritis, anxiety, or musculoskeletal pain, are considered. The existing literature has established that neither clinical gestalt (i.e., clinical judgement) nor signs and symptoms alone can be used to rule out or confirm an AMI.[53-59] Both Nilsson et al.[54] and Bösner et al.[57] demonstrated that GPs clinical assessment only achieved a modest sensitivity for ischaemic heart disease (72 % and 69 %, respectively), while the sensitivity was even lower for ACS (50 %).[57]

Different clinical decisions rules (CDR) have been developed to enhance the clinical assessment in primary care. The early *Grijseels CDR* was derived and validated using clinical features obtained by the GP combined with a pre-hospital ECG in patients with suspected ACS.[60] The CDR recommended *no hospital* in 23 % (sensitivity 91.4%) of the cases, which was overruled in 56 % by clinical gestalt (sensitivity 97.6 %).[60] Similar sensitivity for coronary artery disease (CAD) was achieved in the 2010 *Gencer rule* derivation cohort, without confirming these findings through external validation (sensitivity 86.8 %).[56] The following year, it was demonstrated that GPs more accurately triaged patients as *ACS/no-ACS* than when using the *Bruins Slot CDR*, although without achieving acceptable rule-out safety (sensitivity 93.9 %).[58] The *Marburg Heart Score* (MHS) was established to rule out CAD in primary care.[61] Since 2010, the MHS has been extensively validated

with various sensitivity (75.0-91.4 %).[62-64] Using pooled data from earlier primary care cohorts, the *INTERCHEST (International Working Group on Chest Pain in Primary Care)* CDR was derived for a similar purpose to exclude CAD.[65] However, the CDR did only achieve moderate sensitivities in the validation cohorts (82 % and 88 %, respectively).[65]

As summarised by Harskamp et al., no valid CDR based on history and clinical examination has achieved sufficient rule-out sensitivity for excluding an ACS.[21] The lack of a safe decision aid in the primary care setting, combined with the fear of missing an acute cardiac event, maintain the practice of defensive hospital referrals.[8, 17, 20, 66, 67]

1.4.2 ECG

The 12-lead ECG is a simple, non-invasive, accessible diagnostic tool used in many primary care settings. In Norway, the ECG is broadly implemented, available at 99 % of the out-of-hours (OOH) clinics[68] and used in 92 % of patients presenting with chest pain.[20] In the Netherlands, only 26 % of the OOH clinics had access to ECG in 2014, and more than 80 % used cardiologists for the interpretation.[69] Availability of ambulances and distance to hospital may explain some of these variations, but also different OOH organisation models and perspectives related to the use of diagnostic tests, as suggested by Schols et al.[67, 69]

While ST-segment elevations or other ischaemic findings at the ECG often result in urgent hospitalisation, an ECG has shown to have a low rule-out sensitivity (68 %).[70] The ECG may also appear *normal* in more than 30 % of patients with an ongoing NSTE-ACS.[24] It is, therefore, not possible to rule out an AMI based on the ECG alone, which is a well-known limitation among primary care physicians.[67]

1.4.3 Cardiac troponins

As neither clinical gestalt, CDRs, nor the ECGs are able to exclude an AMI, there is a pressing need for improved diagnostic decision aids in primary care.[71] A hs-cTn is

the biomarker of choice for the assessment of patients with a potential NSTE-ACS.[2, 23] Cardiac troponins may be sampled and analysed bedside as a point-of-care (POC) test or collected in a venous blood sample and analysed at a central laboratory, where a high-sensitivity assay is preferred.[2, 23, 24]

High-sensitivity troponin assays

There is a common consensus that patients with a highly suspected ACS should be rapidly hospitalised and not delayed by prehospital troponin measurements.[1, 72-75] During the last decade, there have been concerns regarding safety and false-negative results as primary care rarely have access to serial hs-cTn measurements, as well as debates on whether troponin measurements should be performed at all.[72-77] In Australia, it has been proposed that a single troponin test might serve primary care in the few cases where low-risk patients have been without symptoms for more than 24 hours.[73] For the diagnosis of AMI, two cTn measurements are required to distinguish chronically elevated levels from acute myocardial injury (i.e., characteristic rise/fall pattern).[23, 24] However, serial cTn sampling has its difficulties as this entails logistic challenges due to time restrictions, transport procedures, and limited options for observation of patients.[72, 75] Usually, most patients will be transferred to a hospital ED if serial cTn measurements are considered necessary. This is also the general routine in Norway.

Point-of-care troponin (POC-Tn) assays

In an international survey from 2014 among 2770 GPs in the UK, US, Australia, Belgium, and the Netherlands, POC-Tn assays were desired by 66 % of the participating GPs to enhance the assessment of acute cardiac disease outside of hospital.[78] Similar was documented by Harskamp et al., where POC-Tn was welcomed among 77 % of the GPs, further increasing to 86 % if the POC-Tn was integrated within a CDR.[79] Another survey demonstrated that POC-Tn was considered valuable by GPs for the rule-out of ACS, where high diagnostic

performance, short time to result, reimbursement of the assay, and capillary rather than venous blood sampling were desired in case of implementation.[80]

After synthesising a systematic review on POC-Tn studies from 1990 to 2012, Bruins Slot et al. concluded that these assays are insufficiently sensitive to exclude an AMI.[81] Several diagnostic studies on POC-Tn assays have been conducted since then, both in primary care[82, 83] and in the prehospital setting.[84-87] However, conventional POC-Tn assays are still not considered safe.[88, 89] These devices have been shown only to be cost-effective in ensuring rapid referrals for high-risk cases due to high specificity.[90, 91] A request for more sensitive POC-Tn assays was raised by Andersson et al. after demonstrating improved diagnostic performance with a central lab hs-cTnT assay (AMI decision limit ≤ 15 ng/L) compared to POC-Tn.[83] Due to large geographical variations in Norway, bedside POC-Tn assays are probably used in increasing scale in many Norwegian primary care settings, without having confirmation in the existing literature.

The HEART score

The HEART *(History, ECG, Age, Risk factors and Troponin)* score was initially derived and validated in the Netherlands by Six and Backus et al. to triage patients presenting with chest pain in hospital EDs.[92-94] The risk score is based on clinical intuition, where 0-2 points are achievable for each acronym letter (Table 1).[92-94]

The HEART score estimates the risk of having a *Major Adverse Cardiac Event* (MACE) within six weeks after presenting with chest pain. A score of 0-3 points indicates low risk for MACE (1.7 %) and consequently the possibility for rapid hospital discharge. A score of 4-6 points indicates an intermediate risk of MACE (13 %), and additional observation and risk management are recommended. Finally, patients are considered as high risk of MACE (50 %) in the case of 7-10 points, with the recommendation of early invasive interventions.[92-94]

Table 1 The original HEART score for patients with chest pain		
History	Highly suspicious for ACS Moderately suspicious Slightly or not suspicious	= 2 points = 1 point = 0 points
ECG	Significant ST-depression Non-specific changes* Normal	= 2 points = 1 point = 0 points
Age	≥ 65 years 46 – 64 years ≤ 45 years	= 2 points = 1 point = 0 points
Risk Factors†	≥ 3 risk factors or previous CAD 1 or 2 risk factors No risk factors	= 2 points = 1 point = 0 points
Troponin	≥ 3 x URL > 1 – < 3 x URL ≤ URL	= 2 points = 1 point = 0 points
Total	**Low risk** **Intermediate risk** **High risk**	**= 0-3 points** **= 4-6 points** **= 7-10 points**

Reprinted from Table I, Paper III; adapted after the original HEART score[92, 94] with permission granted by B. Backus.

* Left bundle branch block, left ventricular hypertrophy, repolarization changes, pacemaker

† Risk factors: Hypertension, diabetes mellitus, current or history of smoking, hypercholesterolaemia, obesity (BMI >30 kg/m²), and family history of coronary artery disease

ACS: acute coronary syndrome; ECG: electrocardiogram; HEART: History, Electrocardiogram, Age, Risk factors, and Troponin; hs-cTnT: high-sensitivity cardiac troponin T; URL: upper reference limit

During the last 15 years, the HEART score has been thoroughly validated and compared to other risk scores in the EDs.[94-97] Modified versions of the score, either by replacing cTn with hs-cTn or lowering the troponin thresholds, have improved low-risk sensitivity.[98-101] However, the safety of the score is still questioned, with miss-rates of AMI and MACE exceeding 3 % in the low-risk groups.[102, 103]

Studies have also evaluated the diagnostic performance of a POC-Tn assay integrated within the HEART score to improve prehospital triage without achieving sufficient sensitivity.[104-107] In the prospective *FamouS Triage (Fast assessment and management of chest pain patients without ST-elevation in the pre-hospital gateway)* study, a sensitivity analysis estimated reclassification of 20 % of the low-risk cohort

if an hs-cTnT assay had been applied.[104] However, when comparing POC-Tn with an in-hospital hs-cTn measurement, the investigators concluded that the POC-Tn assay would be sufficient for the prehospital setting as both assays achieved similar HEART classification in 98 % of the cohort.[108] Still, the lack of sufficient rule-out sensitivity[87, 89, 104, 105] makes it difficult for the EMS and primary care physicians to leave the low-risk patients at home. Consequently, the prehospital HEART score using POC-Tn assays still does not solve the issues with low-risk hospital referrals.

1.5 The 0/1-hour algorithm for hs-cTn

1.5.1 Derivation and validation

Since their introduction in the 1980s, the cTn assays have been through extensive development. The hs-cTn assays led to lower detection limits for changes in cTn concentrations, followed by earlier recognition of a potential AMI than the conventional assays.[50, 109-112] It was also demonstrated that absolute changes between two measurements improved the diagnostic performance compared to relative changes.[113-115] Increased sensitivity opened for a shortened time interval between the first and second troponin measurement, from initially 6-9 hours[41] to 1/2/3-hours algorithms.[112-118]

The first early one-hour rule-out pathway for hs-cTnT was presented in 2012 by the *APACE (Advantageous Predictors of Acute Coronary Syndromes Evaluation)* investigators from Switzerland. Rapid rule-out of AMI in the ED was possible by combining low baseline hs-cTnT values and low absolute changes within one hour.[117] By using data-driven assay-specific cut-offs, developed by derivation and validation methods, they were able to ensure optimal rule-out thresholds (i.e., sensitivity and NPV 100 %) and acceptable rule-in accuracy.[117] The 0/1-hour algorithm for hs-cTnT was further prospectively validated in a European multicenter cohort from Switzerland, Spain and Italy, confirming the high diagnostic performance.[119] An external multicenter validation study across three continents was

later conducted by the *TRAPID-AMI (High-sensitivity cardiac Troponin T Assay for Rapid Rule-out of AMI)* group.[120] Assay-specific 0/1-hour thresholds were also derived and validated for hs-cTnI (Dimension Vista).[121, 122] As neither symptom onset, age, sex, or ECG findings seemed to improve performance, these variables were not included in the initial 0/1-hour algorithms.[117, 121]

In parallel with the development of the 0/1-hour algorithm, excellent performance (NPV and sensitivity 100 %) for immediate rule-out of AMI was demonstrated for a single, undetectable hs-cTnT measurement at ED presentation.[123] In the following years, the direct rule-out approach was further validated for hs-cTnT/I,[124-126] before being included within the first ESC 0/1-hour algorithm.[127] In the 2015 ESC guidelines, assay-specific 0/1-hour algorithms (Figure 2) were presented as an alternative to standard care for hs-cTnT (Elecsys), hs-cTnI (Architect), and hs-cTnI (Dimension Vista) with a *Class IB* recommendation (i.e., I: recommended/indicated, and B: based on data from a single randomised controlled trial (RCT) or large non-randomised studies).[127]

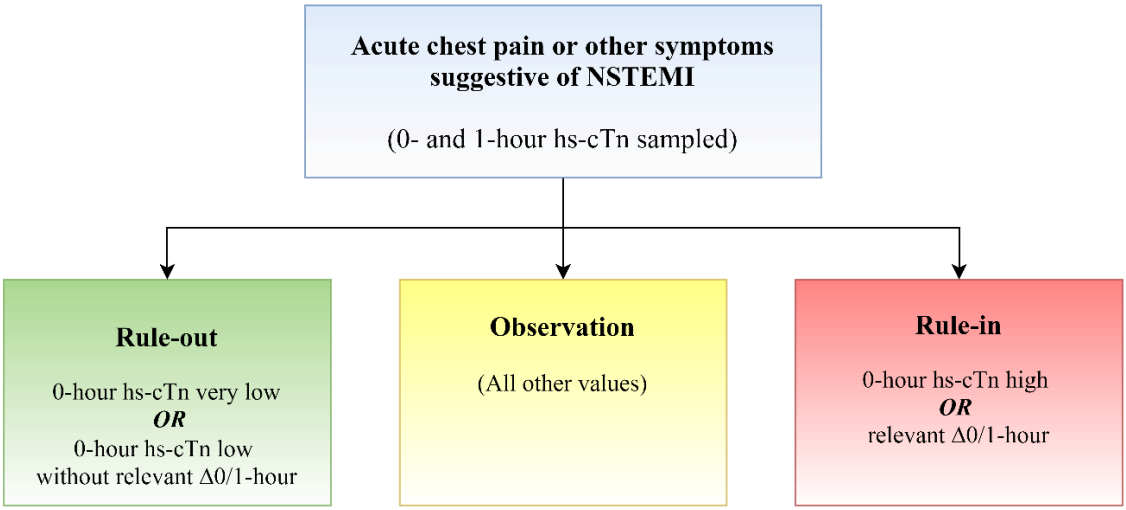

Figure 2 The 2015 ESC 0/1-hour algorithm for high-sensitivity cardiac troponins

The rule-out group is defined by either a very low hs-cTn value at baseline or a low value without a relevant 1-hour change. For the rule-in group, the probability of an NSTEMI is increased by a high 0-hour sample or a significant 1-hour change. All patients with other values remain in the indeterminate observation group, requiring additional hs-cTn measurements.[127]

ESC: European Society of Cardiology; hs-cTn: high-sensitivity cardiac troponin; NSTEMI: non-ST-segment elevation myocardial infarction

Since 2015, the diagnostic performance of the ESC 0/1-hour algorithm has been externally validated across different continents and populations.[128-134] Validation has been conducted in low- or high-risk hospital cohorts,[135-137] among early or late presenters,[138-140] and in various subgroups of patients.[141-144] The performance has been compared with risk scores,[134, 145-149] alternate criteria,[150-156], other biomarkers,[157, 158] and other rapid diagnostic protocols.[132, 158-160] Assay-specific thresholds have also been derived and validated for novel hs-cTnI assays.[160-167] Great safety, efficacy, feasibility, and adherence have then been confirmed for the 0/1-hour algorithm in implementation studies[139, 168, 169], including one RCT.[170]

Due to broad and rapid research, the ESC 0/1-hour algorithm stands out as one of the most thoroughly validated diagnostic protocols for patients with acute chest pain. The algorithm is now widely applicable across most established hs-cTn assays and received a reinforced recommendation in the recent 2020 ESC guidelines on NSTE-ACS.[24] The extensive development from the first cardiac troponin T assay to the ESC 0/1-hour algorithms for hs-cTn is illustrated in Figure 3:

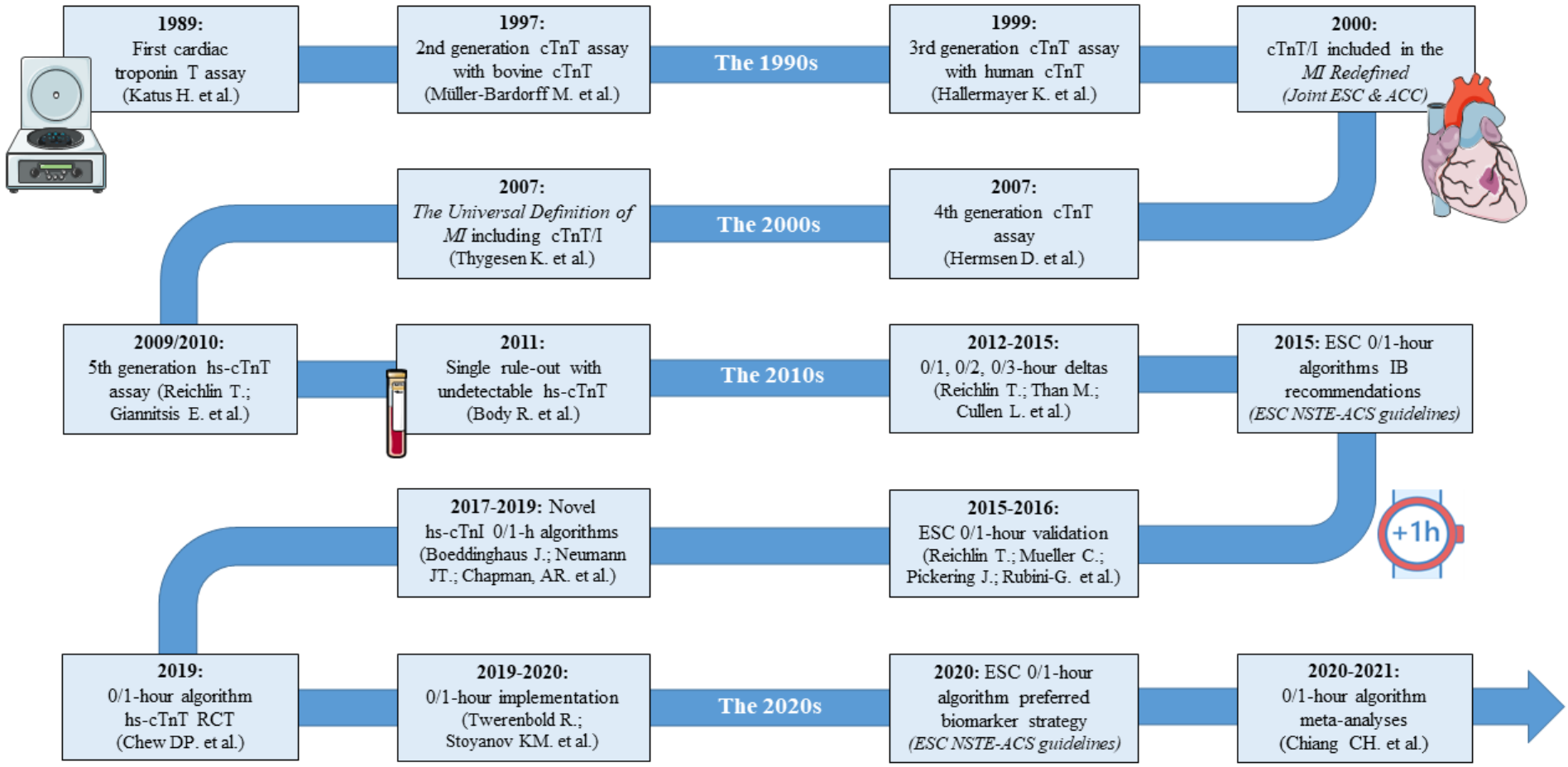

Figure 3 From cardiac troponin T to the ESC 0/1-hour algorithm

ACC: American College of Cardiology; cTnT: cardiac troponin T; ESC: European Society of Cardiology; hs-cTnT: high-sensitivity cardiac troponin T; MI: Myocardial Infarction; RCT: randomised controlled trial. *Inspired by C. Mueller, ESC Congress 2019.*

1.5.2 The observation group

The ESC 0/1-hour algorithm has an overall high efficacy, with the majority assigned to either rule-in or rule-out after the 1-hour result. Nevertheless, between 20-40 % still end up in the indeterminate observation group, requiring additional testing before deciding further disposition.[119-121, 128, 129, 150, 171] The *APACE* investigators demonstrated that patients in the observation zone tend to be males of higher age, with more comorbidities and AMIs, and worse prognosis than patients in the rule-out group.[171, 172]

The 2020 ESC guidelines for NSTE-ACS have specified their recommendations on how to proceed with patients assigned to the observation zone. The guidelines recommend an echocardiogram and a third hs-cTn as the preferred next steps, although without suggesting assay-specific thresholds.[24] To address this issue, novel 3-hour criteria for hs-cTnT were derived and validated in the *APACE* cohort for patients in the observation zone before being externally validated in the *TRAPID-AMI* cohort.[172] In addition to providing high safety for those ruled out, these novel criteria reduced the observation group by 36 %, improving the overall efficacy.[172]

1.5.3 Subgroup validation

Comorbidity

Patients with heart failure, atrial fibrillation, diabetes mellitus, or renal dysfunction (i.e., estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2) tend to have higher circulating levels of cTn and worse prognostic outcomes than healthy individuals.[142, 144, 173-176] The diagnostic accuracy of the 0/1-hour algorithm was decreased among patients with renal dysfunction and diabetes.[142, 144] The efficacy was reduced as more patients were assigned from the rule-out group towards further observation.[142, 144] Due to increased AMI prevalence, the PPV remained high while the rule-in specificity was decreased. Still, the rule-out performance was comparable

to non-disease.[142, 144] Disease-derived 0/1-hour criteria improved the PPV in the diabetes cohort[144] but without demonstrating similar findings for those with renal dysfunction.[142] Nevertheless, as the 0/1-hour delta still managed to assign patients with AMI to rule-in, the algorithm appears applicable also in patients with these conditions.[142, 144]

Age

Increasing age is a strong predictor for chronic elevated cTn levels, more comorbidities, and a higher prevalence of AMI.[141, 177-180] In a sub-analysis from the *TRAPID-AMI* cohort, application of an age-specific 99th percentile URL (28 ng/L for hs-cTnT) reduced the prevalence of AMI from 30 % to 18 % for patients ≥ 65 years of age.[180] As expected, the proportion of patients assigned to the 0/1-hour rule-out group decreased with higher age in a cohort by Boeddinghaus et al.[141] For hs-cTnT, age-specific (≥ 70 years) 0/1-hour criteria increased the rule-in accuracy without improving efficacy, while age-specific criteria for hs-cTnI Architect seemed to improve both.[141]

Sex

Compared to males, females are underrepresented in the existing literature, have fewer coronary angiograms, receive less secondary prevention in case of an AMI, and have worse prognostic cardiovascular outcomes.[181-188] The use of uniform diagnostic cTn thresholds, unawareness, and atypical AMI presentation have been highlighted as contributors to the underdiagnosis of AMI in females.[181, 184, 185]

Sex-specific hs-cTn thresholds for the 99th percentile (i.e., lower thresholds for females, higher for males) have received increased attention[182, 189] and were also recommended in the *4th UDMI*.[23] Concerns have also been raised regarding limited applicability and sparse evidence of improved outcomes.[180, 189-191] According to the ESC 2020 guidelines, age, renal dysfunction, and symptom onset are stronger

confounders of hs-cTn than sex.[24] To avoid confusion with multiple discriminators, the ESC still recommends uniform hs-cTn thresholds.[24]

In the *High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients With Suspected Acute Coronary Syndrome)* trial, the application of sex-specific hs-cTnI thresholds increased the detection of myocardial injury in females by a 5-fold, but still without improving the prognosis.[186] The upcoming *CODE-MI* (*hs-cTn-Optimizing the Diagnosis of acute Myocardial Infarction/injury in women*) trial[192] will probably contribute to further insights on this relevant topic.

1.5.4 Single hs-cTn rule-out

After the ESC 2015 guidelines, further extensive validation of the direct rule-out approach at presentation has demonstrated great rule-out performance.[138, 193-200] The reliable diagnostic utility has been further documented in two recent RCTs; the *LoDED (limit of detection and ECG discharge)* trial, combining undetectable hs-cTn and a non-ischemic ECG,[201] and the *HiSTORIC (High-Sensitivity cardiac Troponin at presentation tO Rule out myocardial InfarCtion)* trial, using hs-cTnI < 5 ng/L and > 2 hour symptom onset time for early discharge.[202] Even though the *LoDED* strategy did not document improved efficacy compared to standard care, and the *HiSTORIC* trial did not reach non-inferiority for their 30-day safety outcome, both trials demonstrate high performance and efficacy for the single rule-out approach.[201, 202]

1.6 Cost-effectiveness

The gatekeeper role of primary care in coordinating access to the more advanced specialist health care services is essential in reducing unnecessary hospital admissions and health care expenditure.[203, 204] Although the AMI prevalence in primary care is

low (i.e., 1.5-6.5 %),[15-17, 19] the fear of missing an ACS results in high referral rates.[8, 17, 205] In the Netherlands, the extensive use of in-hospital health expenditure for low-risk patients with chest pain has been estimated to cost between Euro (EUR) 1360 and 1580.[8, 22, 205] The question has been raised whether it is possible to offer low-risk patients outpatient assessment, which may decrease the pressure on the EDs, reduce health care expenditure, limit the exposure to unnecessary diagnostic procedures, and potential iatrogenic harm.[22, 205, 206]

1.7 Knowledge gaps and rationale for the studies

The diagnostic research on coronary artery disease in primary care is highly sparse, as illustrated by a 2017 meta-analysis reporting only five relevant studies in the past 25 years.[65] As chest pain is a frequent presenting symptom in primary care, an accelerated, safe, and accurate rule-out pathway is highly needed. As of January 2016, the ESC 0/1-hour algorithm stood out as a novel rapid algorithm that appeared safe with high efficacy.[127] However, available validation cohorts had been conducted in hospital settings only, with the following request for validation in settings with lower pretest probability for ACS.[117, 119, 120, 171] In two ED cohorts from Sweden and the Netherlands, patients with elevated hs-cTn levels were excluded in order to explore the 1-hour performance in low-risk patients.[135, 137] Still, these findings may not be transferable to emergency primary care due to a different mix of patients.[207]

According to the 1961 publication by White et al., 750 of 1000 people will report illness during a month, where 250 of these will consult a primary care physician, further admitting only 9 of these to a hospital (Figure 4).[208] The White square was adapted for the Norwegian population in 2012 by Hansen et al., where a higher proportion of people reported symptoms or illness (n=901/1000), 214 would consult a GP, and 14 of these would be hospitalised.[209] Both examples illustrate the biased selection of patients in hospital settings.

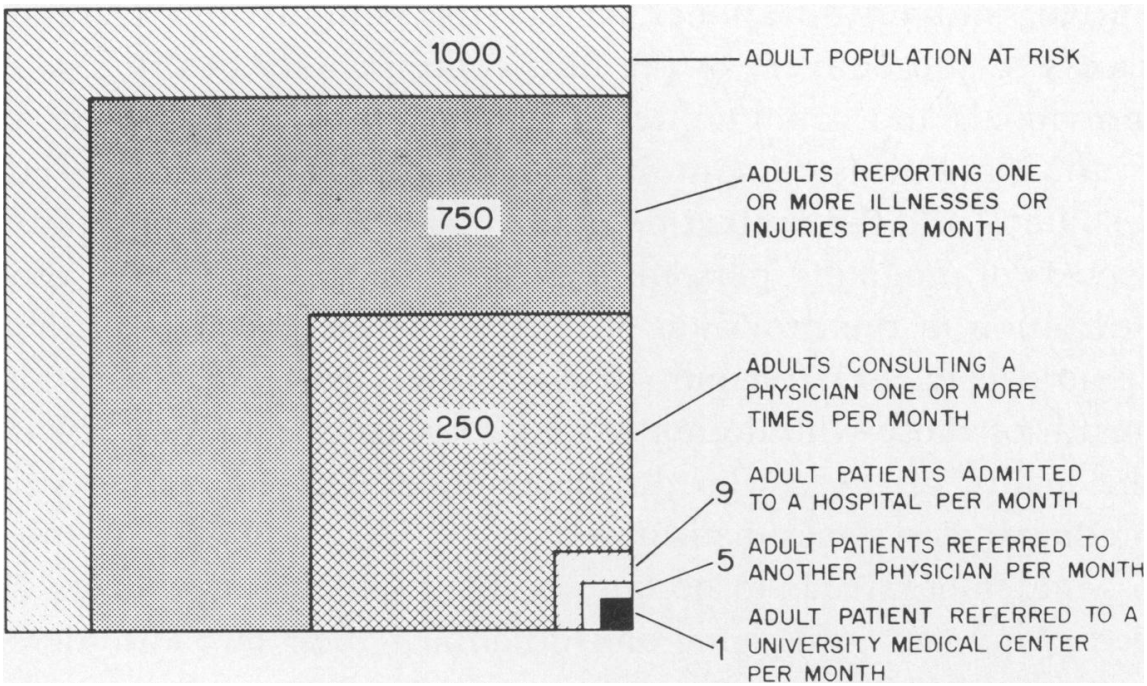

Figure 4 The White Square, from 1961.

Reproduced with permission from The Ecology of Medical Care,[208] Copyright Massachusetts Medical Society.

If results and conclusions from studies in one particular setting are automatically broadly transferred and implemented across different settings or subgroups, there is an increased risk of spectrum/case-mix bias.[210, 211] For the ESC 0/1-hour algorithm, the diagnostic performance achieved in the ED cohorts may be different in emergency primary care. It is, therefore, essential to validate such an algorithm in the relevant population and setting before considering implementation.

With the hypothesis that the ESC 0/1-hour algorithm would benefit emergency primary care with similar high rule-out performance and efficacy as demonstrated in the ED cohorts, the OUT-ACS study *(One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome)* was initiated.

2. Aims

The general aim of the OUT-ACS study and this PhD project was to explore whether the ESC 0/1-hour algorithm for hs-cTnT would enhance the assessment of low-risk patients presenting with chest pain in emergency primary care.

In Paper I, our primary aim was to prospectively validate the diagnostic and prognostic performance of the ESC 0/1-hour algorithm for hs-cTnT in a low-prevalence population of ACS.

In Paper II, the purpose was to investigate the diagnostic performance of the novel criteria for patients assigned to the indeterminate observation group by the ESC 0/1-hour algorithm.

In Paper III, we aimed to compare the diagnostic rule-out ability of a single hs-cTnT measurement to the HEART score in low-risk patients presenting with chest pain in emergency primary care.

Finally, in Paper IV, the main objective was to evaluate the cost-effectiveness of using the 0/1-hour algorithm in the assessment of low-risk patients in emergency primary care compared to routine hospital management.

3. Methods and materials

3.1 Design

The OUT-ACS study was established in January 2016 as a collaboration between the Department of Emergency General Practice at the Oslo Accident and Emergency Outpatient Clinic (OAEOC), the Department of General Practice at the University of Oslo, the Department of Cardiology, and the Department of Medical Biochemistry at Oslo University Hospital, Ullevaal, Oslo, Norway.

A prospective, quantitative, and observational diagnostic design was chosen for the main study. Patient enrolment was conducted at a single site, i.e., the OAEOC in Oslo, Norway, between the 15th of November 2016 and the 23rd of October 2018. Paper II and III present retrospective secondary analyses based on prospectively collected data during the main study (Paper I). In the final paper, a health economic analysis investigated the cost-effectiveness of assessing low-risk patients outside of hospital EDs.

The OUT-ACS study was designed and conducted according to the *2015 STARD (Standards for Reporting Diagnostic Accuracy Studies) guidelines*.[212] For the cost-effectiveness analysis, the *2013 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement*[213] were followed, applicable at the time of the health economic analysis.

A summary of Papers I-IV and their respective aims and methods is presented in Figure 5 on the next page:

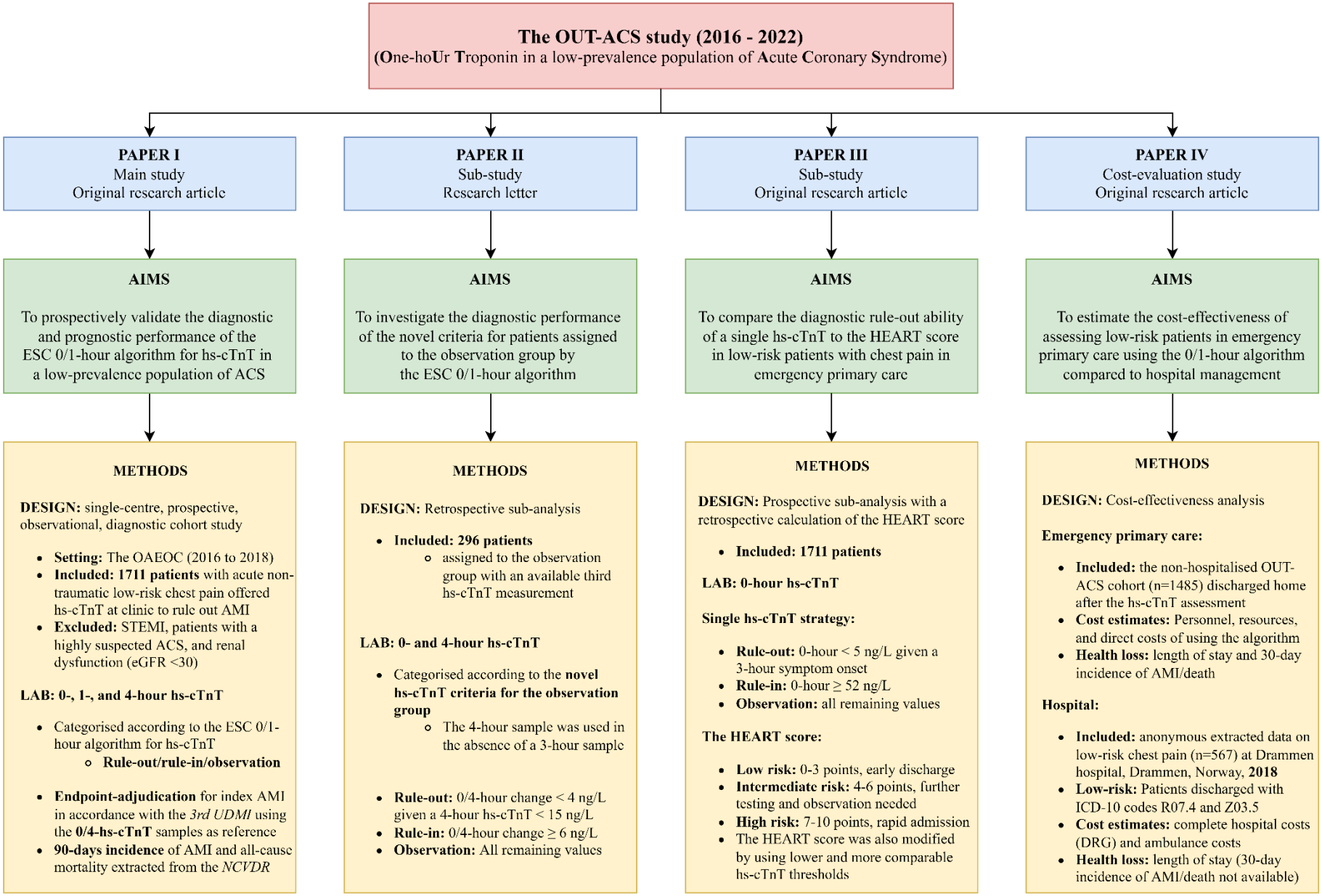

Figure 5 Summary of the papers, their aims and methods

ACS: acute coronary syndrome; AMI: acute myocardial infarction; DRG: diagnosis-related groups; e-GFR: estimated glomerular filtration rate; ESC: European Society of Cardiology; HEART: History, Electrocardiogram, Age, Risk factors, Troponin; hs-cTnT: high-sensitivity cardiac troponin T; NCVDR: Norwegian Cardiovascular Disease Registry; OAEOC: Oslo Accident and Emergency Outpatient Clinic; STEMI: ST-segment elevation myocardial infarction; UDMI: Universal Definition of Myocardial Infarction

3.2 Setting

3.2.1 The Norwegian primary health care system

One of the core values of the Norwegian health care system is equal access to health care services.[214] The health care system is two-tiered, encompassing a robust primary health care (e.g., general practice, OOH/primary care emergency clinics, and short- and long term municipal facilities) and the specialist health care system, including the prehospital EMS and secondary and tertiary general and university hospitals. In Norway, each municipality is responsible for primary health care, and many OOH clinics are organised as inter-municipal cooperation.[214, 215] Although most OOH clinics serve the population after office hours (evenings, nights and weekends), some primary care emergency clinics, usually in the more urban areas, are available 24/7.[216] Both are staffed by primary care physicians/GPs on rotation, with or without nursing staff present.[217] With universal health insurance, EMS and hospitals admissions are free of charge for each inhabitant. In contrast, primary care is based on tariffs with a maximum fee for service per patient ≥ 16 years old.[215] In 2021, the fee during- or after office hours was estimated at EUR 21 and 31.

With referral-based access to Norwegian EDs, patients with acute chest pain cannot present to an ED by themselves without being examined by a primary care physician or the EMS.[214, 215, 218] All patients with acute chest pain are advised to call the emergency medical communication centre through the national phone number *113*.[218] An ambulance is dispatched if an ACS or other severe conditions are suspected. Patients with STEMI or considered critically ill bypass primary care. In a study investigating all somatic admissions in 2014, 42 % of the AMI cases were directly hospitalised by the EMS.[12] The remaining were initially examined by a primary care physician (i.e., 24 % in general practice, 34 % at an OOH clinic, and 1 % private specialists).[12] In 2017, the overall acute hospital referral rates from Norwegian GPs and emergency primary care were 1 % and 11 %, respectively.[13] The symptom-based *A11 Chest pain, not otherwise specified* in the *ICPC-2 (International Classification of Primary Care, 2nd edition)*[219] was the second most

frequent cause for hospital referrals in 2012 and 2017.[10, 13] This is consistent with the second most common discharge diagnosis following an acute somatic admission being the non-specific ICD-10 *(International Statistical Classification of Diseases and Related Health Problems 10th Revision)*[220] *R07 Pain in throat and chest*.[11, 12] In Norway, all patients in need of serial hs-Tn measurements are hospitalised as a standard, and the majority are transported by ambulance between primary care and hospital.

3.2.2 Oslo Accident and Emergency Outpatient Clinic

The OAEOC is the main emergency primary care clinic in Oslo, with approximately 200,000 consultations per year. Oslo had a population of 681,071 inhabitants as of 1 January 2019.[221] The clinic serves the entire city 24/7 and is mainly staffed by registrar level GPs, and nurses. Compared to regular OOH clinics, the OAEOC may appear more advanced in three ways: Firstly, the clinic has 18 beds for short-term observation for up to 24 hours. Secondly, available chest x-ray, and finally, the possibility to have venous blood samples dispatched for analyses at the hospital. Otherwise, the OAEOC serves as a primary care emergency clinic without access to hospital specialists, advanced treatment, or additional diagnostic procedures (e.g., echocardiogram, continuous ECG monitoring, CT scan, or arterial blood gas).

According to the local medical records (Profdoc Vision), the OAEOC has about 85,000 medical consultations per year, where approximately 17 % (n=14,500) of the patients arrive by ambulance. Chest pain is the presenting symptom in 7 % of the cases, constituting 27 % of the admissions at the observation unit. Following standard clinical routine, all patients presenting at the OAEOC are initially triaged by a nurse using the Manchester Triage System.[222] In case of acute chest pain, ongoing heart palpitations, acute fatigue, or syncope in patients > 40 years of age, a 12-lead ECG is immediately recorded before being interpreted by the supervising GP. A primary care physician then performs a clinical assessment, comprising medical history taking, clinical examination, vital signs, and the ECG (Figure 6). A POC-Tn

assay is not available at the clinic. Most Norwegian OOH clinics have two possibilities for patients presenting with chest pain. Either immediate ED referral or discharge home/treatment for other non-cardiac conditions. At the OAEOC, three options are available, where the final decision is made at the discretion of the treating physician:

1. **Hospital transfer:** Patients with STEMI or a highly suspected ACS, clinically unstable, or potentially life-threatening condition, are rapidly hospitalised to avoid further prehospital delay (Figure 6; red box).
2. **Serial hs-cTnT measurements at the clinic:** Patients without urgent need for hospital transfer, but where cardiac-related pain cannot be ruled out without additional testing, might be offered hs-cTnT measurements at the clinic. This group may comprise patients with resolved chest pain but with increased cardiovascular risk profile or non-specific changes at the ECG of unknown clinical relevance, or more atypical presentation such as acute dyspnoea, fatigue or diaphoresis of unknown origin (Figure 6; yellow box).
3. **Discharged home/treatment for other conditions:** Patients with signs and symptoms suggestive of non-cardiac chest pain, e.g., myalgia, dyspepsia, panic disorder, anxiety, or pneumonia. These patients are not offered hs-cTnT measurements to avoid the risk of overdiagnosis and increased false-positive cases (Figure 6; green box).

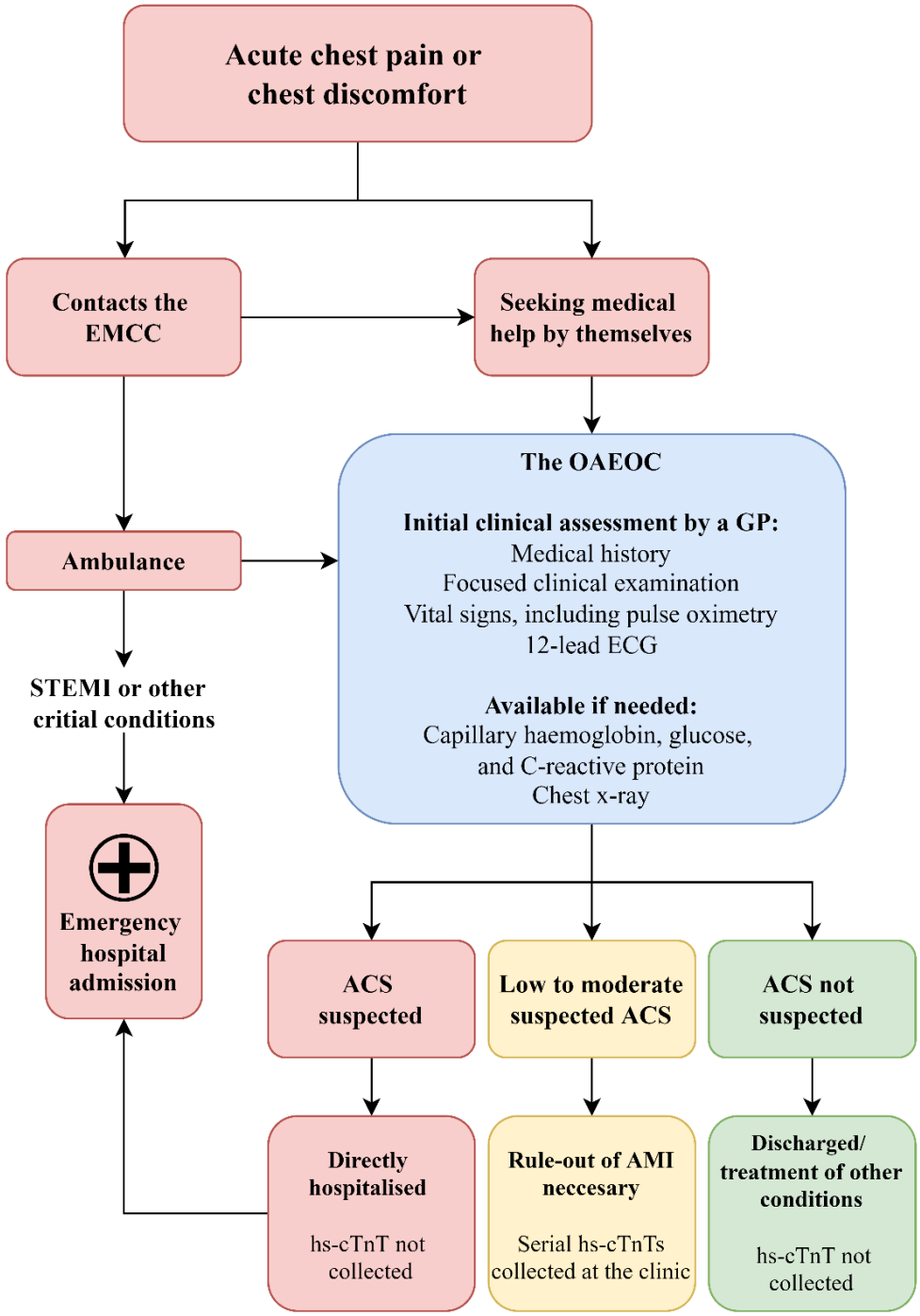

Figure 6 Chest pain routine at the OAEOC prior study inclusion
(Adapted after Online Figure 1; Supplementary Appendix; Paper III).

ACS: acute coronary syndrome; ECG: electrocardiogram; EMCC: emergency medical communication centre (national phone number 113); GP: general practitioner; hs-cTnT: high-sensitivity cardiac troponin T; OAEOC: Oslo Accident and Emergency Outpatient Clinic; STEMI: ST-Elevation Myocardial Infarction

3.3 Participants and eligibility

Between 2016 and 2018, the OUT-ACS study consecutively recruited patients (18 years and older), able to provide written, informed consent, with non-traumatic chest pain admitted at the OAEOC for serial hs-cTnT measurements (Figure 7). The study was embedded in the clinical routine, ensuring a stable inclusion during nights, weekends, and holidays. Following other validation cohorts, patients with renal dysfunction (eGFR <30) were excluded from the final analysis as they tend to have higher baseline levels of hs-cTnT.[142, 174]

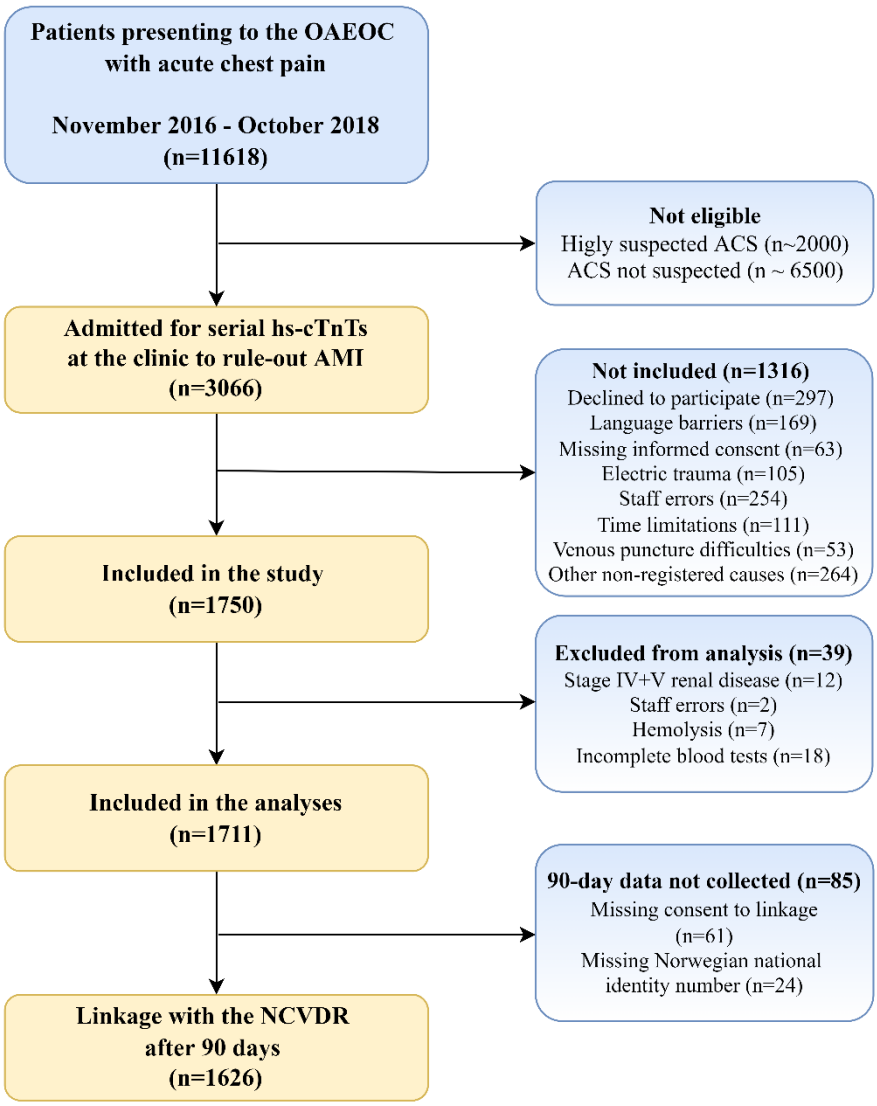

Figure 7 Patient flow

ACS: acute coronary syndrome; AMI: acute myocardial infarction; hs-cTnT: high-sensitivity cardiac troponin T; NCVDR: Norwegian Cardiovascular Disease Registry; OAEOC: Oslo Accident and Emergency Outpatient Clinic (Adapted after Figure 1, Paper III).

3.4 Data collection

A two-week pilot period was initiated on November 15th, 2016, to evaluate the inclusion routine and the study forms. The informed consent form was adjusted after these two weeks to ensure access to 90-day register data (Appendix B). These alterations were accepted by the Regional Ethics Committee within the next month. Without discovering other noteworthy problems or logistic challenges, the study enrolment continued.

As we did not have funding for study personnel during the inclusion period, we strived to keep the flow and patient management as close to the regular routine as possible. The venous 0-hour hs-cTnT was sampled immediately after the patient had been selected for admission at the observation unit. Additional haemoglobin, blood glucose, kidney function tests, potassium, and CRP were collected as a standard. The patients were then approached for study enrolment within the next 60 minutes by regular nurses at the observation unit. The written informed consent (Appendix B) was obtained from all included patients, and relevant baseline characteristics were recorded on the registration form (Table 2 and Appendix A).

The 1-hour study sample was collected as close to 60 minutes as possible. All 1-hour samples collected between 55-90 minutes after the 0-hour sample were accepted as 1-hour samples in the final analysis. The 1-hour study sample was available for the treating physician, instructed to only respond to a 1-hour sample assigning a patient to rule-in to avoid further prehospital delay. The traditional 4-hour hs-cTnT was sampled as a reference test to the 0/1-hour algorithm. Additional ECGs and discharge documents were collected from all participants along with hospital discharge documents in case of hospitalisation. For all non-recruited patients, date, age, sex, and cause of unsuccessful inclusion were anonymously registered to keep track of the total number of patients admitted for hs-cTn measurements at the clinic.

Table 2 Variables recorded during study inclusion

Basics	Norwegian personal identity number (later replaced by a study ID); sex and age; mode of transport to the OAEOC
Time variables (time/date)	Onset of symptoms; timing of hs-cTnT sampling and ECG recordings; length of stay (arrival, admission at the OAEOC observation unit, time of discharge)
Risk factors for cardiovascular disease	Current/history of smoking last ten years, diabetes mellitus; chronic obstructive pulmonary disease; previous history of CAD; hypertension; hypercholesterolemia; other CVD (valvular disease, previous cerebral stroke, cardiomyopathies, atrial fibrillation, other arrhythmias); history of CAD in 1st-degree sibling <60 years
Presenting acute symptoms	Chest pain (constricting, tearing, burning, sharp, respiratory-dependent, position-dependent, palpation-dependent); pain radiation (arms, neck, jaws, upper abdomen, scapulae); acute dyspnoea; acute fatigue; syncope/pre-syncope; observed or reported diaphoresis; nausea or vomiting; palpitations; other pain (upper abdomen or upper back/scapulae only); no pain
Diagnostics	Hs-cTnT values (ng/L); eGFR; ECG 1 and 2 characteristics (ST-segment elevation; ST-segment depression; T-wave inversion; Q-wave; LBBB; RBBB; atrial fibrillation; heart rate per minute)
ICD-10 codes	Recorded by treating physician at OAEOC discharge or documented on hospital discharge documents
Disposition after OAEOC discharge	Home/no follow-up; advised to contact regular GP; referral to hospital outpatient clinic; admitted at a municipality (primary care) short term facility; left during observation; admitted to hospital; direct transfer to the catheterisation lab

Reprinted from Online Table 2; Supplementary Appendix; Paper III.

CAD: coronary artery disease; CVD: cardiovascular disease; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; hs-cTnT: high-sensitivity cardiac troponin T; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision; LBBB: left bundle branch block; OAEOC: Oslo Accident and Emergency Outpatient Clinic; RBBB: right bundle branch block

The comprehensive *Norwegian Cardiovascular Disease Registry (NCVDR)*[223] was assessed to record events of AMI or deaths the following 90 days. Linkage with the national registry was provided by the *Norwegian Institute of Public Health*.[223] The *NCVDR* comprises the Core Registry, which has linkage to the *Norwegian Patient Registry*, the *Norwegian Central Population Registry*, and the *Norwegian Cause of Death Registry*.[224] All patient contacts with the specialist health care system, either in-hospital or outpatient contacts, are automatically registered by ICD-10 codes related to each contact. The registry also obtains data from medical quality registries, e.g., the *Norwegian Myocardial Infarction Registry*.[225]

All collected data were electronically transcribed and stored by TRJ in the Norwegian Services for Sensitive Data platform. The platform has been developed by the University of Oslo, Norway, for the primary purpose of providing storing and post-processing of sensitive data in compliance with the Norwegian privacy regulation.[226]

3.5 Laboratory analyses

The OAEOC routine procedure for hs-cTnT measurements was followed during the study, collecting venous blood samples in 5 ml serum tubes by *Greiner Bio-One*, Austria. The samples were locally stored at room temperature (approximately 20°C) for a maximum of 30 minutes before 10 minutes centrifugation at 3700 rounds per minute. While awaiting courier transport to the central laboratory at Oslo University Hospital, Ullevaal, the serum samples were stored in a refrigerator. At the OAEOC, the local turnaround time, i.e., time from sampling to finished result,[9] is prolonged due to limited transport every 4 hours (i.e., at 04-08-12 am/pm, all year). As the study was only observational, we did not adjust the transport routine during the study.

The Department of Medical Biochemistry at Oslo University Hospital, Ullevaal, has been analysing troponin T since February 1998. Roche Diagnostics, Switzerland, has delivered the equipment, calibration instruments, and reagents. The

Roche technology ElectroChemiLuminescence (ECL) has been used for immunoassay detection, where the 5th generation hs-cTnT assay has been available since April 2009. The hs-cTnT was analysed on the Cobas 8000 e602 and then the Cobas 8000 e801 Module Analyzer, using the Elecsys Troponin T hs STAT assay. The hs-cTnT assay has a 99th percentile URL at 14 ng/L with a coefficient of variation (CV) ≤ 10 %, a limit of detection (LoD) reported at 3-5 ng/L, and a limit of blank at 2.5-3 ng/L.[49, 50, 114, 227]

3.6 Outcome measures

As we considered high rule-out safety to be most central for the emergency primary care setting, the main outcome measure in Papers I-III was the rule-out performance for the adjudicated AMI at the index episode. Rule-out sensitivity and NPV were chosen as safety metrics. In addition, we calculated the rule-in specificity and PPV to explore the diagnostic accuracy and the false-positive rate in our low-prevalence setting. The secondary outcome measure was the prognostic performance of the different strategies, measured by the combined incidence of AMI (including those at index) and all-cause mortality the following 90 days.

In the final health-economic evaluation, the primary outcome measure was the estimated cost per quality-adjusted life-years (QALY) of assessing low-risk patients in emergency primary care using the ESC 0/1-hour algorithm, compared to standard hospital management. The secondary outcome measures were the differences in costs and length of stay when assessing low-risk patients in the two settings.

3.7 Adjudication of AMI diagnosis

For the diagnosis of AMI at the index episode, the 0/4-hour hs-cTnT delta was interpreted in accordance with the *3rd UDMI*[228] available at the time of the study. AMI was diagnosed in case of suspected myocardial ischaemia combined with at least one hs-cTnT > 99th percentile URL and a significant rise or fall in hs-cTnT concentrations (i.e., a 20 % delta for baseline concentrations > 14 ng/L, or 50 % delta for baseline concentration ≤ 14 ng/L).[52, 228] The 50 % criterion has been based on the assumed combined analytical and biological CV of 50-60 % for hs-cTnT values below the 99th, while 20 % CV is clinically accepted for values above.[52, 229] The adjudicators did not distinguish between type 1 and type 2 AMIs.

The adjudication process differed between the hospitalised and non-hospitalised groups of patients. For the hospitalised group, two cardiologists reviewed all collected data from the OAEOC, in addition to hospital procedures and discharge documents. A third cardiologist was consulted in case of disagreements. As the non-hospitalised group were not subject to additional advanced testing, we found it sufficient to use a primary care physician in their adjudication. All collected data from the OAEOC visit were reviewed. In case of disagreement with the treating physician, the case was submitted to the hospital adjudication committee (n=1). The two different processes are illustrated in Figure 8:

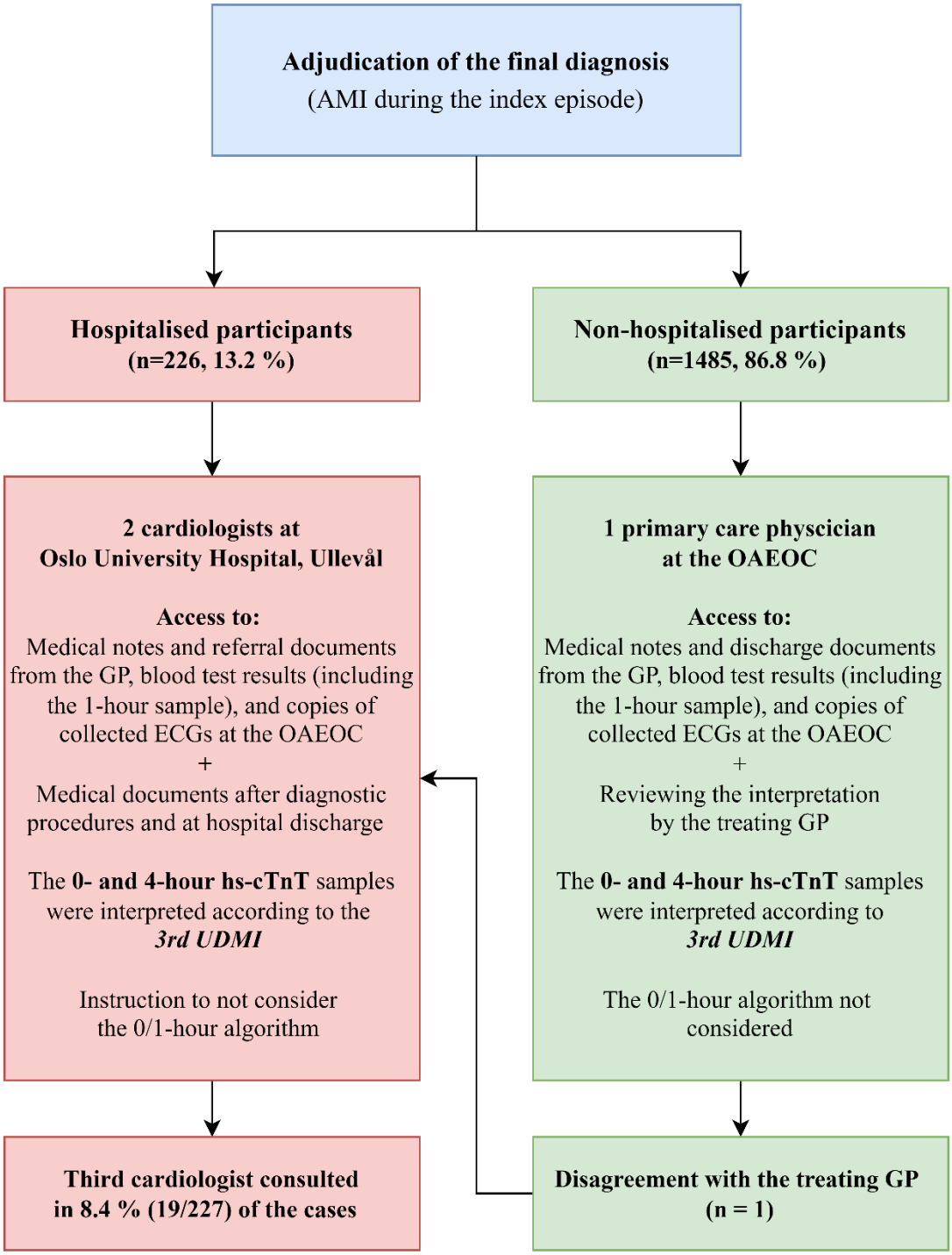

Figure 8 The adjudication of AMI

AMI: acute myocardial infarction; ECG: electrocardiogram; GP: general practitioner; hs-cTnT: high-sensitivity cardiac troponin T; OAEOC: Oslo Accident and Emergency Outpatient Clinic; UDMI: Universal Definition of Myocardial Infarction

3.8 The ESC 0/1-hour algorithm

In Paper I, the diagnostic performance of the 0/1-hour algorithm was validated using the predefined, assay-specific criteria for the hs-cTnT Elecsys assay (Figure 9), as described in the 2015 ESC guidelines.[127] In Paper III, the 0-hour criteria were applied and investigated for the *single hs-cTnT strategy*:

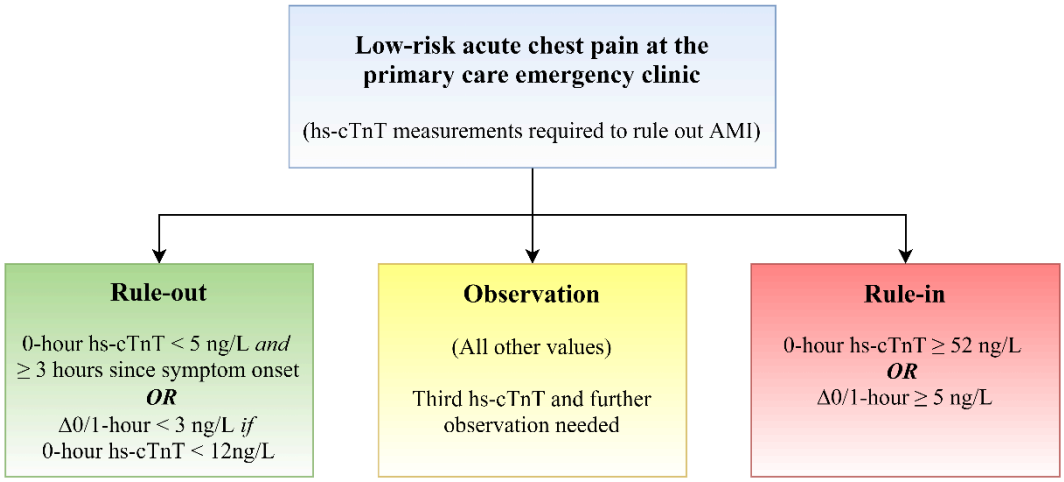

Figure 9: The ESC 0/1-hour algorithm for hs-cTnT (Paper I and III)
AMI: acute myocardial infarction; hs-cTnT: high-sensitivity cardiac troponin T

In Paper II, the novel criteria for patients in the observation group[172] were slightly modified by applying the hs-cTnT criteria with a 0/4-hour interval (Figure 10):

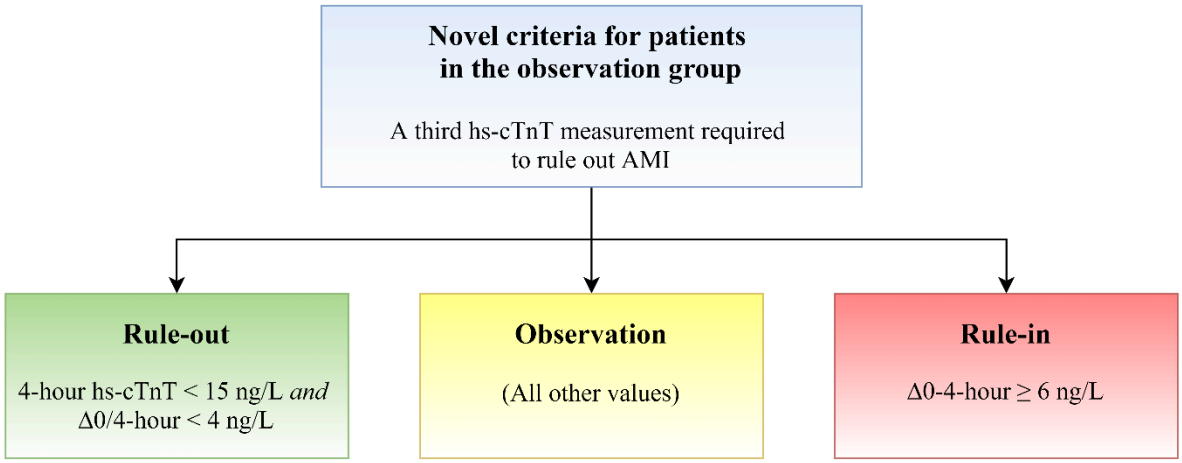

Figure 10: The novel observation group criteria for hs-cTnT (Paper II)
AMI: acute myocardial infarction; hs-cTnT: high-sensitivity cardiac troponin T

3.9 The HEART score

A pre-specified secondary analysis was conducted to investigate the performance of a single hs-cTnT measurement (Paper III). As the HEART score later received increased prehospital attention,[104, 230] and the novel T-MACS *(Troponin-only Manchester ACS)* risk score achieved high rule-out sensitivity,[231] these were both considered relevant for validation in our low-prevalence setting. As relevant variables for the T-MACS score were missing (e.g., radiation to the *right* arm and *observed* diaphoresis), we chose to only proceed with the HEART score as a comparator to the single hs-cTnT strategy.

To reduce the issues of the retrospective design and the subjectivity of the *History* component,[232-234] relevant variables were extracted from the electronic database and standardised (Online Table 3; Supplementary Appendix; Paper III) in accordance with the original HEART score.[92, 94] A dummy ID was constructed for the Microsoft Excel calculations, and variables not included in the HEART score (incl. the adjudicated AMI) were not available. Presenting symptoms were categorised as either typical or non-typical, where 2 points were given in case of typical features only, 1 point if combined typical and non-typical, and 0 points for only non-typical features. Except for *obesity* (i.e., body mass index >30) not being recorded, the criteria for the *ECG, Age, Risk factors* and *Troponin* components were similar to the original HEART score [92, 94] as specified in Table 1, page 24. The 0-hour hs-cTnT was applied for the *Troponin* component, where hs-cTnT ≤ 14 ng/L received 0 points, 15–41 ng/L 1 point, and ≥42 ng/L received 2 points. As lower hs-cTnT thresholds were used in the single hs-cTnT strategy, the performance was also validated using more comparable thresholds. We initially applied the ESC 0-hour criteria in the modified HEART score for a direct comparison. However, this was adjusted during the review process after being recommended to use previously modified thresholds. Inspired by Body et al.,[103] we applied 0 points if hs-cTnT <5 ng/L, 1 point for a value between LoD and URL (5–14 ng/L), and 2 points were given if hs-cTnT >14 ng/L in the modified HEART score.

3.10 Statistical analyses

The statistical analyses and the interpretations of the results were based on collaborative discussions with supervisors and co-authors. The methods selected to assess the diagnostic performance of the algorithm were inspired by the STARD guidelines[212] and comparable international cohorts.[117, 119, 120] As appropriate in Papers I-IV, numbers were presented as frequencies and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR). When comparing variables, comparisons across the subgroups described in the baseline characteristics were calculated using the Pearson $\chi 2$ test or Fisher exact test for categorical variables, or the Kruskal-Wallis test for continuous variables. A two-sided hypothesis testing with a significance level set at $\alpha=0.05$ was chosen. Software used in the calculation were the IBM SPSS, Armonk, NY, USA (version 25.0-26.0), and Stata Corp, College Station, TX, USA (version 15.0-17.0).

A few hs-cTnT measurements were missing due to haemolysis or other errors. By using the median of the non-missing values, imputation was applied for a missing 1-hour sample if the 0- and 4-hour hs-cTnT change was < 3 ng/L (e.g., if hs-cTnT *5 – X – 7 ng/L*, the *X* would be replaced by 6 ng/L). Imputation was also applied for missing 0-hour samples if both the 1- and 4-hour samples were < LoD (5 ng/L). Imputation included 39 more patients in the final analyses. Patients with other missing values were excluded.

3.10.1 Power calculation

The study aimed to validate the ESC 0/1-hour algorithm without deriving alternative thresholds for emergency primary care settings. Hence, the sample size calculation did not include predefined desirable numbers for sensitivity, specificity, or predictive values. The calculation included a desirable sample size based on the AMI prevalence in our setting, which was assumed to be 5 %.[15-17, 19, 53] As hs-cTnT was sampled at three different time points (0, 1, and 4 hours), with measurements clustered within

each patient, statistical methods assuming independence of observations were rendered inappropriate. With a margin of error of 2 %, a critical level of significance of 5 %, and statistical power of at least 80 %, the preferred sample size was calculated to 1039 patients. In addition, we used a design effect (variation inflation factor) of 1.6 to inflate the sample size to 1662 patients due to repeated measurements of hs-cTnT at patient level, performed by the statistician, I. Mdala. As a safety margin for potential exclusion due to drop-outs, haemolysis, or renal dysfunction with eGFR < 30, a desirable sample size of 1750 was chosen.

3.10.2 Diagnostic measures

To validate the diagnostic performance of the different strategies, sensitivity and NPV were chosen as the most relevant safety metrics for the rule-out and low-risk HEART groups. For the rule-in and high-risk HEART groups, specificity and PPV were selected.[210, 212, 235] The optimised sensitivities in the 0/1-hour rule-out/low-risk HEART groups result in subsequently lower specificities.[94, 117, 211] A similar relationship applies to the high specificities in the rule-in/high-risk groups with lower sensitivities.

The ESC 0/1-hour algorithm and the HEART scores have three possible outcomes, i.e., rule-out/observation/rule-in and low/intermediate/high risk, respectively. Consequently, these diagnostic protocols do not provide dichotomised positive or negative results. To avoid the impression that the diagnostic performance is based on one single 2x2-table with excellent sensitivity and specificity, we present the calculated sensitivities and specificities for all groups. For the rule-out/low-risk HEART groups, the added specificity also reflects the true negative rate, less influenced by disease prevalence.[235] Similar transparency was reported in validation cohorts by Mokhtari et al.[128] and Pickering et al.[129] The diagnostic performance of the rule-out and the low-risk HEART groups were, therefore, calculated in a separate

2x2-table against the remaining groups (Figure 11; green box). Similar was then done for the rule-in and high-risk HEART groups (Figure 11; red box).

Diagnostic performance in the ESC 0/1-hour rule-out and low-risk HEART groups

	AMI	No AMI	
Triaged to rule-out **OR** low-risk HEART	**FN**	**TN**	**NPV** = $\frac{TN}{(TN+FN)}$
Triaged to observation or rule in **OR** intermediate or high-risk HEART	**TP**	**FP**	
	Sens = $\frac{TP}{(FN+TP)}$	**Spec** = $\frac{TN}{(TN+FP)}$	

Diagnostic performance in the ESC 0/1-hour rule-in and high-risk HEART groups

	AMI	No AMI	
Triaged to rule-in **OR** high-risk HEART	**TP**	**FP**	**PPV** = $\frac{TP}{(TP+FP)}$
Triaged to observation or rule-out **OR** intermediate or low-risk HEART	**FN**	**TN**	
	Sens = $\frac{TP}{(FN+TP)}$	**Spec** = $\frac{TN}{(TN+FP)}$	

Figure 11 The 2x2-tables used in the calculations of the diagnostic performance

AMI: acute myocardial infarction; ESC: European Society of Cardiology; FN: false negative; FP: false positive; NPV: negative predictive value; PPV: positive predictive value; Sens: sensitivity; Spec: specificity; TN: true negative; TP; true positive

As the predictive values are largely dependent on disease prevalence,[210, 211] we also chose to calculate the less-influenced likelihood ratios (LR) for all groups, including the observation and intermediate-risk groups. The LRs were calculated using the formula LR: (P(group)|AMI/P(group)|non-AMI). An LR value < 0.1 or > 10.0 is usually considered strong evidence for a diagnostic test's ability to exclude or confirm a disease, while LR values around 1.0 imply uncertainty.[236] All diagnostic metrics were presented with corresponding 95 % confidence intervals (CI).

In Papers I and III, the overall diagnostic performance of each approach was illustrated by the area under the receiver operating characteristics (ROC) curve (AUC). The ROC curves were presented as categorical rather than continuous graphs, using two cut-off values, which has been suggested for diagnostic tests with three possible outcomes.[237] The first cut-off highlights the sensitivities and specificities for the rule-out/low-risk groups and the second for the rule-in/high-risk groups. The indeterminate observation/intermediate-risk groups are visualised in-between. We

believe this presentation contributes to the transparency of our results. For Paper III, we also considered using ten cut-off values for each point of the HEART score but settled for the diagnostic decision categories for a more equal comparison. McNemar's test was applied to compare the respective AUCs of the original and modified HEART scores with the single hs-cTnT strategy.

3.11 Cost-effectiveness analysis

Drammen hospital

Cost estimates for the non-hospitalised OUT-ACS cohort were compared with anonymous, administrative data for low-risk patients admitted with chest pain at the general hospital in Drammen, Norway. The low-risk hospital cohort comprises all patients discharged with a non-specific chest pain diagnosis (i.e., ICD-10 R07.4 (chest pain, unspecified) or Z03.5 (observation for other suspected cardiovascular diseases)) in 2018. The few anonymous variables extracted data were minimized to age, sex, codes related to additional procedures, ICD-10 diagnosis at discharge, Diagnosis-Related Groups (DRG), and total length of stay.

Drammen hospital serves as the local hospital for 168,000 inhabitants in Vestre Viken Hospital Thrust.[238] Drammen was chosen as the comparative hospital setting, as the ED population in Oslo would be more selected due to serial hs-cTnT measurements at the OAEOC. Neither hs-cTn nor POC-Tn measurements are available at the emergency primary care clinic in Drammen. Hence all patients requiring troponin assessment are hospitalised, which is also standard in Norway. A repeated ECG, chest x-ray, and a standard venous blood test panel are collected from all patients with acute chest pain in the ED at Drammen hospital (Table S3; Supplementary Appendix; Paper IV). Hs-cTnI is sampled at admission and repeated after six hours, and additional diagnostic procedures are performed if considered

necessary by the physician in charge. The different levels of chest pain management in Drammen (i.e., standard care) and Oslo are illustrated in Figure 12:

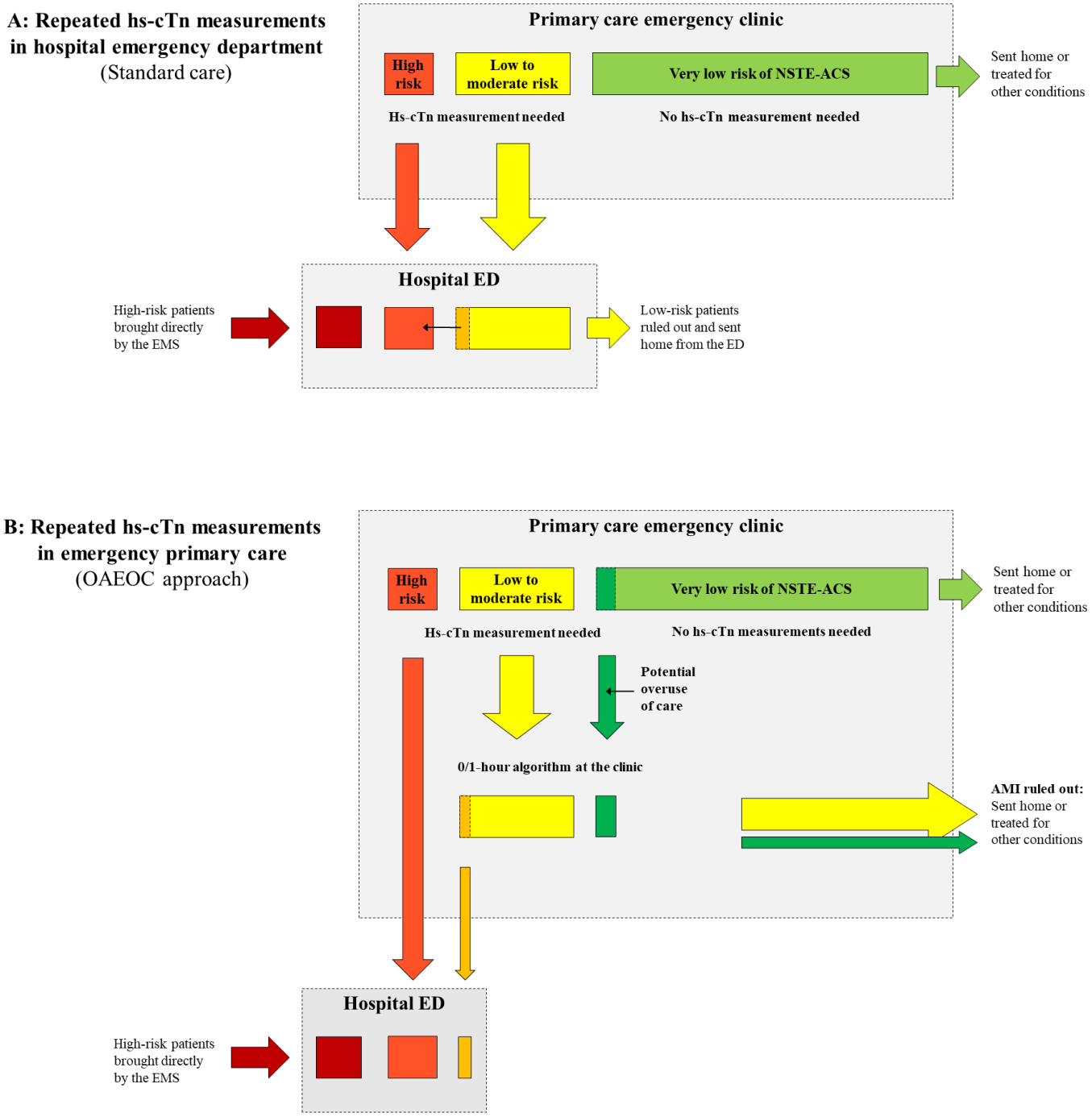

Figure 12 Management of chest pain, standard care versus OAEOC approach

Adapted from Figure 1; Paper IV.
AMI: acute myocardial infarction; ED: emergency department; EMS: emergency medical services; hs-cTn: high-sensitivity cardiac troponin; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; OAEOC: Oslo Accident and Emergency Outpatient Clinic

All cost estimates in Paper IV were based on averages and fees, adjusted to 2020 figures, and presented in Euros (2020 EUR 1.00 = Norwegian Kroner 10.73). For the emergency primary care calculations, average costs of treatment, building and administration, and staff costs per hour at the OAEOC were provided by the City of Oslo Health Agency. Expenses related to personnel, outpatient laboratory and radiological services were then estimated according to *The Norwegian Health Economics Administration (HELFO)* and *The Norwegian Medicines Agency's Guidelines for the submission of documentation for single technology assessment of pharmaceuticals.*[239]

For the hospital setting, the cost estimates comprise the recorded ICD-10 diagnoses and their corresponding DRG. The DRG classification system comprises all costs and procedures associated with an in-hospital stay, including staff, administration, equipment, and building, registered from patient admission to discharge.[239, 240] Average costs related to ambulances, including staff and equipment, were provided by the consultant at the Prehospital Division, Oslo University Hospital, Ullevaal.

A base case (most likely scenario) and a more conservative scenario were calculated for all estimates. In the more conservative scenario, the potential benefits of the OAEOC model were reduced by using:

1. Increased estimates of personnel costs at the OAEOC
2. Worse 30-days outcomes compared to the hospital
3. Less use of resources related to hospital ambulance transport
4. Increased length-of-stay at the OAEOC

A probabilistic sensitivity analysis was conducted by Professor T. Wisløff, including all parameters as probability distributions from the base case model. The distributions were incorporated with probabilities as beta or Dirichlet distributions and costs as gamma distributions.[241] Weights for health-related quality of life were incorporated as beta distributions, restricting weights to values between 0 and 1.

A simple Markov model was incorporated to assess the cost-effectiveness of using the algorithm outside the hospital, where long-term differences between the strategies were included.[242] To estimate the costs per Quality-adjusted life years (QALY), the potential loss of health-related quality of life among patients with a missed AMI[243] was multiplied by the loss of health due to length of stay and costs per patient. We based our analyses on cost-effectiveness thresholds for Norway, recently cited to be between EUR 25,600 and EUR 76,900 per QALY (i.e., NOK 275,000 and 825,000 per QALY).[244]

3.12 Ethics

The OUT-ACS study was conducted in accordance with the Helsinki declaration and approved by the *Regional Committee for Medical and Health Research Ethics Northern Norway* (*REC North*; ref. 2016/1241) and the *Oslo University Hospital Information Security and Privacy Office* (ref. 2016/13308). The OUT-ACS study was also registered at ClinicalTrials.gov (NCT02983123).

Study participation during the enrolment period (November 2016 to October 2018) was based on written informed consent (Appendix B). Informed consent was not considered necessary for the anonymous registration of unsuccessful inclusions or for extracting anonymous administrative data from Drammen Hospital.

After the two-week pilot period, the written informed consent form was adjusted (Appendix B) to obtain access to relevant prognostic data in the following 90 days. The adjustments were approved by *REC North* within the next month. Patients who had already been included were contacted by phone by nurses seeking permission to obtain follow-up data (Appendix D). Following the REC standard, the written informed consent was verbalised in a language accessible for patients without medical education, including short, concise paragraphs based on common knowledge without advanced details. When the *Norwegian Institute of Public Health* was contacted during the Autumn 2018 to establish linkage with the *Norwegian CVD Registry*,[223] the *European General Data Protection Regulation (GDPR)* had been

implemented a few months earlier (May 2018). Hence, increased formal demands for written informed consent were required, and linkage with the registries could not be made. The *Information Security and Privacy Office at Oslo University Hospital* requested a *Data Protection Impact Assessment*, resulting in a new formal application to *REC North*, ensuring data minimization and patient confidentiality. After eight months, the linkage was approved, and the data was collected.

3.13 Funding

In 2016 the study received funding for one month from *The Norwegian Committee on Research in General Practice* to initiate the project. At the same time, the study received a grant from *The Norwegian Medical Association's Fund for Quality Improvement and Patient Safety*.

The PhD student period was initiated in July 2018 and funded by *The Norwegian Research Fund for General Practice*, covering full-time research in three years. The last year was extended to two years, working part-time as a PhD student and clinical rotation at the OAEOC. The funders were not involved in the conception of the study, data collection, statistical analysis, interpretation of results, or writing of the papers.

4. Summary of the papers

4.1 Paper I

Pre-hospital One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome: OUT-ACS Study

Johannessen TR, Vallersnes OM, Halvorsen S, Larstorp ACK, Mdala I, Atar D. *Open Heart. 2020;7:e001296.*

Aims: To investigate the diagnostic and prognostic performance of the ESC 0/1-hour algorithm for hs-cTnT in a low-prevalence population of ACS.

Methods: Single-centre, prospective, observational, diagnostic study, conducted at the OAEOC in Oslo, Norway, between 2016 to 2018. Patients (aged ≥18 years) with non-specific, non-traumatic chest pain were consecutively approached for inclusion. Hs-cTnT was sampled at 0, 1, and 4 hours. Highly suspected ACS were excluded.

Results: Among 1711 patients, 61 (3.6 %) had an AMI. The median age was 56 (IQR 45–68), and 47.7 % were females. Using the 0/1-hour algorithm, 1311 (76.6%) patients were categorised as rule-out. The rule-out performance was high with an NPV of 99.9 % (95 % CI, 99.5–100.0), sensitivity 98.4 % (91.2–100.0), and specificity of 79.4 % (77.4–81.3). In addition, the composite of AMI (including index) and all-cause mortality the following 90 days was low (0.3 %). There were 66 patients (3.9 %) in the rule-in group, where 45 had an AMI. The rule-in accuracy was, therefore, moderate with a PPV of 68.2 % (58.3–76.7) and a sensitivity and specificity of 73.8% (60.9–84.2) and 98.7 % (98.1–99.2), respectively. A total of 334 (19.5%) patients (15 with an AMI) remained in the indeterminate observation group, requiring additional hs-cTnT measurement and observation. The overall diagnostic accuracy of the rule-out and rule-in groups achieved an AUC of 0.96 (0.94–0.98). The total efficacy was high, with 80.5 % of the patients conclusively triaged by the algorithm.

4.2 Paper II

Performance of the novel observation group criteria of the ESC 0/1-hour algorithm in a low-risk population

Johannessen TR, Halvorsen S, Atar D, Vallersnes OM.
Journal of the American Heart Association. 2022;0(0):e024927.

Aims: To investigate the diagnostic and prognostic performance of the novel criteria for patients assigned to the ESC 0/1-hour algorithm observation group in a low-risk population.

Methods: In a retrospective secondary analysis, the novel criteria suggested for patients in the observation group were validated using the 0- and 4-hour hs-cTnT sample.

Results: The novel observation group criteria were applied among 296 patients assigned to the observation group with an available 4-hour hs-cTnT measurement. Ten of these were adjudicated with an AMI at index. The novel criteria triaged 111 more patients towards rule-out with sensitivity and NPV of 100 % (95 % CI, (69.2–100.0) and (96.7–100.0), respectively), although with poor precision due to few events. The rule-out specificity was 38.8 % (33.1–44.7), and there were no AMIs or deaths among the rule-out cases the following 90 days. Additional 14 patients were assigned to the rule-in group, where half of these had an AMI (specificity 97.6 % (95.1–99.0), PPV 50 % (CI 30.2–69.8), and sensitivity 70.0 % (34.8–93.3)). Among the remaining 10.0 % in the observation group, there were three additional AMIs at index and one death during the subsequent 90 days, highlighting the need for additional diagnostic evaluation for this small group of patients. With only 171/1711 patients remaining in the observation group, the overall efficacy of the ESC 0/1-hour algorithm increased from 80.5 % to 90.0 % by applying the additional observation group criteria.

4.3 Paper III

Comparison of a single high-sensitivity cardiac Troponin T measurement with the HEART score for rapid rule-out of acute myocardial infarction in a primary care emergency setting: a cohort study

Johannessen TR, Atar D, Vallersnes OM, Larstorp ACK, Mdala I, Halvorsen S. *BMJ Open. 2021;11(2):e046024.*

Aims: As a single hs-cTn is occasionally sampled, we aimed to compare the diagnostic performance of a single hs-cTnT measurement to the HEART score in patients with non-specific chest pain in emergency primary care.

Methods: A prospective sub-analysis was performed with an additional retrospective calculation of the HEART score. The 0-hour hs-cTnT was used in the analyses. A modified version of the HEART score was also evaluated using lower and more comparable hs-cTnT thresholds than those suggested in the Original HEART score.

Results: The single hs-cTnT strategy assigned 1/3 of the cohort (593/1711) towards rule-out with great performance (sensitivity 100 % (95% CI, 94.1–100.0), NPV 100 % (99.4–100.0), and specificity 34.5% (32.2–36.8)). No additional events were recorded for the next 90 days. More patients were categorised for rapid discharge in the low-risk HEART group (n=871; 50.9 %), but with 5 missed AMIs and insufficient performance (sensitivity 91.8 % (81.9–97.3), NPV 99.4 % (98.7–99.8), and specificity 52.5 % (50.0–54.9)). The sensitivity of the low-risk HEART score was improved using lower troponin thresholds (sensitivity 98.4 % (91.2–100.0) among 639 patients). However, an extensive increase in false-positive cases was observed in the modified high-risk HEART group (PPV 10.7 % (7.6–14.9)), which was not reported for the single hs-cTnT rule-in group (PPV 77.3 % (63.8–86.8)). The corresponding AUCs for the single hs-cTnT strategy, original HEART score and modified HEART score, were 0.85 (0.81–0.89), 0.77 (0.73–0.82), and 0.74 (0.70–0.78), respectively, where the single hs-cTnT strategy seemed to perform better than the HEART scores ($p<0.01$).

4.4 Paper IV

Cost-effectiveness of a rule-out algorithm of acute myocardial infarction in low-risk patients: Emergency primary care versus hospital setting

Johannessen TR, Halvorsen S, Atar D, Munkhaugen J, Nore AK, Wisløff T, Vallersnes OM
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Aims: To estimate the cost-effectiveness of assessing low-risk patients in emergency primary care using the 0/1-hour algorithm compared to routine hospital management.

Methods: In a cost-effectiveness analysis, data and costs estimated from the non-hospitalised patients in the OUT-ACS cohort (n=1485) were compared with anonymous, administrative 2018 data on low-risk patients at a large general hospital in Drammen, Norway (n=567). Estimated health care expenditure in the two settings was compared. A probabilistic sensitivity analysis was conducted to assess uncertainties. The 30-day incidence of AMI and all-cause mortality was investigated in the risk of harm analysis, and the costs per quality-adjusted life-years (QALYs) of applying the ESC 0/1-hour algorithm in primary care were calculated.

Results: The additional costs of assessing one low-risk patient with chest pain using the algorithm in emergency primary care versus routine hospital management were estimated at EUR 192 and EUR 1986, respectively. The estimated reduction in costs per low-risk patient assessable by the algorithm outside hospitals was EUR -1794, with a mean decrease in length of stay of -18.9 hours. Additional non-invasive diagnostic procedures were performed in 31.9 % of the low-risk hospital cohort. With a presumed low, comparable AMI miss-rate in both settings and an average per-person QALY gain of 0.0005 due to reduction in length of stay, the primary care approach was proven cost-effective, which was confirmed by the sensitivity analysis. The potential budget impact in Norway was estimated to be EUR 8.3 to 8.6 million per year.

4.5 Additional unpublished data

Detailed summaries of the final diagnoses at discharge for the non-hospitalised and hospitalised group of the OUT-ACS cohort are presented in Tables 3 and 4 for clarification before the Discussion section.

Table 3 Final OAEOC diagnoses at discharge in non-hospitalised patients

ICD-10 codes		Frequency	Percent
R074	Chest pain, unspecified	599	40.3
R072	Precordial pain	225	15.2
R073	Other chest pain	153	10.3
R55	Syncope and collapse	45	3.0
R002	Palpitations	34	2.3
M791	Myalgia	29	2.0
R42	Dizziness and giddiness	23	1.5
K30	Functional dyspepsia	19	1.3
R101	Pain localized to upper abdomen	19	1.3
K297	Gastritis, unspecified	18	1.2
R060	Dyspnoea	18	1.2
I480	Paroxysmal atrial fibrillation	17	1.1
R104	Other and unspecified abdominal pain	11	0.7
F419	Anxiety disorder, unspecified	9	0.6
I209	Angina pectoris, unspecified	9	0.6
I10	Essential (primary) hypertension	8	0.5
I509	Heart failure, unspecified	7	0.5
K219	Gastro-oesophageal reflux disease without oesophagitis	8	0.5
K802	Calculus of gallbladder without cholecystitis	7	0.5
R53	Malaise and fatigue	7	0.5
	(Other ICD-10 codes, each less than n=7 (< 0.5 %))	220	14.8
Total		**1485**	**100 %**

ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision

Table 4 Final hospital diagnosis at discharge among non-AMI patients (n=166)		
Cardiovascular (n=63, 38.0 %)		
G45.9	Transient cerebral ischaemic attack	2
I10	Hypertension	2
I20.9	Angina pectoris, unspecified	5
I25.1	Atherosclerotic heart disease	7
I26.9	Pulmonary embolism	10
I30.9	Acute pericarditis	3
I35	Aortic valve disorders	2
I40.9	Acute myocarditis, unspecified	1
I42	Cardiomyopathy	2
I44	Atrioventricular block, 2nd degree	1
I45.5	Other specified heart block	2
I47	Tachycardia	5
I48	Atrial fibrillation/flutter	5
I49.3	Ventricular premature depolarization	1
I49.9	Other cardiac arrhythmias	1
I50	Congestive heart failure	7
I71.0	Dissection of aorta	1
I71.2	Thoracic aortic aneurysm	1
I74.8	Embolism of other arteries	1
Z03.5	Observation for other suspected cardiovascular disease	3
Z94.1	Status, transplanted heart	1
Respiratory (n=17, 10.2 %)		
A31	Pulmonary mycobacterial infection	1
J15.9	Bacterial pneumonia	2
J18.9	Pneumonia, unspecified	2
J44.1	COPD	5
J45.9	Asthma	1
J93.9	Pneumothorax	1
R04.2	Haemoptysis	1
R06	Dyspnoea	4
Gastrointestinal (n=15, 9.0 %)		
K25	Gastric ulcer	1
K26	Duodenal ulcer	1
K29	Gastritis	1
K30	Functional dyspepsia	1
K70	Alcoholic hepatitis	1
K75	Inflammatory liver disease	1
K80	Cholecystolithiasis	3
K85	Acute pancreatitis	3
R10	Pain upper abdomen	3
Other (n=71, 42.8 %)		
A46	Erysipelas	1
D62	Acute posthaemorrhagic anaemia	2
F41	Anxiety disorder	2
H81	Vertigo	3
M47.8	Spondylosis	1
M79	Myalgia	7
R00	Palpitations	7
R07	Chest pain, non-specific	35
R09.1	Pleurisy	1
R26.2	Dysbasia	1
R42	Dizziness	3
R55	Syncope	6
S22	Fracture of thoracic vertebra	2

The HEAR score

The diagnostic performance of the HEAR score, i.e., the HEART score without the Troponin component, was initially also calculated for Paper III. Due to word limitations and to avoid misunderstandings, we removed the score from the final manuscript during the revision process. As it still will be briefly mentioned in the following discussion, an overview of the calculation is presented in Table 5:

Table 5 The HEAR score applied in the OUT-ACS cohort (n=1711, AMI 61)

	Low risk (0-3 points)	**Intermediate (4-6 points)**	**High risk (7-8 points)**
n (%)	925 (54.1)	761 (44.5)	25 (1.5)
AMI at index	18	40	3
Diagnostic performance (95 % CIs)	Sensitivity 70.5 % (57.4-81.5)	-	Specificity 98.7 % (98.0-99.2)
	NPV 98.1 % (97.2-98.7)	-	PPV 12.0 % (4.0-30.7)
AMI and all-cause mortality after 90 days	20	47	3

AMI: acute myocardial infarction; CI: confidence interval; HEAR: History, Electrocardiogram, Age, and Risk factors; NPV: negative predictive value; OUT-ACS: One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome; PPV: positive predictive value

5. Discussion

5.1 Methodological considerations

5.1.1 Study design

For the diagnostic validation of the 0/1-hour algorithm in a low-prevalence setting, we chose a prospective, observational design, which was preferred across the few comparable studies in 2016. Consequently, the OUT-ACS study only illustrates how the ESC 0/1-hour algorithm *might* perform in a low-prevalence setting. We could have been bolder and chosen a gold-standard RCT, comparing the traditional 0/4-hour approach with the 0/1-hour algorithm. An RCT was not selected due to limited knowledge of the algorithm at the time. Only two ED cohorts using hs-cTnT had been conducted,[117, 119] highlighting that the algorithm was not validated for a low-prevalence setting. Hence, conducting an RCT in emergency primary care at that time could have been somewhat controversial, especially as the default strategy is to avoid prehospital delay.[1, 74] Also, as RCTs often apply strict inclusion criteria, their results may not always be transferable to the general population.[245, 246] The heterogenic group admitted for hs-cTnT at the OAEOC includes the elderly, patients with atypical presentations, and complex comorbidities. Therefore, the observational design with broad inclusion criteria might be suitable, where bias must be appropriately addressed. Still, we acknowledge that an RCT would have increased the quality of our results and conclusions and be beneficial in assessing the actual safety, feasibility, and efficacy of the algorithm outside of hospital.

5.1.2 Reliability

The 0/1-hour algorithm is based on assay-specific thresholds, where imprecision and instability may cause misclassification. Thus, high reliability of the results is essential for the conclusion of our study. Reliability (Figure 13) comprises the accuracy, reproducibility, robustness, and precision of the results and measurements.[247, 248]

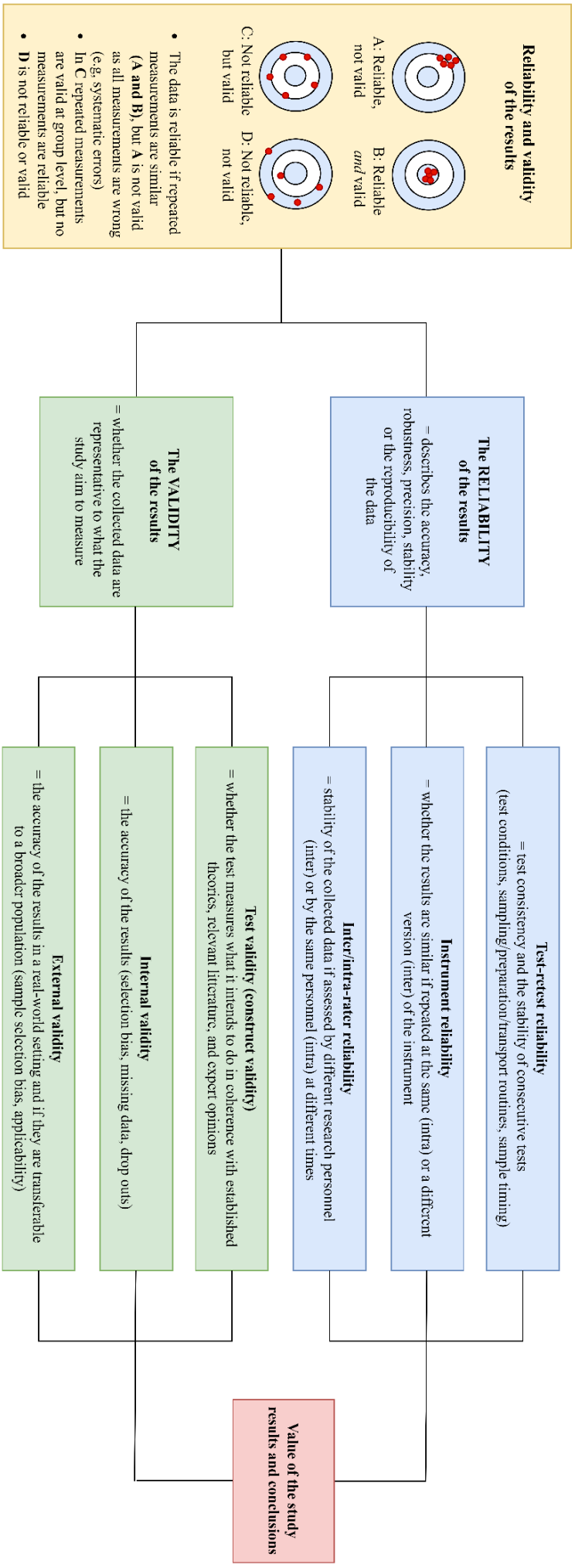

Figure 13 Overview of the assessment of the reliability and validity of the results

Inspired by The Edinburgh Framework by Kelly et al.,[240] modified by TRJ

Test-retest reliability

Testing conditions

To ensure stable inclusion and reduce the burden of the large sample size, we chose to keep the study as close to the regular clinical routine as possible. Except for the written informed consent, registration form and the 1-hour sample, the clinical routine remained unaltered at the clinic during the study. By performing a continuous, consecutive enrolment 24/7 over two years, we have also avoided the limitations of convenience sampling restricted to daytime on weekdays and potential seasonal variations.[249]

We sought to keep the registration form within one page to decrease the personnel workload (Appendix A). Consequently, hypercholesterolemia and hypertension were merged within the broad *Other heart disease* category (including atrial fibrillation, other arrhythmias, heart failure, cardiomyopathy, and stroke). As we later decided to report these two risk factors separately, a retrospective investigation of all retrieved documents was performed by TRJ. Consequently, these numbers might be underreported. We also registered that as many as 72.4 % reported chest pain of constricting character (Paper I). As the category *constricting pain* was first listed, we cannot exclude a so-called question-order bias among some of the given answers.

Sampling

Approximately 1600 patients are admitted for hs-cTnT measurements at the OAEOC every year. Hence, the hs-cTnT procedure, including sampling, preparation, storage, and transport, was a well-established routine before the study. Conducting a study in such an environment, using experienced personnel on fixed rotations, has probably contributed to the high reliability of the collected data and low numbers (n=7/1750) of haemolysis in the samples (Figure 7, page 41).

According to Kavsak et al., different types of sampling tubes (e.g., EDTA versus serum) might affect the hs-cTn analyses, resulting in a plausible reclassification of the 0/1-hour algorithm.[250] Following the local routine, only serum

tubes were used at the OAEOC for hs-cTnT measurements during the study. The serum tubes were stored in a refrigerator for up to four hours before being dispatched for analyses. Still, high quality of hs-cTnT was preserved as the stability remains high with storage at 2–8°C for up to 24 hours.[50, 114] Comparable stability has also been demonstrated for samples stored under similar conditions as the OUT-ACS study.[251]

Timing

The timing of the 1-hour sample was robust, with a median 0/1-hour interval of 65 minutes (IQR 60-70) (Paper I). The precise timing, performed by regular nurses during busy working hours, demonstrates the great feasibility and simplicity of the algorithm. Unfortunately, a 3-hour sample was not available for the retrospective evaluation of the observation group criteria in Paper II. As a result, the novel criteria were validated using the 4-hour hs-cTnT with a 0/4-hour median of 4.33 hours (IQR 4.08-4.84). A wider time interval may result in more patients being assigned to a higher category (i.e., *rule-out* to *observation* and *observation* to *rule-in*), resulting in a safer but less effective algorithm.

Instrument reliability

The Electrochemiluminescence (ECL) immunoassay technique from Roche Diagnostics for detecting cardiac troponin T has been a well-established procedure at Oslo University Hospital, Ullevaal, since 1998. The instrument models, calibrators, and reagent lots have been updated regularly, and the laboratory follows a standardised internal (imprecision) and external (trueness) quality assessment routine, ensuring high accuracy of the results. The imprecision (i.e., CV) for the hs-cTnT assay was < 10 % for concentrations below 20 ng/L and 6 % for concentrations ≥ 20 ng/L, demonstrating a high test-retest reliability of the hs-cTnT measurements. The laboratory participated in two external quality assessment programs during the study; Noklus (Bergen, Norway) and Equalis (Equalis AB, Uppsala, Sweden), and the results were satisfactory during the inclusion period.

Concerns regarding the low criteria used in the 0/1-hour algorithm have been raised. Especially regarding the narrow 1-hour deltas, as 5 ng/L variations have been documented without clinical relevance within the analytical 10 % imprecision profile of the assay.[252-254] To clarify, does the algorithm manage to distinguish a 1-hour delta of 2 ng/L (i.e., rule out if 0-hour < 12ng/L), from 3 ng/L (i.e., observation group and further testing)? Moreover, is a 5 ng/L rule-in delta clinically relevant or just analytical noise? Due to increased imprecision observed at low levels, the Food and Drug Administration in the US has recommended 6 ng/L as the lowest rule-out criteria when using hs-cTnT.[131, 255] Similar precautions have not been advised in Europe.

At Oslo University Hospital, Ullevaal, the hs-cTnT samples were analysed on the Cobas 8000 e602 Module analyzer during the first year of inclusion, before shifting to the new instrument module e801 between October and November 2017. Validation of the new module did not show any significant measurement bias or altered imprecision compared to the previous e602 analyzer. Hence, the reliability of the hs-cTnT measurements was considered satisfactory.

Inter-/intra-rater reliability

The observed inter-rater agreement during the hospital adjudication process was acceptable, as a third cardiologist was consulted in only 19 of 227 cases (Paper I). The interpretation of the 0/1-hour algorithm and the manual transcription of the variables to the Service for Sensitive Data storage system was performed by one investigator (TRJ). Some variables also required interpretation of patient documents, e.g., if symptom presentation or onset was not clear at the registration form. However, performing this process unaccompanied has most likely contributed to increased consistency in the interpretations and improved the reliability of the data. Even after reviewing the data several times, there will always be a risk for typing errors.

Contrary to hospital cohorts, we did not have similar extensive access to complete medical records or multiple registries for the follow-up data. These were mainly obtained through linkage with the *NCVDR*.[223] Also, the AMI events are based on the recorded ICD-10 codes after each in-hospital or outpatient contact and do not reflect potential uncertainty. As the interpretation of the *UDMI* is partly subjective, misclassifications may occur. The ICD-10 codes are also related to the hospital reimbursement codes[240] which, in theory, might impact registration. If an endpoint adjudication committee had evaluated the 90-day data, the reliability and validity would have improved. Still, as the *NCVDR* is considered comprehensive, of good quality, closely regulated, and almost complete,[224] we consider the reliability of the provided data as acceptable.

5.1.3 Validity

Construct validity

Construct validity refers to whether a test is suitable for its purpose, including measuring what it is designed for, suited to answer the aims, and if the results represent the outcomes precisely and accurately (Figure 13).[247, 256] The 0/1-hour algorithm was designed for a rapid rule-out and rule-in of NSTEMI.[117] As multiple conditions may cause increased circulating levels of cTn, the rule-in accuracy is usually in the range of 75-80 %.[119, 120, 128, 129, 131] The algorithm should, therefore, be considered an algorithm for the rule-out of AMI (without ruling out UA) and the rule-in of myocardial injury.[255, 257] It has been thoroughly validated with an improved recommendation in the 2020 ESC guidelines.[24] As the algorithm also relies on objective, assay-specific thresholds, unlike the more subjective *UDMI*[23, 228] and the HEART score[92-94], the consistency and validity of the algorithm are strengthened. We also chose to report valid diagnostic metrics for rule-out safety (i.e., sensitivity, NPV, and LR–) and rule-in accuracy (specificity, PPV, and LR+) in line with the STARD guidelines,[212] contributing to the validity of our results.

Internal validity

Internal validity refers to whether the results and conclusions are accurate (Figure 13). In addition to reliability, the integrity of the results also depends on the effect size and the overall risk of bias.[247, 248]

Power of the study

A small sample size and few events may undermine the results, affecting the validity of our conclusions.[258, 259] In Papers I and III, there were 61 AMIs at the index episode, while the additional observation group analysis only reported ten (Paper II). Even though we reached our precalculated sample size (n=1662), which was further increased to 1750 patients to compensate for dropouts and errors, the study still appears underpowered. The low number of AMIs at the index episode has contributed to the imprecision of our estimates, highlighted by the broad confidence intervals. In addition, few events in a sizeable low-risk cohort inflate the denominator and provide numbers that appear better than they are.[257] According to J. Pickering, at least 150 events should be included for studies deriving diagnostic thresholds.[235] We did not include such numbers in the sample size calculations. Hence, experimental thresholds for the primary care cohort were not derived, and additional subgroup analyses were not performed. Also, with few events after 90 days, we could not provide useful Kaplan-Meier curves. However, if we were supposed to reach 150 AMIs, the sample size should have been increased 2-3-fold. An extended enrolment period with increased use of resources was not feasible at the clinic, as we did not have additional funding. A large sample size in a low-risk cohort may also complicate the results making insignificant results appear relevant.[258] Still, we believe our results demonstrated the potential of using hs-cTn outside of the EDs and the diagnostic performance of the algorithm in a low-prevalence setting.

Adjudication

According to the STARD guidelines, the diagnostic performance of a test should be validated against a reference standard, i.e., the gold standard, for the final diagnosis.[212] The reference standard for AMI is the *UDMI*, where cTn is included.[23,

[228] Hence, without an independent reference standard, all cTn studies investigating the diagnosis of AMI may be subject to incorporation bias.[260] This was also the case in our study, as both the index test (i.e., 1-hour sample) and the reference standard (i.e., the *3rd UDMI* using the 0- and 4-hour sample) were using hs-cTnT.

The adjudication of AMI also differed among the hospitalised and non-hospitalised groups (Figure 8, page 47). For the non-hospitalised cohort, only the 0- and 4-hour hs-cTnTs were interpreted in accordance with the *3rd UDMI*.[228] As the OAEOC does not have access to advanced diagnostic procedures, such were not included in the *UDMI* interpretation for patients discharged home. Hence, we found it sufficient to use a primary care physician in their adjudication. Still, the failure to provide similar investigations for the reference standard may have resulted in verification bias.[260] However, it would not have been ethical or feasible to mandate hospital admission for the whole cohort.

As 29.9 % of the cohort were so-called late presenters (hs-cTnT sampled > 12 hours after symptom onset), some patients with a mildly elevated hs-cTnT, but without a significant 4-hour delta, may represent patients with a small AMI in the plateau phase. Eight rule-in patients were late presenters and adjudicated as non-AMI (Table S4; Supplementary Appendix; Paper I). We cannot dismiss that some of these might have been interpreted as a chronic myocardial injury rather than AMI.

According to the STARD guidelines,[212] the 1-hour index test result should ideally be blinded for the treating physicians and the adjudication committee. As the 0/1-hour algorithm had already been recommended in the ESC 2015 guidelines,[127] we chose to partly implement the algorithm to respond to a 1-hour sample assigning a patient to rule-in to avoid further prehospital delay. It would have been unethical to withhold such patients outside of hospital while awaiting the 4-hour result due to the prolonged local turnaround time and time to decision at the OAEOC. This resulted in early hospitalisation of 46 of the 66 rule-in patients before the 4-hour-sample was drawn. Accordingly, the 1-hour results were also available in the hospital documents reviewed by the adjudication committee. Nevertheless, as the 0/1-hour algorithm had not been implemented in 2019 and the committee was instructed to use the 0/4-hour

hs-cTnT in accordance with the *3rd UDMI*,[228] we consider the adjudication process as sufficient.

Missing data

Follow-up data after 90 days was missing for 5 % of the participants (Figure 7, page 41). After adjusting the written informed consent form (Appendix B), patients already included were approached by phone to obtain permission to use the registries (Appendix D). Some declined, others did not respond. Obtaining 90-day data was also not possible for patients without a Norwegian national identity number (mainly from Sweden), as these were not linked with the national registries. However, we do not have reason to believe that this small group of missed cases influences the validity of the results.

The HEART score calculation was not prospectively planned but added later to improve the relevance of Paper III. Consequently, the risk factor *obesity* was not systematically recorded, which may have reduced the reliability of the HEART scores. At the same time, by standardising the calculation (Online Table 3; Supplementary Appendix; Paper III), we managed to reduce some of the issues related to the retrospective design and the subjectivity of the *History* component.[232-234] However, it is still possible that the performance of the HEART score might have been improved with a prospective design.

The cost-effectiveness analysis

Several assumptions and uncertain estimates may limit the internal and external validity of the results presented in Paper IV. First, we assume that the non-hospitalised group at the OAEOC are comparable to the low-risk hospital cohort. The prospectively collected OUT-ACS variables are reliable and based on direct costs, but the hospital estimates only rely on administrative data and DRG codes. Second, although we tried to include all additional fees per patient contact at the OAEOC, some numbers might be missing, which would favour the primary care approach.

Third, as 30-day event rates were not accessible at Drammen, we used R07.4 data from another Norwegian hospital,[7] assumed to be comparable. Fourth, as the loss of health analyses include very few events, the QALY estimates might be unreliable. A probabilistic sensitivity analysis was conducted to address this issue, verifying the cost-effectiveness of the primary care approach (Supplementary Appendix; Paper IV). Finally, the 0/1-hour algorithm was not implemented at Drammen hospital in 2018. Hence, the 0/1-hour versus 0/6-hour comparison is not equal. The differences are expected to be reduced in the case of 0/1-hour implementation. However, as of January 2022, the algorithm is still not implemented at Drammen Hospital, and Oslo University Hospital, Ullevaal still struggles with broad adoption of the algorithm, one year after implementation. We, therefore, still consider our cost estimates to be relevant.

External validity

Whether the results provided are generalisable to a larger group of patients in emergency primary care, depend on the external validity of the results (Figure 13).[261]

Selection bias

A total of 42.9 % (n=1316/3066) of the patients admitted for hs-cTnT measurements at the OAEOC were not included (Figure 7, page 41). Time restraints, declining participation, and staff errors were the most common causes of unsuccessful inclusion.

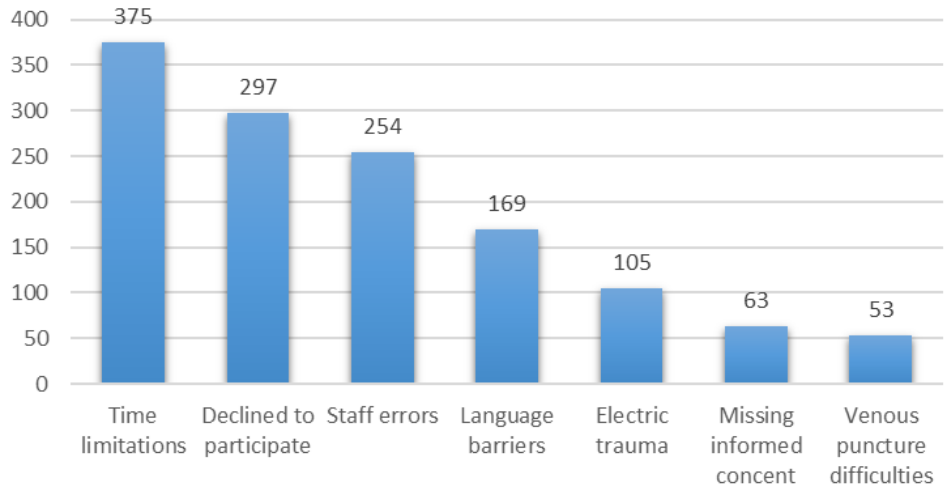

Figure 14 Unsuccessful patient inclusion (n=1316) during the OUT-ACS study

Although the patients were approached for consecutive enrolment, 24/7, all year, there may have been some extent of convenience sampling: First, there is a risk that the more complex, vulnerable, and time-consuming patients were overrepresented in the *time limitations* group. Unfortunately, we cannot explore this further due to the anonymous registration. Second, over half of the unsuccessful inclusions (52 %) are found in the categories *time limitations, staff errors, or venous puncture difficulties*. If the study had been large-scale with available research personnel, these numbers might have been reduced. However, we would probably not have had the same consecutive inclusion during weekends, holidays, and nights, which we consider more important. Third, as the written informed consent was only available for Scandinavian and English-speaking patients, 169 patients were not enrolled due to language restrictions. The short 1-hour window was reported as the main reason why professional translators were not approached more often. In addition, the registration form did not include information on ethnicity or socio-economic status, which could have been valuable in the description of the cohort. Fourth, the category *Missing informed consent* includes patients with delirium, dementia, or acute hallucinations. This complex group probably have higher age, more comorbidity and increased CVD risk, and would have been valuable to include in our cohort. Combined, these four arguments may illustrate how a healthier cohort could have been included in the OUT-ACS study. Consequently, the reported AMI prevalence might be too low,

enhancing the NPV and potentially reducing the generalisability of the results.[261] Still, it is essential to conduct studies in less research-optimal settings, which differs from the large-scale academic hospital centres with infrastructure and more funding.[262] Also, as the primary outcome measure of the OUT-ACS study was to assess the rule-out performance among low-risk patients, it has been considered more acceptable to use a healthier cohort than if the primary purpose was to achieve high diagnostic accuracy of AMI.[261]

Sampling bias

A degree of sampling bias occurs as a matter of course at the OAEOC. Some might consider the OUT-ACS cohort severely biased as only 1750 of 11,618 patients with chest pain were included in the study (Figure 7, page 41). As the performance of the 0/1-hour algorithm does not reflect the whole chest pain population at the clinic, concerns have been raised regarding the external validity of our findings. However, this initial patient selection is necessary and coherent with clinical practice, current recommendations, and guidelines. First, prehospital delay of high-risk patients must be avoided,[1] hence they were not eligible nor relevant for the 0/1-hour algorithm outside of hospital. Second, patients with non-cardiac chest pain were not admitted for hs-cTnT measurements. Using a more liberal indication for troponin measurements would have contributed to an overuse of care, increased false-positive cases, and potentially iatrogenic harm.[263-265] The patient selection (Figure 6, page 40) is also consistent with the actual routine at the clinic and not only an experimental setting during the study, which may increase the external validity.

Nevertheless, it would have been valuable to obtain 90-day data from the whole chest pain cohort for a complete overview of the AMI prevalence at the clinic. This was initially discussed in 2016 but dismissed as study inclusion of high-risk patients could delay immediate hospitalisation. However, inclusion by default could have been an option, which has recently been accepted and planned for an upcoming Swedish 0/1-hour algorithm implementation trial.[266]

The setting of the study

Referral-based access to the ED, also in cases of acute chest pain, is less common in many other countries.[214] Due to different organisation models of the health care system, emergency primary care may not manage acute chest pain nor exist at all. Our approach and conclusions would clearly be generalisable to other countries with similar health care models. In addition, they may also be generalisable to ED settings managing low-prevalence populations not pre-triaged by primary care services.

We also acknowledge that broad implementation of the 0/1-hour algorithm in Norway is not feasible. With large geographical diversities between rural and central districts, management of acute chest pain will differ. For many OOH clinics, the mode of EMS transport depends on accessibility, weather conditions, and distance to hospital.[218] Median drive to the nearest Norwegian OOH clinic was 22 minutes in 2014.[267] In Paper IV, we report a median drive of 47 minutes from the OOH clinic to the nearest ED (Table S5; Supplementary Appendix). The study was also conducted at the OAEOC, centrally localised in Oslo, considered more advanced than most Norwegian OOH clinics. Still, we believe our results of applying a rapid rule-out protocol in primary care also are generalisable to OOH clinics outside the larger cities. Almost 75 % of the Norwegian population have their local OOH clinic located within 0-20 kilometres (mean courier drive of 11 minutes) from an ED (Table S5; Supplementary Appendix; Paper IV), where such a rule-out protocol may be helpful.

Finally, it is essential to highlight that the OUT-ACS study has only investigated the performance for hs-cTnT. Hence, we cannot comment on the diagnostic performance of various hs-cTnI assays. Nevertheless, as assay-specific 0/1-hour criteria have been established for several hs-cTnI assays in the ED setting,[24, 268] we have reason to believe these assays might also benefit emergency primary care. In addition to illustrating the geographical challenges in Norway in terms of available hospital EDs, Figure 15 also shows whether the respective EDs have 24-hour access to an hs-cTnT or hs-cTnI assay.

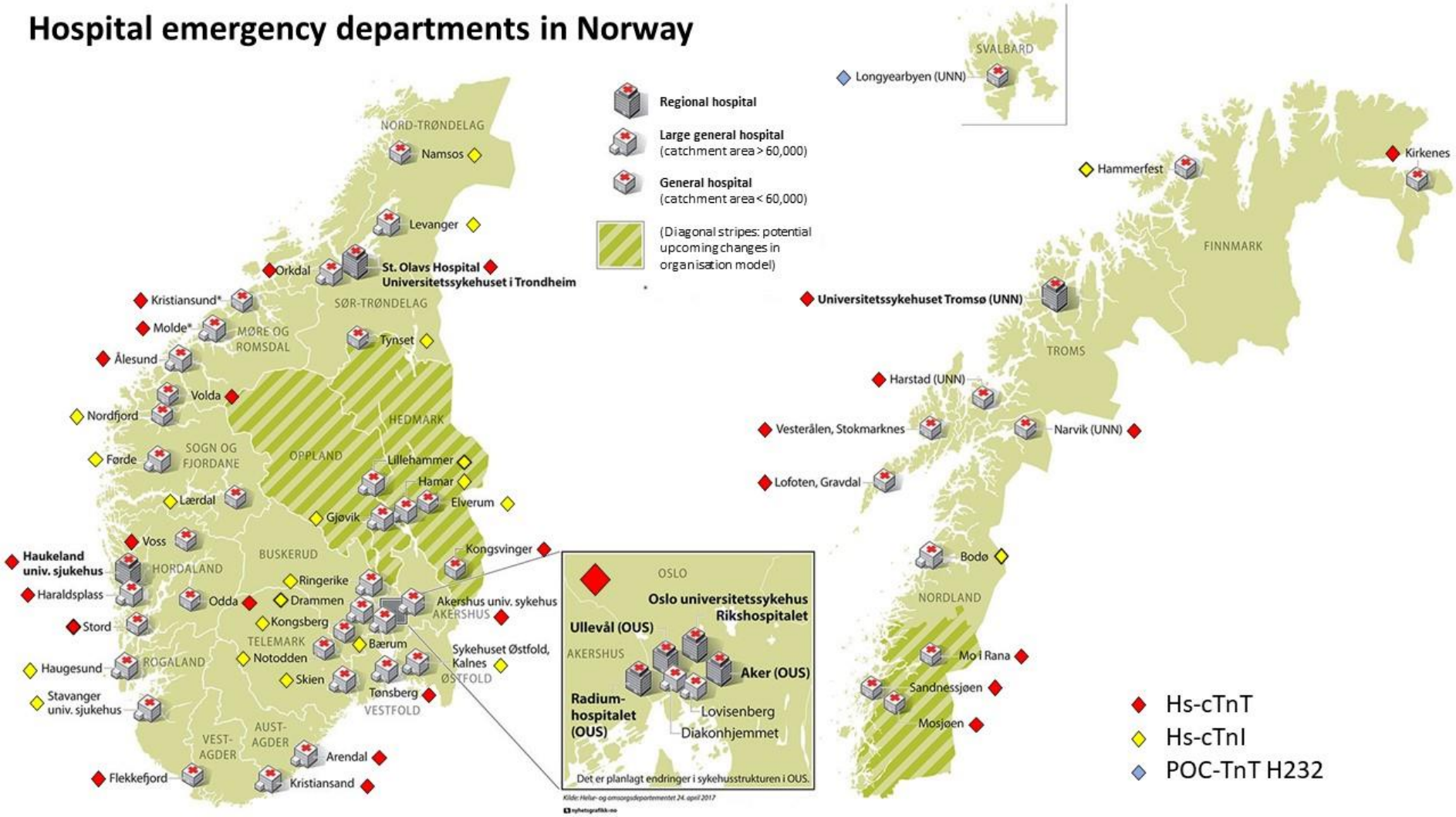

Figure 15 Norwegian hospital emergency departments with a 24-hour access to hs-cTn assay
Illustration adapted from the Norwegian Ministry of Health and Care Services, 2017, modified with hs-cTn assays by TRJ
Hs-cTnI/T: high-sensitivity cardiac troponin I/T; POC-TnT: Point-of-Care Troponin T

5.1.4 Strengths and limitations

Summing up the previous section, we consider the sampled data reliable and robust, although the precision is reduced due to few events. Still, our results appear comparable to international ED cohorts of higher quality. Selection and sampling bias may have affected the external validity of our results, and the cost-evaluation is based on several assumptions. Still, we believe the study may be relevant and applicable to other emergency primary care settings with a similar organisational model.

Conducting the OUT-ACS study in an authentic emergency primary care setting is considered a major strength. Too few diagnostic studies on ACS have been performed in primary care,[65] and the 0/1-hour algorithm has only been validated in hospital cohorts. If a new diagnostic tool should be implemented at the primary care level, it is preferred to have the novel method validated in the relevant setting.[210, 211] Six years after initiating the project, the OUT-ACS study still stands out as the only study validating the algorithm in an authentic low-risk setting outside of hospital.

As the study was embedded in the clinical routine, it may appear more pragmatic than comparable validation cohorts. All eligible patients were approached after the decision of hs-cTnT measurements had been made. Thus, the selection of high-risk/low-risk cases was based on clinical routine, improving generalisability. Hospital validation cohorts have also been criticised for not including patients with atypical symptoms.[255, 257] Following the usual routine, patients with an atypical presentation, such as acute dyspnoea, fatigue or diaphoresis without chest pain, were all eligible if admitted for hs-cTnT measurements. Our cohort is large, with few dropouts. Conducting such a study without research personnel has confirmed the applicability and feasibility of the algorithm.

As the study is observational, our results and conclusions only hypothetically illustrate how the algorithm might perform if implemented in emergency primary care. A real-world implementation trial or a gold standard RCT would have provided more robust results. In addition, we did not investigate the performance of the 0/4-hour protocol, which could have been useful for the comparison.

5.2 Ethical considerations

Urgent hospital transfer is recommended for patients with a highly suspected ACS,[1] which is also the routine at the OAEOC. The OUT-ACS study has received questions regarding the safety of withholding patients for hs-cTnT measurements outside of hospital. Also, concerns about selecting low- and high-risk patients by clinical gestalt instead of applying a validated risk score have been raised. First, the currently validated CDRs for primary care are not sufficiently sensitive to ensure a safe AMI rule-out.[21] Second, other validated risk scores, such as the GRACE (*Global Registry of Acute Coronary Events*),[269] EDACS (*Emergency Department Assessment of Chest pain Score*),[270] and TIMI (*Thrombolysis in Myocardial Infarction*)[271] are all developed for hospital settings. Hence, these are not directly transferable without validation,[207] and even in the EDs, their rule-out performance is not adequately safe.[103, 272]

As the HEART score has been validated in the prehospital setting,[104, 105, 230] it stands out as a potential risk score for emergency primary care. The final results of the prospective *Famous Triage* trial were published this year, where the strategy of not referring low-risk patients (i.e., ≤ 3 points) was non-inferior to standard care (i.e., all patients hospitalised) for the primary safety endpoint.[273] However, as also low-risk patients with a positive POC-Tn result (i.e., > 40 ng/L) were hospitalised, the efficacy was reduced, and the conclusion was based on a small non-referred group (n=149) with few events (n=2; 45-day MACE 1.3 %).[273] The authors further elaborated on whether a future POC hs-cTn assay might improve safety and efficacy.[273] Whereas hs-cTnT with lower thresholds increased the low-risk sensitivity in Paper III, the efficacy decreased, and more false-positive high-risk referrals were generated. Therefore, balancing efficacy and safety might be challenging when using the HEART score in a low-prevalence setting.

Others have investigated whether the HEAR score (i.e., HEART without Troponin) may aid patient selection before troponin measurements.[105, 107, 274, 275] As the low-risk/high-risk selection at the OAEOC is based on clinical gestalt, it was also

relevant to evaluate whether the HEAR score could aid this selection. The previously unpublished results (Table 5, page 64) verify that a HEAR score ≤ 3 points would have categorised 54.1 % of the OUT-ACS cohort as low-risk with 18 AMIs and poor safety. If the low-risk HEAR had been used to select patients suitable for measurements at the clinic, the remaining 46 % (n=786/1711) would require hospital admission, which is far more than the 13 % in the OUT-ACS cohort (Paper I). Hence, we do not see the benefits of applying this score in our low prevalence setting.

Our results in Paper III align with the *RAPID-TnT (Rapid Assessment of Possible ACS in the Emergency Department with High-Sensitivity Troponin T)* RCT, where clinical risk scores did not further improve the safety of the 0/1-hour rule-out group.[148] A similar conclusion was made by Chapman et al., as added risk scores only reduced efficacy without enhancing the performance of rapid hs-cTn pathways.[276] Other ED cohorts have presented similar findings.[103, 277, 278] Body et al. did also documented that clinical gestalt in combination with a non-ischaemic ECG and initial troponin concentrations below the URL achieved a rule-out sensitivity of 100 % for MACE after 30 days.[59] We, therefore, consider the OAEOC approach, selecting patients by clinical gestalt followed by the ESC 0/1-hour algorithm, as adequate management for low-risk patients in emergency primary care.

5.3 Discussion of main results

For acute chest pain, the ED referral rate from primary care is high due to diagnostic uncertainty and the fear of missing an AMI. If a new diagnostic decision aid for chest pain should be implemented in primary care, the ability to provide high rule-out safety will be central. In the OUT-ACS study, high rule-out safety was demonstrated for the ESC 0/1-hour algorithm (Paper I), the novel observation group criteria (Paper II), as well as the single hs-cTnT rule-out approach (Paper III).

As anticipated, due to low disease prevalence,[211] all PPV accuracy measures were moderate (Papers I-III). However, the PPVs have been in the same range in ED

cohorts with higher AMI prevalence.[117, 119, 120, 129] There may be two reasons for this. First, the original 0/1-hour algorithm was derived and validated to achieve an optimal high NPV for rule-out and a lower but reasonable PPV (70-80 %) for rule-in.[24, 117] Second, the EDs have a higher proportion of adverse conditions (e.g., heart failure, sepsis, acute kidney failure, pulmonary embolism or other cardiac-related conditions), with the following increase in false-positive cases due to myocardial injury.

A total of 19.5 % of the patients remained in the indeterminate observation group, which is slightly lower than found in ED settings (25-30 %).[24] By comparing the baseline characteristics, patients in the observation group had more comorbidities, higher age, and more total events than the rule-out group (Paper I), similar to the ED cohorts.[24, 171, 172] A strategy for how to proceed with this complex group of patients is, therefore, necessary before considering implementation outside of hospital. The ESC recommends a third hs-cTn measurement and echocardiogram as the next steps.[24] The novel criteria for the observation group by Lopez-Ayala et al.,[172] have proven to be applicable also in a low-risk emergency primary care setting using a 4-hour interval (Paper II).

In the non-hospitalised group (n=1485/1711) at the OAEOC, most patients were discharged with a non-specific, non-cardiac chest pain diagnosis (Table 3, page 62). Such diagnoses were less common among the 226 hospitalised patients (Table 4, page 63). Only 6 % of the large rule-out group required hospitalisation, and none of these ended up with a cardiac-related diagnosis at discharge (Paper I). Hence, the algorithm also seemed to effectively identify patients in need of hospital, irrespective of having an AMI (Figure 16). Although only 60 of 226 OUT-ACS hospitalisations were adjudicated with an AMI, we do not consider the remaining 166 admissions unnecessary as most had conditions requiring a hospital-level of care.

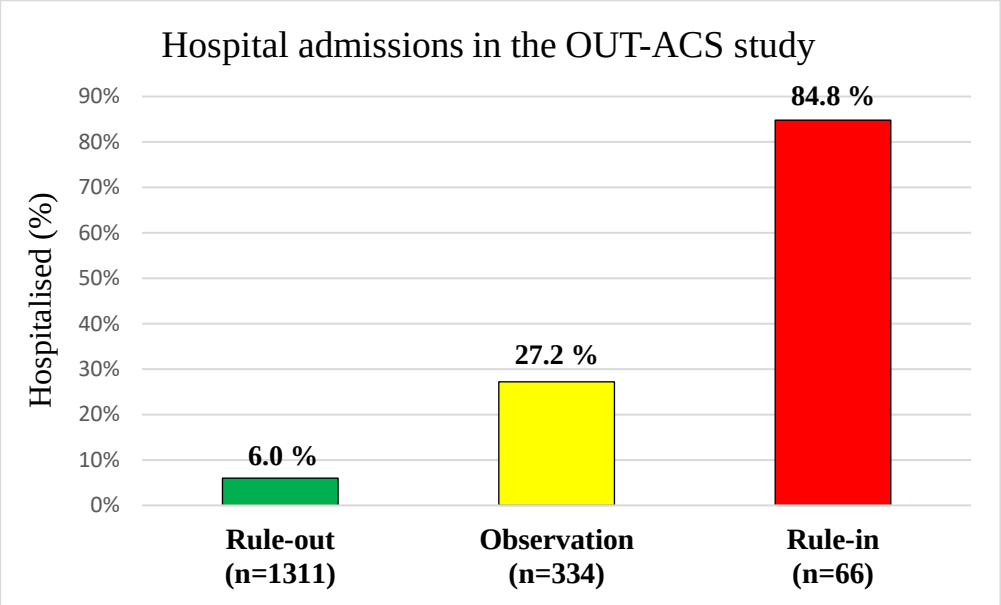

Figure 16 Patients hospitalised across each of the 0/1-hour algorithm groups
OUT-ACS: One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome

By investigating resource use and the potential diagnostic outcomes of hospital admission of low-risk patients with chest pain, studies from the Netherlands have revealed extensive use of health care expenditure (EUR 1360,[8] EUR 1448[22], and EUR 1580)[205] with limited added diagnostic value. These numbers are directly comparable to the estimated EUR 1483 per low-risk patient assessed at Drammen hospital. In addition, the low-risk hospital cohort was admitted for 22.3 hours (Paper IV), which is similar to Bjørnsen et al., reporting 22.0 hours for the R07.4 cohort at St. Olav's University Hospital in Norway.[7] There may be three reasons for the prolonged length of stay: Firstly, low-risk patients may probably have a low priority in the busy EDs. Secondly, there is an increased risk of additional advanced testing once admitted. Finally, neither Drammen nor St. Olav's Hospital had implemented the 0/1-hour algorithm during the time of the OUT-ACS study. In the *REACTION-US (Rapid Evaluation of Acute Myocardial Infarction in the United States)* sub-study, ≥ 35 % of the 0/1-hour rule-out group had additional non-invasive testing, with limited diagnostic yield and increased length of stay (26.6 hours) compared to those who did not (5.7 hours, $p<0.001$).[279] Similar numbers were found in our low-risk hospital cohort, where 32 % received additional diagnostic procedures (Paper IV).

However, if the 0/1-hour algorithm were implemented as a standard, an extensive reduction in costs, length of stay, and additional diagnostic procedures would be expected in the EDs, as documented in previous implementation trials.[168-170, 280] Still, the costs of assessing the low-risk cohort in emergency primary care are expected to be less, i.e., EUR 192 (Paper IV) versus EUR 927 in the ED.[280]

With the present 0/4-hour routine and the prolonged turnaround time at the OAEOC, the hs-cTnT assessment could take up to 10 hours. The turnaround time and time to decision are estimated to be extensively reduced (to 3.4 hours per patient) if implementing the algorithm at the clinic (Paper IV). However, we consider two main requirements necessary before implementation in emergency primary care:

1. short distance to an available hs-cTn assay (i.e., 24/7 hospital ED)
2. possibility for a simple, short-time observation at the clinic

Regarding the first requirement, a more optimal turnaround time is probably possible for 32 of 169 Norwegian OOH/primary care emergency clinics (catchment area of 1.68 million (31.4 %) inhabitants), all located on hospital grounds (Table S5; Supplementary Appendix; Paper IV). The number is inflated to 75 % having access to a 0/1-hour algorithm at their local OOH clinic if the acceptable distance to hospital ED is 0-20 kilometres. For clinics needing courier transport, it may also be possible to transport the 0- and 1-hour samples combined after 1 hour to simplify logistics. A precise sampling interval (1 hour) is most central as this directly affects the diagnostic performance of the algorithm. A prolonged turnaround time will only affect the time to decision and patient flow in the clinic.[9]

As for the second requirement, we do not consider an observation unit mandatory for implementation. Most patients eligible for hs-cTnT measurements at the clinic are young, have resolved chest pain, and are not considered in urgent need of hospital transfer (Paper I). Due to prolonged time awaiting the 0/4-hour results at the OAEOC, patients have been admitted to the observation unit for hospitality. As the turnaround time is expected to be extensively reduced with the 0/1-hour algorithm (Paper IV), most of these patients may wait seated in a suitable waiting area with a

simple observation routine, including new assessment and potential hospital admission in case of recurrent or worsening symptoms.

5.3.1 Potential of overdiagnosis

In 1974, Ivan Illich addressed potential issues with modern diagnostics and overuse of care in the historic publication *Medical Nemesis*.[281] Twenty-five years later, Fisher and Welch warned about how medical growth and improved diagnosis with lower thresholds may contribute to increased disease prevalence due to the inclusion of milder cases, which contribute to falsely improved outcomes and spectrum shift of a disease.[282] In addition, more use of care may lead to increased use of resources, detection of pseudo-diseases, lower thresholds for treatment and procedures, and unintended iatrogenic harm.[282] The special edition issue *Too much medicine* was launched by the British Medical Journal (BMJ) in 2002,[283] the *Less is more* series in the Journal of American Medicine Association (JAMA) in 2010,[284] and the global *Choosing Wisely Initiative* by the American Board of Internal Medicine in 2012.[285] Norway became a member of the *Choosing Wisely Initiative* in 2018.[286]

Similar concerns, as discussed by Fisher and Welch,[282] have been raised for high-sensitivity cardiac troponins.[264, 287] In Australia, both hospital admissions of low-risk patients with chest pain and non-critical hs-cTn measurements have been marked as potential inappropriate use of care.[265] Inspired by the model presented by Bell et al.,[287] the following section will evaluate the potential risk of overdiagnosis by using the 0/1-hour algorithm in emergency primary care:

1 - The potential of overdetection:

For hs-cTnT, the 99th percentile URL is established at 14 ng/L,[50, 114] i.e., 1 % of healthy individuals will have a baseline hs-cTnT above the 99th. The ESC 0/1-hour algorithm applies optimised hs-cTn thresholds to ensure high rule-out safety.[24, 117] As the rule-out criterion comprises a 0-hour sample <12 ng/L, patients within the upper range of normal (12-14 ng/L) will never be triaged as rule-out with the

algorithm. Investigating the 0-hour criterion, 328 patients in our study were assigned to the observation group (Figure 17), where 102 had a 0-hour sample within the 99th.

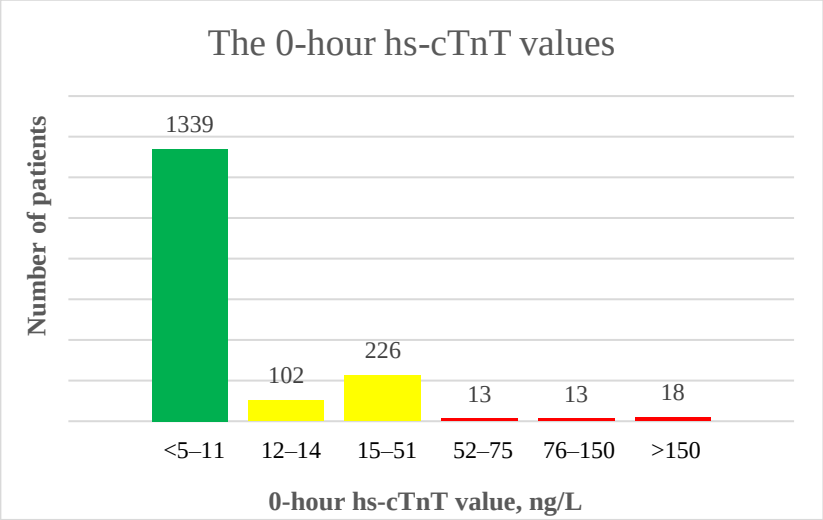

Figure 17 The OUT-ACS cohort according to the 0-hour hs-cTnT sample

The 0-hour values are coloured according to the algorithm (i.e., rule-out/green, observation/yellow, and rule-in/red), and further divided by different hs-cTnT strata

Excluding patients within the normal range from rapid rule-out might be considered overdetection. On the other hand, 11 % (7/61) of the adjudicated AMIs had 0-hour samples below the 99th. As three of these also had a 1-hour result < 15 ng/L, these might be considered subclinical cases. However, these findings are similar to Hoeller et al., where 6-23 % of the AMIs across four different hs-cTn assays had levels below the 99th percentile URL upon ED arrival.[288]

The 0-hour rule-in criterion is also problematic, as it does not apply the delta described in the *UDMI*.[23, 24, 252] Patients with a 0-hour hs-cTnT ≥ 52 ng/L are assigned to rule-in, where rapid admission for additional procedures, often invasive, are recommended.[24, 127] The direct rule-in encompasses 44 patients in our study, where 77 % had an AMI (Paper III). Rapid detection may be beneficial for those with an early AMI. Still, it may also contribute to unnecessary hospitalisations of false-positive cases as cardiac troponin is not a specific biomarker of AMI.[264] Cardiac troponins may also leak into the circulation in case of acute or chronic non-ischaemic myocardial injury or following cell apoptosis.[289] In total, 21 of 66 (32 %) of the

OUT-ACS cohort had a false positive rule-in, where ten of these were discharged home. We do not consider the remaining eleven hospitalised patients as overdetection, as they all had conditions requiring a higher level of care (Table S4; Supplementary Appendix; Paper I).

2 - Increased incidence of AMI:

The conventional 4th generation cTnT assay had decision thresholds for AMI at 30 ng/L (i.e., CV 10 %),[45] with insufficient sensitivity. Hs-cTn assays detect changes earlier at lower levels and identify more patients with myocardial injury (i.e., defined at the 99th percentile) than the conventional assays.[290-292]

Clinical gestalt alone has been shown to have an ACS miss rate of 8.2 %.[58] If the hs-cTnT approach had not been available at the OAEOC, some of the 61 AMI cases would probably have been discharged home. As a result, the ESC 0/1-hour algorithm has increased the detection of AMI in our low-prevalence setting. However, having access to serial hs-cTnT opens for detecting more subclinical cases of unknown clinical relevance, which might contribute to a spectrum shift of the disease and falsely improved outcomes of the algorithm.[282, 287, 293-295]

3 – Increased use of care:

Early detection of a suspected AMI usually results in advanced diagnostic procedures, followed by secondary medical prevention if the diagnosis is confirmed.[24] In the *High-STEACS* trial, transition to hs-cTnI resulted in 17 % more patients reclassified as myocardial injury, as well as increased use of secondary prevention (2-fold) and coronary angiography (3-fold).[291] However, additional use of percutaneous interventions (PCI) or improved 1-year outcomes were not observed.[291] Similar findings were reported in an Australian pre-/post-implementation study (n=124,357), where the additional hs-cTnI cases of myocardial injury did not increase the rates of PCIs or AMIs.[292]

In our low-risk hospital cohort, 32 % had additional diagnostic procedures performed during the index episode (Table S3; Supplementary Appendix; Paper IV), contributing to increased length of stay and costs. As we do not have access to these

procedures in emergency primary care, we hypothesise that additional advanced testing among low-risk patients could be substantially reduced if this group initially were managed in primary care. This approach could also reduce ED crowding and health care expenditure, which is beneficial for other patients.

4 – Potential benefits and harms:

Paper IV demonstrated a substantial reduction in cost and length of stay per low-risk patient assessed outside of hospital. We also evaluated the potential harm of missing an AMI. The combined rate of AMI and all-cause mortality the following 30 days was only 0.3 % in the non-hospitalised group (n=1485). Three of the four AMIs were hospitalised within the first ten days. None of these had a significant delta in the 0-, 1- or 4-hour hs-cTnT sample or ischaemic findings at their ECGs during the index episode. Some of these might have had unstable angina (UA) at index, evolving to an AMI the following days. In theory, these few cases might have been recognised earlier if initially assessed in the ED. However, it is challenging to detect these few among the large low-risk cohort. Hospital admission of the whole group to avoid potential delayed diagnosis for these three cases would have contributed to extensive overuse of care and potential iatrogenic harm.

Easy access to hs-cTn measurements may also result in inappropriate use. Experienced senior personnel at the OAEOC have estimated that 10-15 % of patients admitted for hs-cTnT measurements at the clinic are obvious non-cardiac cases (Paper IV). However, the OAEOC is mainly staffed by less experienced registrar GPs, who may more often choose hs-cTnT measurements due to time limitations and uncertainty. Also, a lower acceptable risk for missed ACS has been shown to correlate with higher acceptance for unnecessary referrals among GPs.(77) For the OAEOC, it is either some inappropriate hs-cTnT measurements versus no testing at all followed by a higher AMI miss-rate and increased low-risk referrals.[8, 17, 58, 59] The OAEOC has, therefore, chosen to use serial hs-cTnT measurements since 2009, where the 0/1-hour algorithm now may enhance the safety and efficacy of the local routine (Paper I), in addition to being cost-effective (Paper IV). As the algorithm has

proven to be most beneficial for the rule-out of AMI, we believe it is especially well suited for assessing low-risk patients in emergency primary care.

5.3.2 AMI rule-out and acceptable miss-rate

High referral rates reflect the diagnostic uncertainty and the considerable differences between emergency primary care and hospital EDs.[207] For acute chest pain, over 80 % end up with a non-cardiac diagnosis at discharge.[8] Difficulties interpreting the ECG, the fear of mistakes, higher workload, and not knowing the patients during OOH shifts contributes to increased defensive medicine among GPs.[67, 295] According to Malterud et al., it is essential to acknowledge uncertainty in the decision-making process, especially in a non-selected primary care setting, where complexity, multimorbidity and atypical presentations are common.[296] In a survey by Harskamp et al., 70 % of Dutch GPs reported a low acceptable miss-rate (0.1-1.0 %) for atypical ACS, and 75 % aimed for a maximum of 25-50 unnecessary hospital referrals.[79] This is comparable with ED clinicians, where almost 50 % would not accept an ACS miss rate > 1 %.[297]

The combined 90-day incidence of AMI and all-cause mortality was only 0.3 % for the rule-out group (Paper I). Does this imply that it is acceptable to discharge this group without further cardiovascular testing? The calculated likelihood ratios may support this decision. By combining the estimated probability of the disease with the test performance (LR), Fagan's nomogram, based on Bayes' theorem, is known to aid decisions without additional calculations.[298, 299] The nomogram visualises the post-test probability of having a disease based on the diagnostic test. The respective LRs of the 0/1-hour rule-out, rule-in, and observation groups are presented in a nomogram in Figure 18 for visualisation:

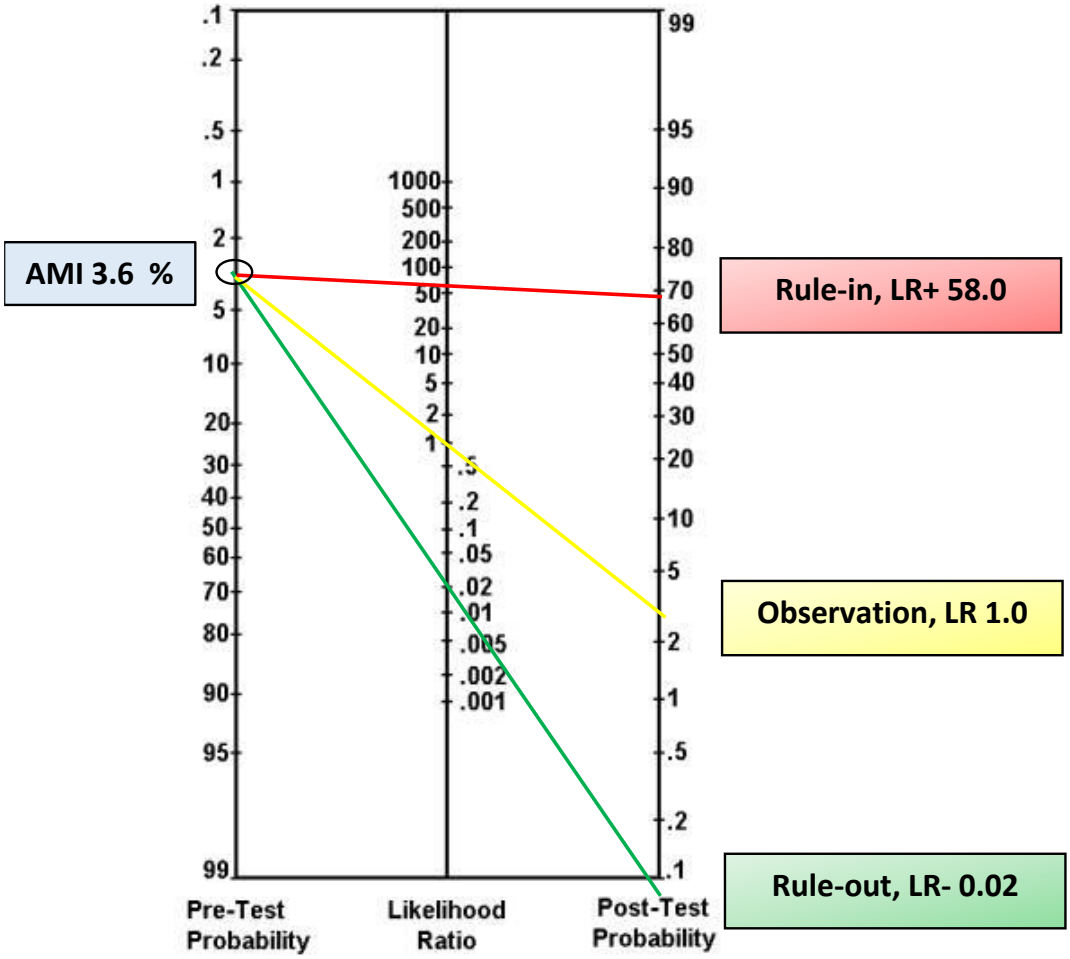

Figure 18 The OUT-ACS likelihood ratios presented in a nomogram

AMI: acute myocardial infarction; LR: likelihood ratio

There is increasing evidence that additional in-hospital observation and further advanced diagnostic procedures in low-risk patients with chest pain are non-beneficial and without improved outcomes.[8, 22, 205, 300, 301] According to Kline et al., patients with an ACS probability < 2 % after clinical examination and a negative cardiac biomarker will not benefit from additional ED assessment.[302] In Figure 17, the post-test probability of the rule-out group is far below the suggested stop-testing threshold. This corresponds well with the 2021 chest pain guidelines, which recommend avoiding further testing in low-risk patients (i.e., a 30-day risk of MACE ≤ 1 % after clinical examination and troponin measurements).[2] As the OUT-ACS observation and rule-in groups have post-test probabilities exceeding 2 %, further testing is justified,[302] which is also recommended in current guidelines.[2, 24]

After ruling out an AMI, referring the patient to the ED may still be necessary. Only 6 % of the rule-out group were hospitalised (Figure 16, page 83), and 4.5 % of the non-hospitalised group were referred to a cardiac outpatient clinic within a few days (Paper IV). Similar findings were observed in an ED implementation study where the ESC 0/1-hour algorithm was overruled in 12 % of the rule-out cases.[168] In case of disregarding the rule-out decision, Twerenbold et al. suggested proceeding with similar management as recommended for the observation group.[303] For the OAEOC, this would indicate either a third hs-cTnT measurement at the clinic (Paper II) or hospitalisation.

5.3.3 Unstable angina and risk prediction

The ESC 0/1-hour algorithm was designed as a diagnostic protocol for NSTEMI and not for the rule-out of UA or other acute conditions.[117, 119] The performance of the algorithm seems to decrease when the primary endpoint includes UA or MACE.[128, 135, 146, 304] However, the clinical relevance of diagnosing UA at index has been debated. With improved precision, the hs-cTn assays detect lower circulating cTn levels than the earlier conventional assays, reclassifying more UA as AMI.[49, 290] Patients with UA have similar low 1-year mortality rates as patients with non-cardiac chest pain, but higher risk of AMI and cardiovascular comorbidities.[305] In an early study by Reichlin et al., only the smaller group of UA patients with a 1-hour hs-cTn delta of ≥ 2 ng/L had poorer outcomes.[306] The Norwegian *WESTCOR (Aiming Towards Evidence-Based Interpretation of Cardiac Biomarkers in Patients Presenting With Chest Pain)* study derived and validated lower 0/1-hour deltas (< 1 ng/L) to identify both NSTEMI and UA in the ED at index.[304] As expected, the lower deltas achieved higher rule-out sensitivity than those applied by the ESC 0/1-hour algorithm for hs-cTnT (95 % versus 63 %), although at the expense of decreased rule-out efficacy (17 % versus 70 %).[304] The rule-out sensitivity for the ESC 0/1-hour algorithm was higher (94 %) for the secondary endpoint of 30-day MACE.[304] In a study from the *SWEDEHEART* registry, patients with UA and hs-cTnT levels ≤ 14 ng/L had lower cardiovascular risk and fewer outcomes than those with

myocardial injury (i.e., values above the 99th percentile URL).[307] As the additional criteria for the observation group seem to enhance safety and efficacy for patients with intermediate hs-cTnT values,[172] the *WESTCOR* algorithm may appear less applicable.

Elevated baseline level of hs-cTn has also proven to be a robust cardiovascular risk predictor in patients without an AMI.[173, 175, 308-311]. Adamson et al. demonstrated that the risk of having an obstructive coronary artery disease (CAD) increased by 33 % for every doubling of the hs-cTn value.[309] With increased international attention towards biomarker-based risk stratification, it is expected that hs-cTn will have a key role in selecting patients in need of additional cardiac assessment in the future, also among patients without AMI.[312]

5.3.4 Current evidence

During the last three years, the knowledge on the diagnostic performance of the 0/1-hour algorithm has been strengthened with implementation studies, providing real-world evidence on efficacy and safety.[139, 168-170] With the 2019 *RAPID-TnT* RCT, non-inferiority was demonstrated for the ESC 0/1-hour algorithm compared to standard care, and high safety and efficacy were confirmed.[170] The two randomised groups did also have comparable sample size (n=1642 and 1646) and AMI prevalence (4.0 % and 3.6 %)[170] to the OUT-ACS cohort (Paper I). Although not significant, the 1-year follow-up analysis revealed an unexpected hazard ratio of 1.32 (95 % CI 0.95-1.83) of AMI or death in the 0/1-hour arm compared to standard care.[313] It is unclear whether this is random, as the broad confidence interval reflects few events, or if it might be related to potential iatrogenic harm, as discussed in Section 5.3.1.

Additional pooled evidence has been investigated in two large meta-analyses by Chiang et al.[268, 314] The OUT-ACS cohort was included in the most recent, synthesizing data from 32 studies across 20 unique cohorts (n=30,066) to evaluate the performance of the ESC 0/1, 0/2 and 0/3-hour algorithms.[268] The 0/1- and 0/2-hour algorithms were superior to the traditional 0/3-hour algorithm with the pooled

sensitivities of 99.1 %, 98.6 %, and 93.7 %, respectively. However, the heterogeneity across the cohorts was high, with AMI prevalence ranging from 4 % to 37 %.[268]

5.3.5 Patient perspective

Studies investigating the patient perspective of acute chest pain are sparse. Compared to the clinician, low-risk patients with chest pain overestimate their risk of AMI, demonstrating the need for improved communication.[315] In a pragmatic randomised US trial, 898 patients with low risk were assigned to standard care versus intervention using a clinical decision aid for shared-decision making.[316] More patients were involved in the decisions in the intervention group, with improved insights about their ACS risk and fewer admissions for additional procedures compared to standard care.[316]

In 2020, Ferry and colleagues published a qualitative study, approaching patients before (n=23) and after (n=26) implementing a rapid rule-out strategy in the ED.[317] In both periods, there were discordance between the physicians' experience of the symptoms (i.e., reassured by the objective rule-out of AMI by troponins) versus the patients', reporting insufficient reassurance due to persistent symptoms.[317] Discussion of potential differential diagnoses, referral to outpatient testing, and the timing of the given summary were highlighted for improved reassurance.[317] These recommendations are consistent with the routine at the OAEOC. Some patients are referred to an outpatient clinic within a few days, while many are advised to contact their regular GP (Table S3; Supplementary Appendix; Paper I). An alternative diagnosis is most often suggested (e.g., gastritis, myalgia, panic attacks, or anxiety disorders) to explain their presenting symptoms. This is also in line with the recent 2021 recommendations for the management of acute chest pain, where shared decision-making after initial assessment has been recommended for clinically stable patients.[2]

6. Clinical implications

The high proportion of patients with chest pain, both in emergency primary care and hospital EDs, contributes to crowded waiting rooms at both levels. In addition to causing frustration among patients and staff, crowding is harmful as triage, assessment, and treatment of patients with adverse conditions are delayed.[318] Direct ED access and the absence of comprehensive primary health care, managing non-urgent illness, home visits, and assisting long-term facilities, have been listed as two of the most important reasons for the situation in Canadian EDs.[318] Similar problems were presented in the BMJ classic *The Gatekeeper and the Wizard: a fairy tale* from 1989.[319] The fairy tale illustrates how the gatekeeper achieves high NPV and should test for normality, while the more advanced wizard is better at assessing patients with disease. It is, therefore, still highly relevant and potentially transferable to low-risk patients with chest pain.[319]

Chest pain in primary care is most often benign. Still, it might be difficult to detect those few with an AMI. As primary care physicians, we make decisions based on clinical gestalt and simple diagnostic tests, which are inadequately safe to exclude an AMI. As gatekeepers, we request improved decision aids to prevent unnecessary hospital referrals. The acceptable AMI miss-rate is low, but at the same time, it is impossible to refer them all, and we should not. While awaiting the promising high-sensitivity POC-Tn assays, the ESC 0/1-hour algorithm may benefit emergency primary care due to its high efficacy, feasibility, and rule-out safety. Implementation of the algorithm should be possible if the distance to the hospital ED is acceptable.

Although the HEART score appears promising, prehospital versus in-hospital HEART classification differs in 25 % of the cases as paramedics tend to overestimate the risk.[234] Also, within the EDs, registrar clinicians miscalculate up to 15 % of the HEART scores.[320] If a new decision aid is being considered for implementation, a simple, reliable, and safe rule-out strategy would be favourable. The 0/1-hour algorithm is based on objective hs-cTn measurements and has proven applicable among junior physicians in the EDs.[128] Hence, the algorithm should also be user-friendly for GPs on OOH rotation. We do not consider the addition of risk scores

necessary as the diagnostic performance of the 0/1-hour algorithm appears adequate. Also, if the 0/1-hour approach is implemented, single hs-cTn measurements may be less relevant. Even though a 0-hour sample < 5 ng/L facilitates a safe, direct rule-out in patients with symptoms ≥ 3 hours (Paper III), the 1-hour sample will, in most cases, be collected before the 0-hour result is available. Even for clinics located on hospital grounds, the optimal turnaround time for hs-cTn is at a minimum of *one* hour.[24] Hence, it is possible to collect the 1-hour sample while awaiting the 0-hour result, which will increase the rule-out efficacy from 33 % to 77 % (Paper I and III). If the clinic requires a courier routine to hospital lab, combined transport of the two samples may simplify logistics. Combined transport of two samples rather than one may also be recommended if GPs or municipality short- and long-term facilities order hs-cTn measurements.

In Paper IV, we have shown the potential cost-effectiveness of implementing the algorithm in emergency primary care. A substantial reduction in hospital referrals, cost per low-risk patient, length of stay, and overall health care expenditure was hypothetically demonstrated. Such an algorithm may also enhance the assessment of low-risk patients, ensure earlier detection of atypical AMIs, and shorten the potentially distressful time spent waiting for the decision.

Combined, our findings presented in this thesis may illustrate an unexploited potential of using hs-cTn beyond the cardiovascular community. Expanding the role of emergency primary care using the 0/1-hour algorithm may enhance the assessment of low-risk chest pain outside of the congested EDs. As most patients presenting in emergency primary care do not have an AMI, such assessment will be in line with the comprehensive gatekeeper function of primary care, ensuring optimal patient assessment at the lowest adequate level.

7. Future perspectives

The actual feasibility of the 0/1-hour algorithm in emergency primary care should be further investigated in an implementation study. Such a study would also report a true reduction in length of stay, enlighten potential causes of protocol violations, and further explore the generalisability. Due to large geographical diversities and various emergency primary care organisation models, a Norwegian multicentre study across different settings would be preferred. There is increased focus on improved and more research in primary care, where the clinical research networks in the Netherlands and UK have proven to be successful.[321, 322] The newly established Norwegian Primary Care Research Network, which provides an infrastructure for research in primary care, may be of significant value in enhancing research in emergency primary care in the future.[323] This network also opens for international collaboration. Unfortunately, the OUT-ACS study did not perform biobanking of the collected blood samples. Therefore, such storage should be prioritised in case of a new study to have possibilities for external validation of future biomarkers and diagnostic protocols.

The future of enhanced chest pain assessment outside of hospital looks promising. The diagnostic safety and efficacy of prehospital conventional POC-Tn assays will be further enlightened in the following years. In the upcoming *ARTICA* trial, patients will be randomised to GP assessment versus standard care based on the prehospital HEART score and a POC-Tn assay.[324] In a prospective validation cohort, an accelerated diagnostic protocol using POC-Tn in rural hospitals in New Zealand will be investigated.[325] Finally, in the forthcoming *PRESTO (PRe-hospital Evaluation of Sensitive TrOponin*) trial, the T-MACS score will be prospectively validated with a POC-Tn assay in the pre-hospital setting.[326]

Although the OUT-ACS study has shown the potential applicability and safety of the 0/1-hour algorithm for hs-cTnT in emergency primary care, it will probably not be broadly implemented in the future. The promising high-sensitivity POC-Tn assays are rapidly evolving, with multiple upcoming validation studies and novel assays expected. The currently commercially available *LSI Medience PATHFAST, Siemens*

Atellica VTLi, and *Quidel TriageTrue* claim high analytical sensitivity and precision.[327] Two ED derivation cohorts found comparable performance for the *TriageTrue* and *PATHFAST* assays to a central lab assay when POC-specific 0/1-hour criteria were applied.[328, 329] However, these findings have not been verified in studies using recommended whole blood samples.[330] Therefore, a prospective validation of POC hs-cTn using the 0/1-hour algorithm in emergency primary care would be highly relevant. Such a study could also be conducted as an RCT, randomising low-risk patients to either POC hs-cTn assay or a laboratory-based assay, involving multiple centres, preferably international collaboration. Also, as we did not have relevant variables to calculate the T-MACS score in Paper III, prospective validation of the T-MACS score, using a POC hs-cTn assay in emergency primary care, should be considered.

8. Conclusions

With the results from the observational OUT-ACS study, the ESC 0/1-hour algorithm for hs-cTnT appears to be safe and efficient in the assessment of patients with acute chest pain in a low-prevalence population of ACS. Although the rule-in accuracy for AMI was moderate, the false-positive cases had other acute conditions requiring hospital level of care (Paper I).

The diagnostic performance and efficacy of the algorithm was further improved with the novel 4-hour criteria for patients assigned to the indeterminate observation group (Paper II).

In the case of a single hs-cTnT measurement, a single undetectable hs-cTnT value (< 5 ng/L in patients with symptom onset for more than 3 hours ago) had superior rule-out ability compared to the low-risk HEART score. The low-risk performance was enhanced with the modified HEART score but at the cost of increased false-positive high-risk cases (Paper III).

Finally, assessing low-risk patients with chest pain in emergency primary care rather than in the hospital ED appears cost-effective. This approach seems to contribute to an extensive reduction in hospital referrals, direct costs, length of stay, and overall health care expenditure (Paper IV).

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Appendix A – Registration form (in Norwegian)

Personnummer: _____

Registreringsskjema for pasienter inkludert i troponinstudien ved Observasjonsposten

Alder: _____ Kjønn: ◯ Mann ◯ Kvinne

Ankomst legevakt dato/kl._____
- ◯ Egen hjelp
- ◯ Med ambulanse
- ◯ Andre instanser

Overført til Observasjonsposten dato/kl._____

Utskrevet fra Observasjonsposten dato/kl._____

Debut akuttsymptomer dato/kl._____

Tidspunkt for blodprøvetakning :
- nr 1. dato/kl._____
- nr 2. dato/kl._____
- nr 3. dato/kl._____

Risikofaktorer for akutt hjertesykdom

Kols?	◯ Ja	◯ Nei
Røyk (røyker, sluttet å røyke for under 10 år siden)?	◯ Ja	◯ Nei
Diabetes?	◯ Ja	◯ Nei
Annen hjertesykdom (høyt BT, høyt kolesterol, hjertesvikt, hjertesykdom/ikke koronarsykdom)?	◯ Ja	◯ Nei
Koronarsykdom (angina, hjerteinfarkt, stentet, bypassop.)?	◯ Ja	◯ Nei
Hjertesykdom i familien (før fylte 60 år)?	◯ Ja	◯ Nei

Symptomer som førte til at pasienten oppsøkte Oslo Legevakt

Brystsmerter?	◯ Ja	◯ Nei
Utstrålende smerter (hals, kjeve, arm og/el. mage)?	◯ Ja	◯ Nei

Type smerte?
- ◯ Pressende/trykkende/klemmende smerte
- ◯ Stikkende smerte
- ◯ Skjærende smerte
- ◯ Brennende smerte
- ◯ Smerter ved innpust
- ◯ Smerter ved berøring/bevegelse

Tungpust?	◯ Ja	◯ Nei
Hjertebank?	◯ Ja	◯ Nei
Besvimelse/nærbesvimelse?	◯ Ja	◯ Nei
Akutt utmattelse?	◯ Ja	◯ Nei
Kvalme/uvelhet/oppkast?	◯ Ja	◯ Nei
Kaldsvett/klam hud?	◯ Ja	◯ Nei

Utskrevet fra Observasjonsposten med ICD-10 diagnose: _____

Gått under behandling?	◯ Ja	◯ Nei
Til eget hjem uten videre oppfølging?	◯ Ja	◯ Nei
Hjem med råd om oppfølging hos fastlege?	◯ Ja	◯ Nei
KAD?	◯ Ja	◯ Nei
Henvist hjertemedisinsk poliklinikk?	◯ Ja	◯ Nei
Innlagt sykehus?	◯ Ja	◯ Nei

Appendix B – Written informed consent

OUT-ACS study at the Observation Unit at Legevakten i Oslo, 19.12.16

Request for participation in a clinical trial

Troponin study; at the Observation Unit at Legevakten i Oslo (Oslo Accident & Emergency Outpatient Clinic)

Background and purpose
This is an invitation for you to participate in a research study which involves the faster diagnosis of a heart attack. This involves earlier blood tests than is the standard today. You have been invited to join this study because you have been transferred from the Department of Emergency General Practice (Allmennlegevakten) to the Observation Unit (Observasjonposten) for further observation after having experienced chest pain. On account of your symptoms upon your arrival, the emergency room doctor would like to take some blood test to exclude acute heart disease as the cause of your symptoms.

The Department of Emergency General Practice at Oslo Accident and Emergency Outpatient Clinic is a part of the city of Oslo's Health Agency. The Health Agency is responsible for this study.

What does the study involve?
By accepting to be part of this study you are consenting to one extra blood test being taken than what is usually done when diagnosing a heart attack. The first test will be taken when you arrive at the Observation Unit, the second after an hour and the last one will be taken after 4-6 hours. The nurse will also ask you some questions regarding the symptoms you experienced before your arrival at the emergency room, when they occurred, and about your risk factors for heart disease. This will be used as information during the study. Your participation will not prolong your stay at the observation unit or result in different treatment. It will, on the other hand, allow for a quicker diagnosis of a heart attack as the cause of your symptoms. When necessary, this will also allow for a faster hospital admission for further treatment and diagnostics.

During the study we will collect and register your personal information. The results of the three blood tests will be collected and we will also keep copies of the ECGs taken during your stay. If you require a hospital admission, we will ask the hospital to send us a copy of your papers after your have been discharged. This is so we can register if the final diagnosis was a heart attack.

We also want to collect information about you three months after your stay at the emergency room. This to check if you have had acute heart disease after discharge. We will do this either by contacting you by phone or obtain information from health registries at the hospitals.

Potential advantages, disadvantages and serious adverse events
There are few disadvantages to participating in the study. If you choose to participate it will entail one extra blood sample from your arm. The nurses are well trained in this procedure, and the procedure itself has very few reported side effects, with only a small risk of injury or harm. Some may experience nausea and discomfort during the procedure. There have been a minimal number of reports of nerve damage caused by the needle prick during a blood test.

The advantage of participating in the study is that we will be able to clarify much faster if your symptoms are caused by a heart attack. It will allow for a diagnosis four hours earlier than todays tests. This will then cause a quicker hospital admission for further diagnostics and treatment.

OUT-ACS study at the Observation Unit at Legevakten i Oslo, 19.12.16

Voluntary participation
Participation in the study is voluntary. You can withdraw your consent to participate in the study at any time and without stating any particular reason. This will not have any consequences for your further treatment. If you withdraw from the study you have the right to ask for all your information and test results to be deleted. This is unless these have already been used in analysis and statistics, or used in scientific publications. If you wish to participate, sign the declaration of consent on the final page.

If you have questions concerning the study or wish to withdraw from it, you may contact the Observation Unit at Legevakten i Oslo by telephone number 23 48 70 41 and asking for the project coordinator, dr. Tonje R. Johannessen, general practitioner at Allmennlegevakten at Legevakten i Oslo. If she isn't available at that time, she will contact you during her next work day.

What will happen to the samples and your personal information?
The samples and data that are registered about you will only be used in accordance with the purpose of the study as described above. All the data and samples will be processed without name, personal identification number or other directly recognisable type of information. A code number links you to your data and samples through a list of names. Only doctors and research assistants connected to this study have access to the list of names and your contact information. At the end of the study, this information will be deleted. When the study is published, it will not be possible to identify participants through the results of the study. Information regarding treatment and further follow-up appointments will be anonymized and saved in an office at Legevakten i Oslo.

The coordinator of the study is responsible for your personal information and that it is handle in the appropriate way. Your information will be anonymous and deleted, at the latest, five years after the study has ended.

Right to access and material storage
If you agree to participate in the study, you are entitled to have access to the information registered about you. You are further entitled to correct any mistakes in the information we have registered. If you withdraw from the study, no further information or material will be collected about you. Data that has already been collected will not be deleted.

Funding
The study is funded by research funding granted by The Norwegian Committee on Research in General Practice and the Norwegian Medical Association's Fund for Quality and Patient Safety.

Insurance
You are insured in accordance with the Norwegian Law on compensation of patient injury. The director of Ullevål University Hospital of Oslo is responsible for the correct processing of data.

Approval
The Troponin Study was approved by the Regional Committees for Medical and Health Research Ethics (REC) 30.08.2016, case number 2016/1241.

OUT-ACS study at the Observation Unit at Legevakten i Oslo, 19.12.16

Consent for participation in the Troponin Study

I am willing to participate in the study.

Place and date Study participant's signature

Participant's name in capital letters

I confirm that I have given information about the study.

Place and date Signature and role in the study

Dan Atar
Professor Dr.Med/Project Leader

Tonje Rambøll Johannessen
General Practitioner/Project Coordinator

Appendix C – Written informed consent (in Norwegian)

[OUT-ACS studien på Observasjonsposten ved Legevakten i Oslo, 19.12.16, versjon nr. 3]

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKT:

TROPONINSTUDIEN VED OBSERVASJONSPOSTEN VED LEGEVAKTEN I OSLO 2016-2017

Dette er et spørsmål til deg om å delta i et forskningsprosjekt hvor vi skal forsøke å avdekke om man raskere kan avklare akutt hjerteinfarkt ved ta en tidligere hjerteblodprøve enn det man gjør i dag. Du har blitt utvalgt til denne studien, da du er overført fra Allmennlegevakten til Observasjonsposten for videre observasjon. Legen på legevakten ønsker å ta blodprøver av deg for å utelukke akutt hjertesykdom som årsak til dine symptomer.

Allmennlegevakten ved Legevakten i Oslo, som er en del av Helseetaten i Oslo kommune, er ansvarlig for denne studien.

HVA INNEBÆRER PROSJEKTET?

Ved å takke ja til deltagelse i dette forskningsprosjektet, samtykker du til at vi kan vi ta en ekstra blodprøve enn det vi vanligvis gjør for å undersøke om man har akutt hjerteinfarkt. Første blodprøve vil bli tatt når du kommer til Observasjonsposten, andre prøve etter en time og siste etter 4-6 timer. Sykepleier vil også stille deg noen spørsmål om hvilke symptomer du hadde før du kom til legevakten, når disse oppsto og litt om din risiko for hjertesykdom. Dette vil bli brukt som tilleggsinformasjon i studien. Deltagelse i prosjektet vil ikke medføre lengre opphold på Observasjonsposten eller annen behandling. Det vil derimot raskere bli mulig å påvise akutt hjertesykdom hos deg, noe som innebærer tidligere overføring til sykehus for behandling og videre utredning hvis nødvendig.

I prosjektet vil vi innhente og registrere opplysninger om deg. Resultatet fra de tre blodprøvene vil bli innsamlet og vi ønsker også å innhente kopi av EKG-ene som har blitt tatt under oppholdet. Dersom du har behov for sykehusinnleggelse, vil vi be om å få tilsendt epikrisen (oppsummering fra sykehusoppholdet) etter at du er utskrevet. Dette for å se om endelig diagnose var hjerteinfarkt.

Vi ønsker også å innhente opplysninger om deg tre måneder etter ditt opphold på legevakten. Dette for å undersøke om du har hatt akutt hjertesykdom etter utskrivelsen. Dette vil vi gjøre enten ved å kontakte deg på telefon eller innhente informasjon fra helseregistre på sykehusene.

MULIGE FORDELER OG ULEMPER

Det anses å være svært få ulemper med å delta i dette forskningsprosjektet. Dersom du velger å delta innebærer dette at vi tar en ekstra blodprøve fra armen din. Dette er en prosedyre som er godt kjent for sykepleierne som utfører den, og som i seg selv har svært få rapporterte bivirkninger med liten risiko for skade og ubehag. Noen kan oppleve uvelhet og kvalme i forbindelse med nålestikk og prøvetakning. Noen ytterst få har rapportert nerveskade etter blodprøvestikk.

Fordeler med deltagelse er at vi tidligere kan avklare om symptomene hos deg kan skyldes akutt hjertesykdom. Dersom du deltar i studien vil dette kunne påvises opptil fire timer tidligere enn i dag, noe som innebærer raskere overføring til sykehus for videre undersøkelser og evt. behandling.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen nederst på side 3. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for din videre behandling. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Observasjonsposten ved Legevakten i Oslo på tlf. 23 48 70 41 med forespørsel til dr. Tonje R. Johannessen, allmennlege ved Allmennlegevakten ved Legevakten i Oslo, ansvarlig for prosjektet. Dersom vedkommende ikke er på jobb når du ringer, vil hun kontakte deg første arbeidsdag.

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres fra deg skal kun brukes slik som beskrevet i hensikten med forskningsprosjektet, det vil si en studie som vurderer om man raskere klarer å avdekke eller utelukke akutt hjertesykdom på Legevakten i Oslo enn det man gjør i dag. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Opplysningene vil være innelåst på et kontor på Oslo Legevakt. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun leger og forskningsassistenter knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Ved studiens slutt vil navnelisten slettes. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Opplysninger om behandling og oppfølging vil bli lagret i anonymisert form på et kontor på Legevakten i Oslo..

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

FORSIKRING

Oslo Universitetssykehus Ullevål ved administrerende direktør er databehandlingsansvarlig.

Deltagere i studien er forsikret på vanlig måte gjennom Pasientskadeloven.

ØKONOMI

Studien er finansiert gjennom forskningsmidler fra Allmennmedisinsk forskningsutvalg/AFU og Den norske legeforenings fond for kvalitetsforbedring og pasientsikkerhet.

GODKJENNING

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk/REK nord den 30.08.16, saksnummer 2016/1241.

[OUT-ACS studien på Observasjonsposten ved Legevakten i Oslo, 19.12.16, versjon nr. 3]

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato	Deltakers signatur
	Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato	Signatur
	Rolle i prosjektet

Dan Atar

Professor Dr.Med/Prosjektleder

Tonje Rambøll Johannessen

Allmennlege/Prosjektansvarlig

Appendix D – Additional consent

Additional consent to the OUT-ACS study, version no. 1, 17th January 2017

Consent to obtain 90-day follow-up data from patients included in the OUT-ACS study

Obtaining additional consent for included participants with consent form issued before 19th December 2016

Name:

Norwegian national identity number:

«We are approaching you by phone today as you, during a recent visit at the Oslo Accident and Emergency Outpatient Clinic, participated in the ongoing heart study at our Observation Unit.

We now ask for your permission to obtain additional follow-up data from hospital health registries. We aim to determine whether you have been admitted with an acute cardiac event (such as a heart attack) within the following 90 days after discharge from our Observation Unit. We believe this additional information will be valuable for the study in assessing whether our recommendations to you at discharge were adequate.

If consenting to our using the registries, your verbal consent will be recorded in this form. There will be no further demands. We will then proceed to see whether you have been registered with an acute cardiac event in the hospital registries three months after discharge.

You have the full right to decline this request.»

□ **YES – Verbal consent to obtain 90-day data given**

□ **NO – Verbal consent not given**

Place and date:

Nurse signature/name:

Appendix E – Additional consent (in Norwegian)

Ekstra samtykke til Troponinstudien, versjon nr. 1, 17.01.17

Oppfølging av troponinpasientene tre måneder etter utskrivelse fra Observasjonsposten

Innhenting av ekstra samtykke for pasienter med samtykkeskjema utgitt før 19.12.16.

Navn:

Personnummer:

«Vi kontakter deg pr tlf. i dag da du deltok i hjertestudien på vår observasjonspost da du var innlagt her på Legevakten i Oslo for kort tid siden.

Vi lurer på om du synes det er i orden at vi tre måneder etter ditt opphold her på legevakten undersøker med sykehusregistrene om du har vært innlagt med akutt hjerteinfarkt etter utskrivelsen. Vi synes dette er viktig for å vurdere om våre anbefalinger til deg ved utskrivelsen var gode nok.

Alt du trenger å gjøre er å samtykke til dette over telefonen her i dag. Du vil ikke bli kontaktet utover dette. Vi vil deretter undersøke om du er oppført i sykehusregistrene etter tre måneder.

Du har all rett til å si nei til deltakelse.»

☐ **JA - Samtykker til innhenting av data etter tre måneder**

☐ **NEI - Ønsker ikke innhenting av data etter tre måneder**

Sted og dato:

Sykepleier:

Papers I - IV

I

openheart

Pre-hospital One-Hour Troponin in a Low-Prevalence Population of Acute Coronary Syndrome: OUT-ACS study

Tonje R Johannessen ,[1,2] Odd Martin Vallersnes ,[1,2] Sigrun Halvorsen ,[3,4] Anne Cecilie K. Larstorp,[4,5] Ibrahimu Mdala ,[1] Dan Atar [3,4]

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[1]Department of General Practice, Institute of Health and Society, University of Oslo, Oslo, Norway
[2]Oslo Accident and Emergency Outpatient Clinic, City of Oslo Health Services, Oslo, Norway
[3]Department of Cardiology, Oslo University Hospital Ullevaal, Oslo, Norway
[4]Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[5]Department of Medical Biochemistry, Section of Cardiovascular and Renal Reseach, Oslo University Hospital Ullevaal, Oslo, Norway

Correspondence to
Dr Tonje R Johannessen; t.r.johannessen@medisin.uio.no

ABSTRACT

Objective The European Society of Cardiology 0/1-hour algorithm for high-sensitivity cardiac troponin T (hs-cTnT) has demonstrated high rule-out safety in large hospital validation cohorts. We aimed to validate the algorithm in a primary care setting, where patients have a lower pretest probability for acute coronary syndrome.

Methods This prospective, observational, diagnostic study included patients with acute non-specific chest pain admitted to a primary care emergency clinic in Oslo, Norway, from November 2016 to October 2018. hs-cTnT was measured after 0, 1 and 4 hours. The primary outcome measure was the diagnostic performance of the 0/1-hour algorithm, the 90-day incidence of AMI or all-cause death the secondary.

Results Among 1711 included patients, 61 (3.6%) were diagnosed with AMI. By applying the algorithm, 1311 (76.6%) patients were assigned to the rule-out group. The negative predictive value was 99.9% (95% CI 99.5% to 100.0%), the sensitivity and specificity 98.4% (91.2–100.0) and 79.4% (77.4–81.3), respectively. Sixty-six (3.9%) patients were triaged towards rule-in, where 45 were diagnosed with AMI. The corresponding positive predictive value was 68.2% (58.3–76.7), sensitivity 73.8% (60.9–84.2), and specificity 98.7% (98.1–99.2). Among 334 (19.5%) patients assigned to the observation group in need of further tests, 15 patients had an AMI. The following 90 days, five new patients experienced an AMI and nine patients died, with a low incidence in the rule-out group (0.3%).

Conclusion The 0/1-hour algorithm for hs-cTnT seems safe, efficient and applicable for an accelerated assessment of patients with non-specific chest pain in a primary care emergency setting.

Trial registration number NCT02983123.

Key questions

What is already known about this subject?

► Ruling out acute myocardial infarction in primary care is challenging due to limited diagnostic decision aids. The favourable diagnostic performance of the 0/1-hour algorithm for high-sensitivity cardiac troponins has earlier been validated in hospital studies, with high rule-out safety and efficacy.

What does this study add?

► In this observational diagnostic study, the same algorithm seems safe, efficient and accurate, also in a primary care emergency setting, where the patients with acute chest pain have a lower pretest probability for acute coronary syndrome.

How might this impact on clinical practice?

► By implementing this algorithm for rapid and safe triage done by general practitioners outside of hospitals, the overall costs, the risk of overdiagnosis, and patient crowding in the emergency departments may be reduced.

INTRODUCTION

Rapid triage of suspected acute coronary syndrome (ACS) is crucial in patients presenting with acute chest pain. In addition to clinical assessment and the ECG, cardiac troponins are gold standard biomarkers in the diagnosis of acute myocardial infarction (AMI).[1 2] Due to limited diagnostic tests, the AMI diagnosis is challenging in the prehospital emergency setting,[3–5] and the value of prehospital risk stratification with point-of-care troponins with or without risk assessment scores has received increased attention during the last decade.[6–8] Still, there is no prehospital strategy that safely excludes AMI outside of hospitals.[5 8 9]

The introduction of high-sensitivity assays for cardiac troponins opened for rapid diagnostic pathways in hospitals,[10–12] and the diagnostic utility of the 2015 European Society of Cardiology (ESC) 0/1-hour algorithm for high-sensitivity cardiac troponin T (hs-cTnT)[2] has been confirmed in large validation studies from hospital emergency departments (EDs).[13–18] However, there is a need for validation of the algorithm also in a primary care setting, where the patients have a lower pretest probability for ACS.[13 14 16 18]

We aimed to validate the 0/1-hour algorithm for hs-cTnT in a low-prevalence population for ACS by applying the algorithm in a primary care emergency setting.

Furthermore, we registered the incidence of new AMIs or all-cause deaths during the 90 days following the initial assessment.

METHODS

Study design and setting

The One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome or OUT-ACS study is a single-centre, observational, prospective, diagnostic cohort study, conducted at Oslo Accident and Emergency Outpatient Clinic (OAEOC) in Norway. The OAEOC is the main primary care emergency outpatient clinic in Oslo, with approximately 200 000 consultations per year and has an observation unit with 18 beds. The OAEOC serves the entire city (681 071 inhabitants as per 1 January 2019)[19] 24/7 all year.

The emergency care system in Norway is two-tiered, with an active gatekeeping function in primary care, regulating access to the hospitals. Hence, patients with acute symptoms are initially assessed outside of hospital. Patients considered critically ill (approximately 50% of all AMIs) bypass the gatekeeping system and are directly brought to hospital by ambulance services.[20] The remaining patients are treated in primary care or sent on to the hospital after primary care assessment. The primary care emergency clinics differ from hospital EDs by having less advanced diagnostic resources and therapeutic options and are mainly staffed by general practitioners (GPs).

Participants

During the enrolment period (November 2016–October 2018), the study consecutively recruited patients, 18 years or older, with non-traumatic chest pain or discomfort admitted to the prehospital OAEOC observation unit for assessment of cardiac troponins (figure 1). Patients admitted for cardiac troponin measurements after electric trauma were not included, nor were patients with a highly suspected ACS (comprising AMIs with or without ST-segment elevations, and unstable angina pectoris), as they were rapidly sent on to the hospital after initial assessment by the GP.

Data collection

The GP obtained a medical history and performed a physical examination of all patients presenting with chest complaints, including pulse oximetry and ECG. Capillary C reactive protein, haemoglobin, blood glucose and chest X-ray were the only additional tests available. Whether the patient was directly hospitalised due to a suspected ACS, sent home with no additional tests or admitted to the prehospital observation unit for cardiac troponins was left to the discretion of the individual GP, following regular practice at the clinic. Further details are illustrated in online supplementary figure S1 in appendix.

The 0-hour hs-cTnT was sampled immediately after admission to the observation unit. The 1-hour study sample was drawn by the regular nursing staff after written informed consent was obtained. Details regarding risk factors, symptom presentation and time intervals were recorded in a predefined form. In addition, the regular 4-hour hs-cTnT, kidney function tests and additional ECGs were collected, and hospital discharge documents were gathered from all hospitalised participants.

New incidents of AMI or all-cause death the following 90 days were obtained through linkage with the Norwegian Cardiovascular Disease Registry.[21] This national register gathers data from the Norwegian Patient Registry, the Norwegian Cause of Death Registry and the Norwegian Central Population Registry. In addition, cardiovascular codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10),[22] are automatically reported to the Norwegian Cardiovascular Disease Registry after hospital admissions and hospital outpatient clinic visits.[23] For this study, we extracted primary and secondary ICD-10 chapter I21-22 (AMI) codes, date of the incidence and date of death.

Laboratory analysis

Following the standard procedure at the OAEOC, venous blood samples were collected in serum tubes and stored locally at room temperature (approximately 20°C) for a maximum of 30 min before centrifugation. The serum was stored in a refrigerator before being sent on to the Central Lab at Oslo University Hospital Ullevaal for analysis every 4 hours. The 1-hour samples were collected 55–90 min after the 0-hour sample. hs-cTnT was analysed on the Cobas 8000 e602 and later the Cobas 8000 e801 Module Analyzer using the Elecsys Troponin T hs STAT assay (Roche Diagnostics, Switzerland). For hs-cTnT, the 99th percentile of a healthy reference population is 14 ng/L, with a coefficient of variation (CV) of <10 %, a limit of detection of 5 ng/L, a limit of blank of 3 ng/L and stability of cTnT with storage at 2°C–8°C of 24 hours.[24 25] A stability of 24 hours has also been demonstrated for samples stored under the conditions in our study.[26] During the study period, the laboratory regularly analysed EQA (external quality assessment) material from Noklus (Bergen, Norway) and Equalis (Equalis AB, Uppsala, Sweden) with good performance. The CV was 10% at concentrations of <20 ng/L and 6% at concentrations of ≥20 ng/L.

The 0/1-hour algorithm for hs-cTnT

The 0/1-hour rule-in/rule-out algorithm for hs-cTnT follows assay-specific cut-off values[13] as described in the 2015 ESC guidelines on non-ST-elevation myocardial infarction.[2] Patients are classified into rule-out, rule-in or further observation, according to the 0-hour (0h) hs-cTnT sample alone, or the absolute 0-1 hour change (Δ0–1h) (figure 2). During the study, the 1-hour hs-cTnT measurement was available to the GP treating the patient at the observation unit to avoid a prehospital delay among patients assigned towards rule-in by the 1-hour sample.

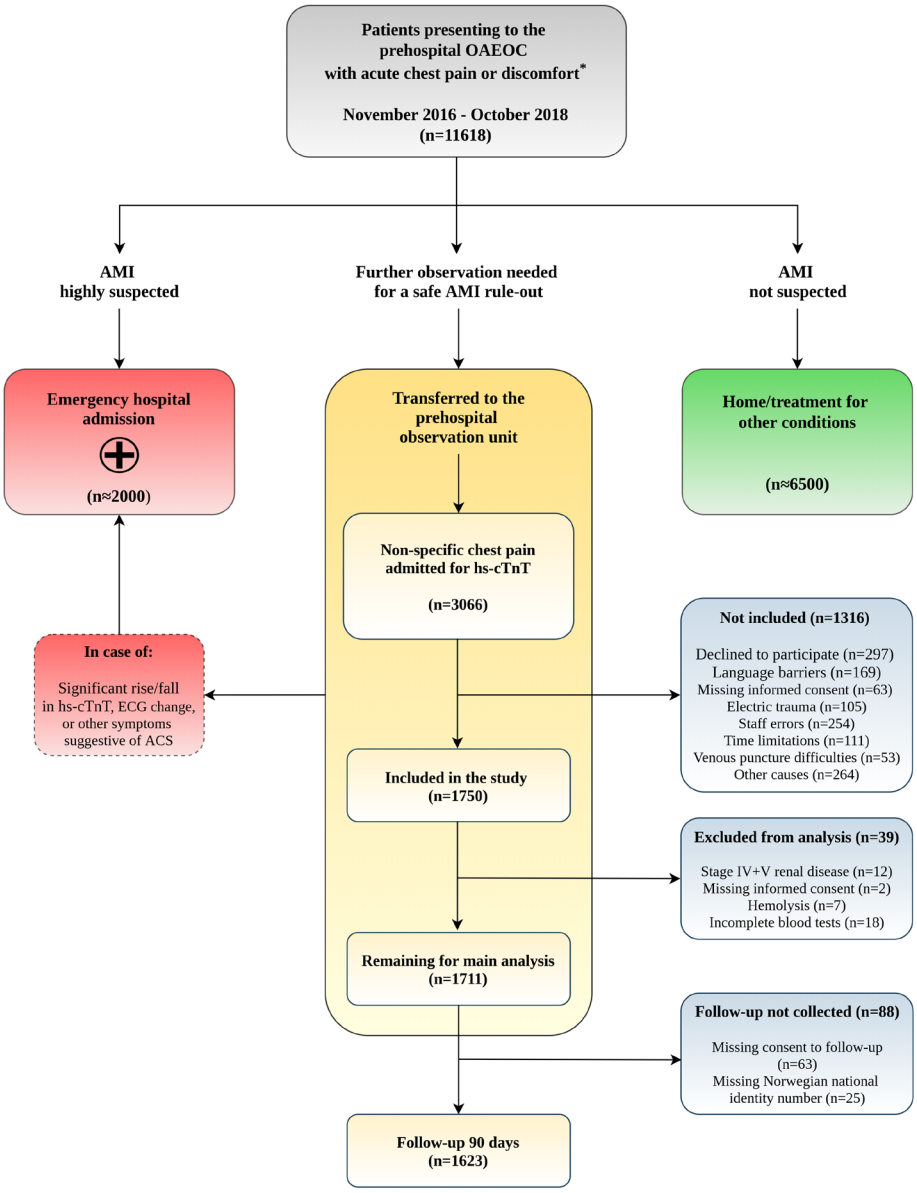

Figure 1 Patient flow diagram. Management of acute chest pain at the OAEOC and patient flowchart during the study. *, critically ill patients are directly hospitalised by the ambulance services. ACS, acute coronary syndrome; AMI, acute myocardial infarction; hs-cTnT, high-sensitivity cardiac troponin T; OAEOC, Oslo Accident and Emergency Outpatient Clinic.

Final diagnosis

In addition to the clinical assessment and the repeated ECGs, the standard hs-cTnT of Δ0–4 hours served as a reference standard for ruling out AMI for all patients discharged home. The treating GP interpreted the Δ0–4 hours according to the 'Third Universal Definition of Myocardial Infarction' (applicable at the time of the study), comprising a significant rise/fall pattern of hs-cTnT with at least one value above the 99th percentile of a healthy reference population, in combination with ischaemic symptoms, or pathological ECG changes. For baseline values above the 99th percentile, a relative change of 20% or more was considered significant; for baseline values below the 99th percentile, the relative change had to be at least 50%.[1]

Two independent cardiologists at Oslo University Hospital adjudicated the final AMI diagnosis for all hospitalised patients, with access to all collected data from both the OAEOC and the hospital admission during the index episode, including the 1-hour hs-cTnT measurement. The adjudication process was based on the 'Third Universal Definition of Myocardial Infarction'.[1] A third cardiologist was consulted if there was any disagreement in the adjudication (in 19 of the cases).

Outcome measures

The primary outcome of the study was the diagnostic performance of the 0/1-hour algorithm for AMI at the index episode, and the safety in the rule-out group, as measured

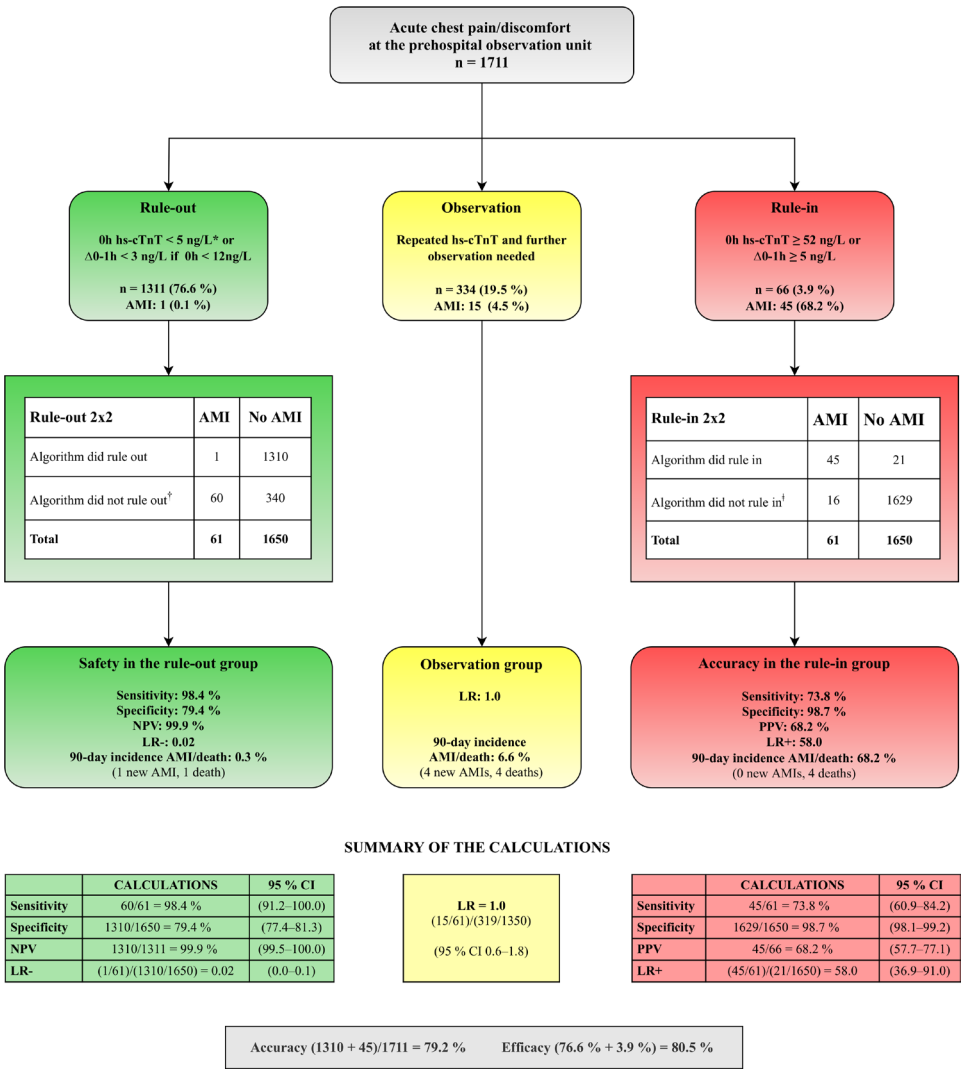

Figure 2 Prehospital validation of the ESC 0/1-hour algorithm. The patients were assigned to rule-out, rule-in or the observation group according to the baseline hs-cTnT value or the 0–1 hour absolute change,[2] where high safety is demonstrated in the rule-out group. Summary of the calculations with corresponding 95 % CI are presented at the bottom. *, given a >3-hour symptom onset before the first hs-cTnT sample; †, rule-in and observation group combined; ‡, rule-out and observation group combined. AMI, acute myocardial infarction; ESC, European Society of Cardiology; LR, likelihood ratio; hs-cTnT, high-sensitivity cardiac troponin T; NPV, negative predictive value; PPV, positive predictive value.

by the negative predictive value (NPV) and the sensitivity. The index episode was defined as the event resulting in prehospital hs-cTnT sampling. In the rule-in group, we measured the diagnostic accuracy (the positive predictive value (PPV) and the specificity) to address whether the algorithm resulted in too many false positives when applied in a low-prevalence setting.

Secondary outcome measures were AMI (including the adjudicated AMI at the index episode) or all-cause death during the subsequent 90 days as a prognostic evaluation of the algorithm. In addition, the proportion of patients correctly triaged by the 0/1-hour algorithm (ruled-out without AMI or ruled-in with AMI) and the overall efficacy, that is, the proportion of patients assigned to either the rule-out or the rule-in group, were estimated.

Statistical analysis

The categorical variables are presented as numbers and percentages; the continuous variables are presented as medians and IQRs. Comparisons of categorical variables were made using the Pearson χ^2 test or the Fisher exact test, whereas the Kruskal-Wallis test was used when comparing continuous variables. We used two-sided hypothesis testing, and the significance level was set at α=0.05. The sample size calculation is described in detail in the online supplementary appendix.

Since the 0/1-hour algorithm has three outcomes (rule-out, rule-in and observation), it does not provide a dichotomic positive/negative test result. The diagnostic performance of the algorithm is, therefore, calculated for the rule-out and the rule-in groups separately. In

Table 1 Baseline characteristics of the study participants

	Total n=1711	Rule-out n=1311	Observation n=334	Rule-in n=66	P value
Female sex, n (%)	816 (47.7)	640 (48.8)	150 (44.9)	26 (39.4)	0.177
Age, median (IQR)	56 (45–68)	52 (42–62)	72 (62–83)	65 (53–82.3)	<0.001
Risk factors for CVD, n (%)					
Current/history of smoking	449 (26.2)	368 (28.1)	61 (18.3)	20 (30.3)	0.001
Previous coronary artery disease	317 (18.5)	165 (12.6)	135 (40.4)	17 (25.8)	<0.001
Hypertension	448 (26.2)	293 (22.3)	139 (41.6)	16 (24.2)	<0.001
Hypercholesterolaemia	422 (24.7)	295 (22.5)	110 (32.9)	17 (25.8)	<0.001
Other CVD*	288 (16.8)	146 (11.1)	123 (36.8)	19 (28.8)	<0.001
Diabetes mellitus	171 (10.0)	106 (8.1)	55 (16.5)	10 (15.2)	<0.001
COPD	80 (4.7)	38 (2.9)	37 (11.1)	5 (7.6)	<0.001
Family history of CVD	690 (40.3)	564 (43.0)	101 (30.2)	25 (37.9)	<0.001
Presenting acute symptoms, n (%)					
Chest pain	1485 (86.8)	1174 (89.5)	252 (75.4)	59 (89.4)	<0.001
Constricting	1239 (72.4)	978 (74.6)	206 (61.7)	55 (83.3)	<0.001
Sharp	404 (23.6)	339 (25.9)	57 (17.1)	8 (12.1)	<0.001
Tearing	64 (3.7)	54 (4.1)	7 (2.1)	3 (4.5)	0.157
Burning	208 (12.2)	166 (12.7)	32 (9.6)	10 (15.2)	0.226
Respiratory dependent	302 (17.7)	250 (19.1)	41 (12.3)	11 (16.7)	0.014
Chest-wall tenderness	205 (12.0)	170 (13.0)	33 (9.9)	2 (3.0)	0.022
Movement dependent	219 (12.8)	183 (14.0)	35 (10.5)	1 (1.5)	0.005
Other pain (abdomen, back or neck)	48 (2.8)	32 (2.4)	14 (4.2)	2 (3.0)	0.175
No pain	177 (10.3)	104 (7.9)	68 (20.4)	5 (7.6)	<0.001
Pain radiation	1000 (58.4)	802 (61.2)	154 (46.1)	44 (66.7)	<0.001
Dyspnoea	901 (52.7)	689 (52.6)	178 (53.3)	34 (51.5)	0.962
Palpitations	637 (37.2)	501 (38.2)	117 (35.0)	19 (28.8)	0.195
Syncope/presyncope	460 (26.9)	353 (26.9)	88 (26.3)	19 (28.8)	0.917
Acute fatigue	571 (33.4)	432 (33.0)	110 (32.9)	29 (43.9)	0.187
Nausea and/or vomiting	732 (42.8)	578 (44.1)	123 (36.8)	31 (47.0)	0.043
Diaphoresis	561 (32.8)	448 (34.2)	93 (27.8)	20 (30.3)	0.081
First ECG, n (%)					
Non-ischaemic	1515 (88.5)	1187 (90.5)	282 (84.4)	46 (69.7)	<0.001
Non-specific changes†	196 (11.5)	124 (9.5)	52 (15.6)	20 (30.3)	<0.001
Symptom onset to first hs-cTnT (hours), n (%)					
<3	182 (10.6)	150 (11.4)	25 (7.5)	7 (10.6)	0.109
3.0–5.99	609 (35.6)	474 (36.2)	114 (34.1)	21 (31.8))	0.637
6.0–11.99	409 (23.9)	287 (21.9)	100 (29.9)	22 (33.3)	0.002
12.0–23.99	224 (13.1)	177 (13.5)	35 (10.5)	12 (18.2)	0.159
>24	287 (16.8)	223 (17.0)	60 (18.0)	4 (6.1)	0.054

All values are presented as n (%) and median (IQR). P values are for comparisons across the three triage groups using the Pearson χ^2 test or the Fisher exact test for categorical variables, and the Kruskal-Wallis test for continuous variables.
The median time interval between the hs-cTnT samplings of 0 and 1 hour was 65 min (IQR 60–70) with no difference across the groups.
*Includes atrial fibrillation, other arrhythmias, cardiomyopathies, cerebral stroke, heart failure or valvular disease.
†Non-specific changes in either the ST segment, T inversions, Q waves, atrial fibrillation or left/right bundle branch block of unknown clinical significance.
COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; hs-cTnT, high-sensitivity cardiac troponin T.

addition, the likelihood ratios (LRs) were obtained for all three groups. The area under the receiver operating characteristic (ROC) curve was constructed to report the overall diagnostic accuracy, with two cut-off values to include the intermediate observation group.[27 28]

A few cases of missing hs-cTnT values (due to errors or haemolysis) were separately handled by imputation using the median of the non-missing values. This was only done for a missing 1-hour value if the values of 0 and 4 hours were less than 3 ng/L apart, or for a missing 0-hour test if

the remaining values were all below the limit of detection (<5 ng/L). IBM SPSS V.25.0 and STATA V.15.0 were used in the calculations.

The study is registered at ClinicalTrial.gov and is conducted in accordance with the STARD (Standards for Reporting of Diagnostic Accuracy Studies) guidelines[27] (online supplementary table S1).

Patient and public involvement

This research was designed and conducted without patient involvement.

RESULTS

Participants

During the patient enrolment period, 11 618 patients presented to the OAEOC with acute chest pain or other symptoms suggestive of AMI. After the initial clinical assessment by the GP, hs-cTnT measurements was not considered necessary for approximately 6500 patients (ACS not suspected), while an estimated 2000 patients were directly transferred to the hospital with a highly suspected ACS and hence not available for study enrolment.

All 3066 consecutive patients admitted to the observation unit at the OAEOC for cardiac troponins were potentially eligible for the study. Of these, 1750 patients were included in the study (figure 1). Thirty-nine patients were excluded from the final data analyses, and 90-day follow-up data were not collected for 88 patients (figure 1). The 4-hour hs-cTnT was not sampled from 102 (6 %) patients in need of hospital transfer during the observation, 45 with an AMI, the remaining with other acute illnesses. These patients were not excluded from the study, and hospital documents were also collected for them.

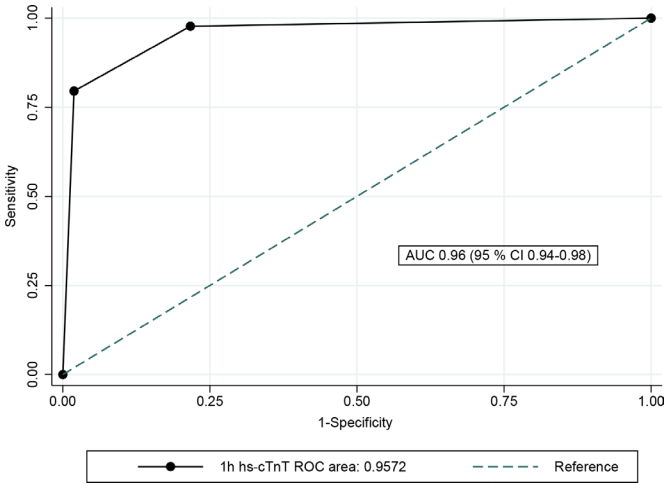

Figure 3 Overall diagnostic accuracy of the 0/1-hour algorithm for hs-cTnT. The overall diagnostic accuracy for AMI during the index episode was demonstrated by the area under the ROC curve at 96.0% (95 % CI 0.94% to 0.98%). The AUC was achieved by using two cut-off values to include the observation group: (1) rule-in: sensitivity 45/61=0.74 and specificity (1310+319)/1650=0.99, (2) rule-out: sensitivity (15+45)/61=0.98 and specificity: 1310/1650=0.79. AMI, acute myocardial infarction; AUC, area under the curve; hs-cTnT, high-sensitivity cardiac troponin T; ROC, receiver operating characteristic.

Characteristics of the study participants

The study population (n=1711) had a median age of 56 (IQR 45–68) years, and 47.7% were women. The patients were categorised into either rule-out (n=1311, 76.6 %), rule-in (n=66, 3.9 %) or observation group (n=334, 19.5 %) according to the 0/1-hour algorithm for hs-cTnT. The baseline characteristics of the patients are shown in table 1. A large proportion (29.9 %) of the patients were late presenters (>12 hours duration of symptoms), and the rule-out group had significantly less comorbidity than the two other groups.

AMI and hospitalisation

Only 3.6% (61/1711) of the patients were adjudicated with an AMI diagnosis during the index episode: 1 patient in the rule-out group, 15 patients in the observation group and 45 among the rule-ins. The median age of patients with AMI was 65 years (IQR 55–73), 26 (42.6 %) of them were women. Sixty of the patients with AMI were hospitalised. Details regarding the hs-cTnT values among the patients with AMI are listed in online supplementary table S2.

In total, 13.2% (226/1711) of the patients were transferred to the hospital, 6.0% (79/1311) in the rule-out group, 27.2% (91/334) in the observation group and 84.8% (56/66) in the rule-in group. Among the hospitalised patients who did not have an AMI, 74 patients had at least one hs-cTnT value above the upper reference limit (online supplementary table S3).

Applying the 0/1-hour algorithm

The diagnostic performance of the 0/1-hour algorithm when applied in a primary care emergency setting is demonstrated in figure 2. The safety in the rule-out group is substantiated by a high sensitivity of 98.4%, an NPV of 99.9% and a negative LR of 0.02. The rule-in accuracy has a high specificity of 98.7 %, a moderate PPV of 68.2 % and a positive LR of 58.0. The observation group in need of further tests received an indeterminate LR for AMI of 1.0. One of 1311 patients (0.08 %) in the rule-out group was wrongly classified. Details regarding misclassification by the 0/1-hour algorithm are listed in online supplementary table S4.

The diagnostic performance of the 0/1-hour algorithm is also demonstrated by the ROC curve, constructed by two cut-off values defining the observation group between the rule-in group (sensitivity 73.8% and specificity 98.7%) and the rule-out group (sensitivity 98.4% and specificity 79.4%). This resulted in an area under the curve (AUC) of 0.96 (95 % CI 0.94 to 0.98) (figure 3). The total accuracy and overall efficacy was 79.2% and 80.5%, respectively.

Table 2 Prognostic performance of the 0/1-hour algorithm after 90 days

Patients, n (%)	AMI index*	Total AMI 90 days†	Deaths 90 days	AMI + deaths 90 days‡
Disposition after OAEOC				
Rule-out (n=1241)	1 (0.1)	2 (0.2)	1 (0.1)	3 (0.3)
Primary care	1	2	1	3
Hospital	0	0	0	0
Observation (n=320)	15 (4.5)	19 (5.7)	4 (1.3)	22 (6.9)
Primary care	0	3	1	4
Hospital	15	16	3	19
Rule-in (n=62)	45 (68.2)	45 (68.2)	4 (6.4)	45 (68.2)
Primary care	0	0	0	0
Hospital	45	45	4	45
Total (N=1623)	61 (3.6)	66 (4.1)	9 (0.6)	70 (4.3)

The patients were divided into the 0/1-hour algorithm classification and disposition after OAEOC discharge. Time to first incident of AMI is reported, including index episode, in addition to all-cause death the following 90 days. Follow-up data were not available for 2019 due to technical data-extraction reasons from the national registries, shortening the follow-up period for the 53 patients recruited to the study in October 2018.
*AMI at index admission: total (N=1711); rule-out (n=1311); observation (n=334); rule-in (n=66).
†Including AMI at index.
‡Five patients with AMI subsequently died (four in the rule-in group and one in the observation group) and hence were not counted twice.
AMI, acute myocardial infarction; OAEOC, Oslo Accident and Emergency Outpatient Clinic.

90-day prognostic performance

During the first 90 days following admission to the observation unit, five new patients experienced an AMI, and there were in total nine deaths among the 1623/1711 patients (94.9 %) consenting to linkage with the national registry (table 2). The total incidence of AMI or all-cause death among the rule-out patients was 0.3% (the one death occurred on day 90). None of the 10 rule-in patients who were discharged home had an AMI or died the following 90 days, nor did the one false negative in the rule-out group.

DISCUSSION

Our study demonstrated that the 0/1-hour algorithm for hs-cTnT, when used in combination with clinical assessment and the ECG, safely rules out AMI, also in a low-prevalence setting outside of hospital. For the rule-out group, we found a high rule-out safety with an NPV of 99.9%, a sensitivity of 98.4% and a very low 90-day incidence of AMI or death (0.3%). Our high NPV is comparable to previous hospital validation cohorts with NPVs exceeding 98%.[13–16 18] For the rule-in group, the specificity is high (98.7 %), but with a moderate PPV of 68.2%, as expected when a test is applied on a low-prevalence population.[29] The AUC of 96.0% shows the overall diagnostic accuracy of the algorithm. In addition, a high efficacy has been demonstrated, with 80.5% of the patients assigned to either rule-out (76.6 %) or rule-in (3.9 %) by the algorithm. Also, as an LR−/+ below 0.1 or above 10.0 is considered strong evidence for ruling out or in a diagnosis,[30] our LR− of 0.02 and LR+ 58.0 reflect the high diagnostic performance of the algorithm.

Compared with the rule-out group, the patients assigned to the observation group (19.5 %) were older, had more comorbidity, higher baseline hs-cTnT values, and higher rates of AMI or death the following 90 days, which is probably why 27.2% of them were sent on to hospital, compared with 6.0% in the rule-out group. The LR of 1.0 in our observation group also reflects that the algorithm was not able to rule the patients in or out; hence, this group requires repeated hs-cTnT and further assessment.[12 30 31]

In our study, the majority of patients with AMI were late presenters and had a median age of 65 years, which is lower than the Norwegian average for patients with AMI (73.6 years).[32] This is probably because early presenters with ongoing symptoms and elderly patients with several comorbidities were more likely to be considered as high-risk for ACS and directly hospitalised.

Recently, troponin assays, as well as hospital admissions for chest pain in a low-risk patient population, have been reported as examples of overuse of care.[33] In our study, 21 of the rule-ins did not have an AMI. Ten of these patients were sent home with further management in primary care (table 2); none of them were readmitted with an AMI or died the following 90 days. The remaining 11 patients were hospitalised with other acute conditions that required hospitalisation (online supplementary table S4). Therefore, we do not think these 11 patients represent overuse of care, as the algorithm detects acute myocardial injury in addition to AMI.[1 2 34] It is also essential to recognise that the algorithm only rules out AMI and not unstable angina.[1 2 34]

The algorithm performed well in our setting and could improve the prehospital assessment of patients with low-risk for ACS. Prehospital implementation of the 0/1-hour algorithm might also reduce crowding in the EDs and the need for hospitalisation of low-risk patients. Furthermore, accelerated rule-in in primary care will enable earlier hospital transfer for patients with atypical AMI (eg, women, diabetics and elderly patients). Further studies are warranted, investigating the cost-effectiveness of a prehospital implementation of the high-sensitivity 0/1-hour algorithm.

Strengths and limitations

Not including patients with highly suspected ACS provided a selected study population, which might be considered a limitation. On the other hand, this study aimed to validate the algorithm in a primary care emergency setting with a low prevalence population, complementary to previous hospital ED studies. It is essential that primary care clinics should never delay hospitalisation by offering repeated hs-cTnT sampling if an acute AMI is suspected.[4] Accordingly, prehospital hs-cTnT sampling is only available at the OAEOC for patients considered low to moderately suspicious for ACS (online supplementary figure S1). The patients admitted to the observation unit comprise low-risk patients and patients with atypical symptoms such as acute dyspnoea without chest pain, acute fatigue and diaphoresis. Similar low-risk patients are found among patients with chest pain in EDs in systems of care where patients primarily present directly to the hospital ED. However, as admission to the OAEOC observation unit is dependent on assessment by a GP, high-risk patients were identified and sent on to hospital prior to study enrolment, rendering a selected low-risk, low-prevalence study population. We consider our selected low-prevalence population a strength more than a limitation for the purposes of our study, and our results are probably generalisable to other primary care emergency settings with a capacity for short-term observation of low-risk patients.

Our 3.6% AMI prevalence is low. The diagnostic performance of the algorithm is based on a limited number of events and calls for cautious interpretation of the numbers, especially the high LR+ (58.0) and the excellent NPV of 99.9%.[29]

The study did not evaluate the 0/1-hour algorithm for patients with chronic kidney dysfunction stages IV and V (estimated glomerular filtration rate of <30 mL/min/1.73 m^2), as these patients were excluded from the final analyses. Furthermore, the informed consent form was only available in Norwegian and English, preventing the recruitment of 169 patients due to language barriers. By having the consent form available in additional languages, the population studied might have been more representative. The study also lacks information about the patients' country of origin.

Patients were approached for study enrolment by the regular nursing staff continuously, including holidays, weekends and nights, thus reducing potential selection bias. Still, 1316 of the patients admitted for prehospital hs-cTnT measurements were not included in the study (figure 1). Approximately half of them were missed due to time limitations (n=111), staff errors (n=254) and other not reported causes (n=264), as is to be expected in a study without additional designated research staff. Apart from missed inclusions due to language barriers, we do not think the non-included patients impact on the generalisability of our results.

The cardiologists did not adjudicate patients who were discharged home from the OAEOC. It was not ethical or feasible to offer these patients additional tests at the hospital. The resulting uncertainty concerning the final diagnosis is a limitation. Nonetheless, the incidence of AMI and death during the subsequent 90 days were very low in the rule-out group. In addition, the 1-hour study samples were available for the treating GP to avoid a delay in hospital transfer for patients with a significant 1-hour increase. Accordingly, the 1-hour sample was also available in the records used by the adjudication committee.

Finally, since this study is an observational study, it only demonstrates how the 0/1-hour algorithm might perform if implemented in a primary care setting. An implementation study investigating how the algorithm actually performs in real-life practice outside of hospital EDs is warranted.

CONCLUSION

The 0/1-hour algorithm for hs-cTnT seems safe, effective and applicable for implementation in a low-prevalence population for ACS outside of hospital when used in combination with clinical assessment and ECG. This might enable a faster assessment of patients presenting with acute non-specific chest pain in a primary care emergency setting, reduce unnecessary hospitalisations and hence decrease healthcare expenditure.

Twitter Tonje R Johannessen @tonjerj

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Contributors All authors have contributed in the conception, drafting and revision of the article, and approved the final version for publication.

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Competing interests DA has received speaker's honoraria and consultancy fees from Amgen, Astra Zeneca, Bayer Healthcare, BMS, Boehringer-Ingelheim, Merck, Novartis, Pfizer and Sanofi-Aventis, and research grants from the institution by Medtronic and BMS. SH has received speaker's honoraria and consultancy fees

from Amgen, Astra Zeneca, Bayer Healthcare, BMS, Boehringer-Ingelheim, Merck, Novartis, Pfizer and Sanofi-Aventis, and has no conflicts in relation to this study.

Patient consent for publication Not required.

Ethics approval Written informed consent was obtained from all participants. The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committees (Regional Committee North for Medical and Health Research Ethics (number 2016/1241) and the Oslo University Hospital Information Security and Privacy Office (number 2016/13308)).

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Data availability statement Data may be made available upon reasonable request.

ORCID iDs
Tonje R Johannessen http://orcid.org/0000-0001-9368-1471
Odd Martin Vallersnes http://orcid.org/0000-0003-1213-392X
Sigrun Halvorsen http://orcid.org/0000-0001-7561-7644
Ibrahimu Mdala http://orcid.org/0000-0002-5204-1934
Dan Atar http://orcid.org/0000-0003-1513-8793

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ONLINE SUPPLEMENTARY APPENDIX

Supplementary material to the paper:

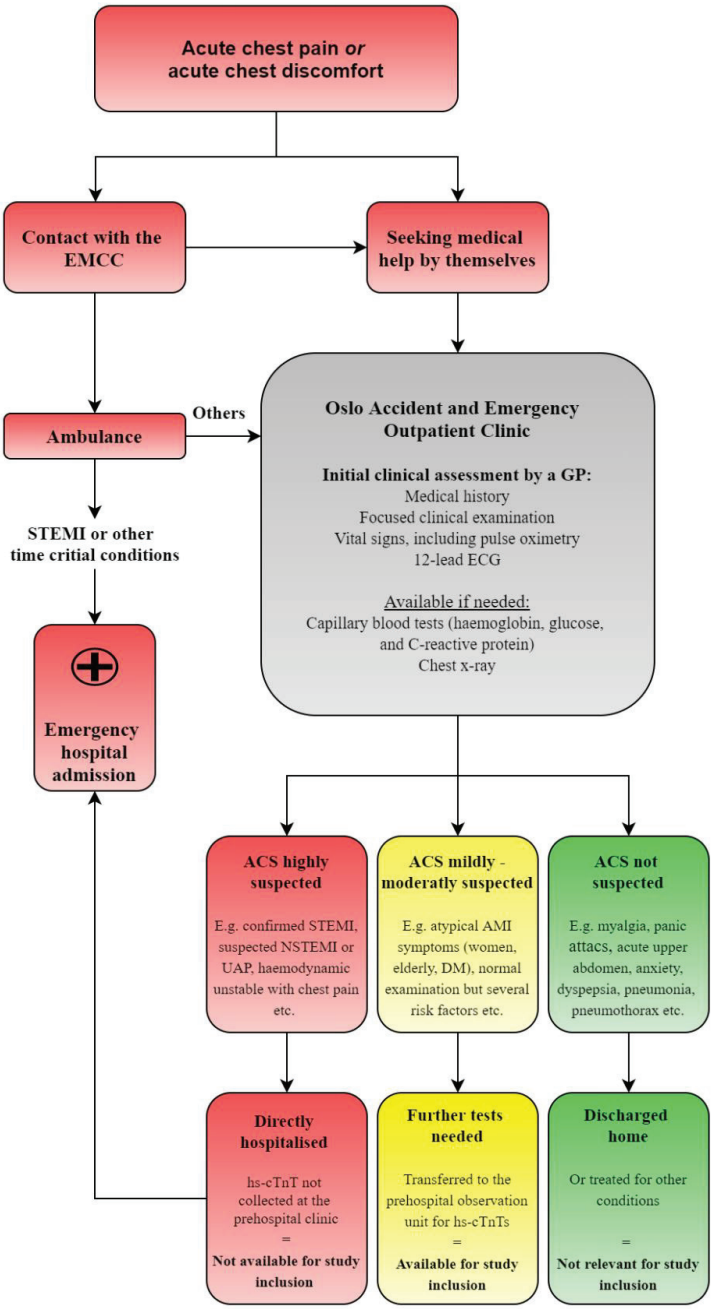
Pre-hospital One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome

The OUT-ACS study

By Tonje R. Johannessen, Odd Martin Vallersnes,
Sigrun Halvorsen, Anne Cecilie K. Larstorp, Ibrahimu Mdala and Dan Atar

Johannessen TR*, et al. Open Heart* 2020;**0**:e001296. doi:10.1136/openhrt-2020-001296

Figure S1 Patient management at Oslo Accident and Emergency Outpatient Clinic prior study enrollment



ACS: acute coronary syndrome; AMI: acute myocardial infarction; DM: diabetes mellitus; ECG: electrocardiogram; EMCC: emergency medical communication centre; GP: general practitioner; hs-cTnT: high-sensitivity cardiac troponin T, NSTEMI; non-ST-segment Elevation Myocardial Infarction; STEMI; ST-Elevation Myocardial Infarction, UAP: unstable angina pectoris

Sample size

We estimated the minimum sample size required based on a presumed AMI prevalence of 5 % in a general practice chest pain population (1-3). A power of 80 %, with a critical level of significance of 5 % resulted in an initial minimum sample size of 1039 patients. However, hs-cTnT was sampled at three different time points (0h, 1h and 4h) for each patient. Due to this clustering effect of the data at the patient level, the initial sample size was inflated using a design effect of 1.6 to give a minimum sample size of 1662 patients.

Table S1 STARD checklist for studies on diagnostic accuracy (4)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
ABSTRACT	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
METHODS *Study design*	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	6	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5, Figure S1
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5, Figure S1
	9	Whether participants formed a consecutive, random or convenience series	5
Test methods	10a	Index test, in sufficient detail to allow replication	6-7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	7
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	7, Figure 2
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	8
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Analysis	14	Methods for estimating or comparing measures of diagnostic accuracy	8-9

	15	How indeterminate index test or reference standard results were handled	Table 2, 15
	16	How missing data on the index test and reference standard were handled	9
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	n.a.
	18	Intended sample size and how it was determined	Supplementary appendix
RESULTS			
Participants	19	Flow of participants, using a diagram	10, Figure 1
	20	Baseline demographic and clinical characteristics of participants	11, Table 1
	21a	Distribution of severity of disease in those with the target condition	12, Table S2
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	29	Where the full study protocol can be accessed	n.a.
	30	Sources of funding and other support; role of funders	19

n.a.: not available

Table S2 Hs-cTnT in patients with acute myocardial infarction

	Total AMI (n=61)	Rule-out (n=1)*	Observation (n=15)	Rule-in (n=45)	
Manifestation at the OAEOC, n					
0h ≥52 ng/L	34	-	-	34	
Δ0-1 hour	11	-	-	11	
Δ0-4 hour	8	1	7	-	
Altered clinical presentation†	8	-	8	-	
Time interval from symptom onset to first hs-cTnT, n				**> 52 ng/L** (n=34)	**Δ0-1 hour** (n=11)
< 2 hours	1	-	-	-	1
2 – 2.99 hours	6	-	3	2	1
3 – 5.99 hours	16	-	5	8	3
6 – 11.99 hours	25	-	5	14	6
12 – 23.99 hours	10	1	1	8	-
> 24 hours	3	-	1	2	-

Hs-cTnT manifestation and symptom duration prior first hs-cTnT sampling among patients with AMI. Further subdivided according to the 0/1-hour algorithm.

ECG: electrocardiogram; hs-cTnT: high-sensitivity cardiac troponin T

* The one false-negative case also underwent endpoint adjudication, as she was not hospitalised for further tests. She was categorised as a potential AMI even though none of her hs-cTnT values exceeded 14 ng/L (Δ0-4 hour > 50 %, hs-cTnT: 5 – 6 – 13 – 8 ng/L at 0 – 1 – 4 – 12 hours, respectively) due to increased focus on sex-specific thresholds for hs-cTn.(5)

† Including relevant change between initial and repeated ECGs

Table S3 Distributions of the prehospital hs-cTnT values

	At least one hs-cTnT > URL (n=293)	All hs-cTnT < URL (n=1418)	Total (n=1711)
According to the 0/1-hour algorithm			
Rule-out	**2**	**1309**	**1311**
Observation	**230**	**104**	**334**
Rule-in	**62**	**4**	**66**
AMI versus non-AMI			
Significant rise/fall	**67**	**3**	**70**
AMI	58	3	61
No-AMI	9	0	9
No rise/fall	**226**	**1415**	**1641**
Disposition after OAEOC			
Primary care	**172**	**1313**	**1485**
No follow-up	34	360	394
Contact regular GP	104	872	976
Admitted municipal STF	15	8	23
Referral to hospital outpatient clinic	18	49	67
Left during observation	1	24	25
Hospital	**132**	**94**	**226**
AMI	58	2	60
No-AMI with significant rise/fall	9	0	9
No-AMI without significant rise/fall	65	92	157
90-day incidence of AMIs or all-cause death	**65**	**5**	**70**

Distribution of hs-cTnT values sampled (0, 1 or 4 hours) during the prehospital observation, classified by hs-cTnT values below or above the URL (14 ng/L). Further subdivided according to the 0/1-hour algorithm, final adjudication, disposition after ended observation at the OAEOC, and 90-day prognosis for AMI or all-cause death.

AMI: acute myocardial infarction; GP: general practitioners; hs-cTnT: high-sensitivity cardiac troponin T; OAEOC: Oslo Accident and Emergency Outpatient Clinic; STF; short-term facility; URL: upper reference limit

Table S4 Characteristics of misclassified patients according to the 0/1-hour algorithm

	Sex	Age	Symptom onset to hs-cTnT (hours)	Hs-cTnT at OAEOC			According to the 0/1h algorithm	Disposition after OAEOC	Final diagnosis (ICD-10)
				0h	1h	4h			
False negative (n=1)	F	70	18.0	5	6	13	Rule-out	Primary care	Pain upper abdomen, gastralgia (R10.1)
False positives (n=21)	M	81	15.8	47	42	49	Rule-in	Primary care	Chest pain, unspecified (R07.4)
	M	59	5.3	11	4	6	Rule-in	Primary care	Chest pain, unspecified (R07.4)
	F	64	5.4	10	4	4	Rule-in	Primary care	Chest pain, unspecified (R07.4)
	F	53	3.5	11	17	10	Rule-in	Primary care	Chest pain, unspecified (R07.4)
	F	42	3.5	8	13	8	Rule-in	Primary care	Precordial pain (R07.2)
	M	92	7.3	61	65	61	Rule-in	Primary care	Tendency to fall (R29.6)
	M	56	15.6	71	73	75	Rule-in	Primary care	Syncope (R55.0)
	M	84	8.6	52	50	45	Rule-in	Primary care	Acute upper respiratory infection, unspecified (J06.9)
	F	83	16.0	63	62	64	Rule-in	Primary care	COPD, exacerbation (J44.1), heart failure (I50.9)
	M	85	22.0	26	31	33	Rule-in	Primary care	Urethrotrigonitis (N30.0)
	M	42	22.8	18	5	8	Rule-in	Hospital	Chest pain, unspecified (R07.4)
	M	88	14.6	62	60	53	Rule-in	Hospital	Chest pain, unspecified (R07.4)
	M	92	86.1	71	66	58	Rule-in	Hospital	Chest pain, unspecified (R07.4), paroxysmal AF (I48.0)
	M	41	3.2	39	47	X	Rule-in	Hospital	Tachycardia (R00.0)
	M	50	4.7	6	11	X	Rule-in	Hospital	Tachycardia (R00.0)
	M	73	2.9	90	90	X	Rule-in	Hospital	Ventricular tachycardia (I47.2)
	M	69	4.5	170	177	X	Rule-in	Hospital	Atherosclerotic heart disease (I25.1)
	M	93	2.9	60	60	X	Rule-in	Hospital	Atherosclerotic heart disease (I25.1), angina pectoris (I20.9)
	M	64	2.7	14	21	41	Rule-in	Hospital	Acute myocarditis, unspecified (I40.9)
	F	86	5.9	38	33	X	Rule-in	Hospital	Heart failure (I50.9), chest pain, unspecified (R07.4), essential hypertension (I10)
	F	87	103.9	161	165	161	Rule-in	Hospital	PE (I26.9), heart failure (I50.9), chronic AF (I48.2)

AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; hs-cTnT: high-sensitivity cardiac troponin T; ICD-10: international classification of diseases 10th revision; OAEOC: Oslo Accident and Emergency Outpatient Clinic; PE: pulmonary embolism; X: not sampled due to early hospitalisation

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II

Journal of the American Heart Association

RESEARCH LETTER

Performance of the Novel Observation Group Criteria of the European Society of Cardiology (ESC) 0/1-Hour Algorithm in a Low-Risk Population

Tonje R. Johannessen, MD; Sigrun Halvorsen, MD, PhD; Dan Atar, MD; Odd Martin Vallersnes, MD, PhD

The 2020 European Society of Cardiology (ESC) guidelines on non–ST-segment elevation acute coronary syndrome recommend a third high-sensitivity cardiac troponin (hs-cTn) measurement for patients assigned to the observation group by the ESC 0/1-hour algorithm.[1] Recently, novel 3-hour criteria for patients in the observation group were proposed for use in the emergency department.[2] In the OUT-ACS study (One-hour Troponin in a Low-Prevalence Population of Acute Coronary Syndrome), the diagnostic performance of the ESC 0/1-hour algorithm for hs-cTnT was prospectively validated among low-risk patients with chest pain in an emergency outpatient setting. Although demonstrating high efficacy and rule-out safety (Figure), 19.5% of the cohort was assigned to the indeterminate observation group where 15 patients had an acute myocardial infarction (MI).[3]

Motivated by the recently suggested criteria,[2] we investigated how the novel hs-cTnT thresholds may perform with a 4-hour interval among low-risk patients with chest pain in an emergency outpatient setting.

We used data from the observational OUT-ACS study (NCT02983123), conducted at an emergency outpatient clinic not based at a hospital, in Oslo, Norway, between 2016 and 2018.[3] Details of the study methodology are outlined in a previous publication.[3] Data supporting the following analysis are available from the corresponding author upon reasonable request. Patients considered at high risk of acute coronary syndrome were rapidly hospitalized and not included. Patients with chest pain regarded as low risk but needing a safe rule-out of MI were eligible for inclusion and serial hs-cTnT measurements at the clinic. Hs-cTnTs were sampled at 0, 1, and 4 hours and the samples were dispatched for analysis.[3] In this retrospective analysis, the 0- and 4-hour hs-cTnTs samples were used. Patients in the OUT-ACS observation group were re-assigned to either rule-out, rule-in, or further observation (Figure) by using a 4-hour interval in combination with the suggested hs-cTnT thresholds.[2]

The diagnostic performance was measured by the sensitivity, specificity, and negative and positive predictive values for acute MI, calculated using Stata 17.0 (Stata Corp, College Station, TX, USA). Acute MI was adjudicated by 2 cardiologists using the Third Universal Definition of MI,[4] which was applicable at the time of the study. A third cardiologist was involved in case of disagreements. Data on MI and deaths during the subsequent 90 days were obtained from the Norwegian Cardiovascular Disease Registry.[3] Study participation was based on written informed consent, and the OUT-ACS study was approved by the Regional Ethics Committee and Oslo University Hospital Information Security and Privacy Office.[3]

Key Words: acute coronary syndrome ■ acute myocardial infarction ■ chest pain ■ outpatient ■ troponin

Correspondence to: Tonje R. Johannessen, MD, Department of General Practice, Institute of Health and Society, University of Oslo, 1130 Blindern, NO - 0318 Oslo, Norway. Email: t.r.johannessen@medisin.uio.no

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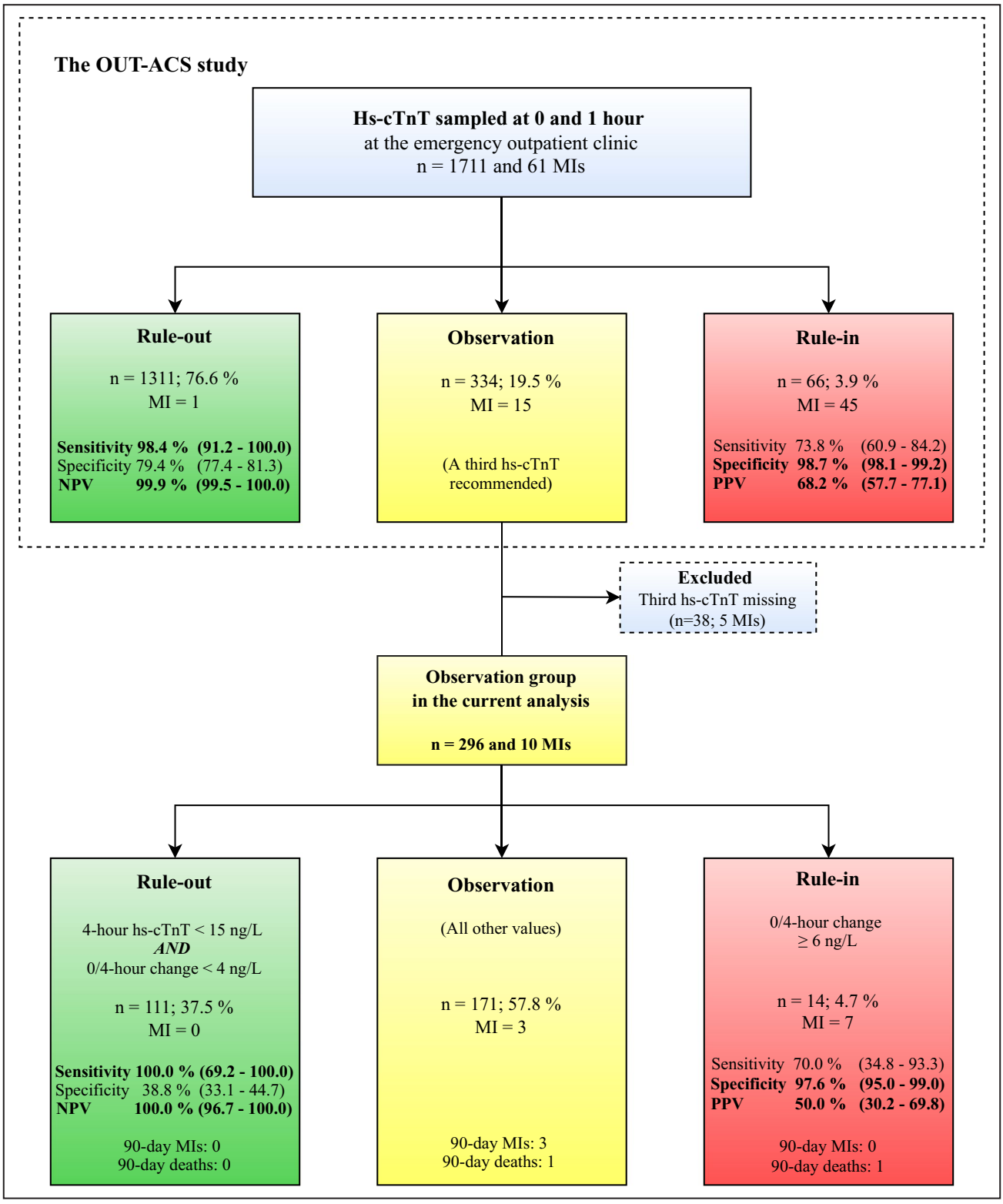

Figure. Diagnostic performance of the novel observation group criteria in a low-risk population.
The suggested hs-cTnT criteria for the observation group[2] were applied with a 0/4-hour interval. Results from the main OUT-ACS publication[3] are presented in the upper delineated panel. The corresponding 95% CIs are reported in parentheses. OUT-ACS indicates One-hour Troponin in a Low-Prevalence Population of Acute Coronary Syndrome; hs-cTnT indicates high-sensitivity cardiac troponin T; MI, myocardial infarction; NPV, negative predictive value; and PPV, positive predictive value.

In the OUT-ACS study, 334 of 1711 (19.5%) patients were assigned to the observation group (median age 72 years [IQR, 62–83]; 44.9% were female) by the ESC 0/1-hour algorithm.[3] Among them, 38 were excluded because of a missing 4-hour hs-cTnT measurement. Hence, this subanalysis encompasses 296 patients in the observation group, including 10 with an MI (Figure). The median 0/4-hour interval was 4.33 hours (interquartile range, 4.08–4.84). Applying the proposed thresholds,[2] 111/296 (37.5%) were assigned towards the rule-out group (Figure). The corresponding safety metrics sensitivity and negative predictive value were both 100.0%, with 95% CI, (69.2–100.0) and (96.7–100.0), respectively. None in the rule-out group experienced an MI or died during the following 90 days. Among the 14 patients triaged towards rule-in, 7 were diagnosed with an MI (specificity 97.6% [95% CI, 95.0–99.0] and positive predictive value 50.0% [95% CI, 30.2–69.8]). With only 171/1711 remaining in the observation group, the overall efficacy of the 0/1-hour algorithm increased to 90%.

High rule-out safety and increased overall efficacy were demonstrated by applying the newly suggested thresholds for the 0/1-hour observation group. Compared with Lopez-Ayala et al, the broader sampling interval between the measurements (0/4-hour) may have contributed to more patients being triaged upwards (from *rule-out* to *observation* and from *observation* to *rule-in*), thus increasing safety. Noticeably, the suggested 0/3-hour rule-in delta (≥6 ng/L)[2] is smaller than the delta validated for the ESC 0/2-hour hs-cTnT rule-in algorithm (≥10 ng/L)[1] Applied in a low-prevalence setting using a 4-hour window, the positive predictive value was lower than in the validation cohort (ie, 50.0% and 78.4%, respectively).[2] However, our results are limited by few events and high imprecision, as visualized by the broad CIs. Nevertheless, the results are encouraging in terms of reducing the number of patients remaining in the observation group. Compared with the rule-out group, patients in the observation group have higher age and cardiovascular risk.[1–3,5] We, therefore, believe it is advisable to consult a cardiologist for the remaining 10% in the observation group, either for direct hospital transfer or for a cardiac outpatient consultation. Because a safe MI rule-out strategy is essential in the outpatient setting, our results may illustrate the potential benefits of the observation group criteria if the ESC 0/1-hour algorithm is considered for future implementation in a low-risk setting. A larger study further exploring these findings is needed.

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Affiliations

Department of General Practice, University of Oslo, Norway (T.R.J., O.M.V.); Oslo Accident and Emergency Outpatient Clinic, City of Oslo Health Agency, Oslo, Norway (T.R.J., O.M.V.); Department of Cardiology, Oslo University Hospital Ullevaal, Oslo, Norway (S.H., D.A.); and Institute of Clinical Medicine, University of OsloNorway, (S.H., D.A.).

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III

BMJ Open

Comparison of a single high-sensitivity cardiac troponin T measurement with the HEART score for rapid rule-out of acute myocardial infarction in a primary care emergency setting: a cohort study

Tonje R Johannessen ,[1,2] Dan Atar ,[3,4] Odd Martin Vallersnes ,[1,2] Anne Cecilie K Larstorp ,[4,5] Ibrahimu Mdala ,[1] Sigrun Halvorsen [3,4]

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For numbered affiliations see end of article.

Correspondence to
Dr Tonje R Johannessen; t.r.johannessen@medisin.uio.no

ABSTRACT

Objective This study aims to compare the rule-out safety of a single high-sensitivity cardiac troponin T (hs-cTnT) with the History, ECG, Age, Risk factors and Troponin (HEART) score in a low-prevalence primary care setting of acute myocardial infarction (AMI).

Participants Patients with non-specific symptoms suggestive of AMI were consecutively enroled at a primary care emergency clinic in Oslo, Norway from November 2016 to October 2018.

Methods After initial assessment by a general practitioner, hs-cTnT samples were drawn. AMI was ruled-out by a single hs-cTnT <5 ng/L measured ≥3 hours after symptom onset. The HEART score was calculated retrospectively; a score ≤3 of 10 points was considered low risk. We also calculated a modified HEART score using more sensitive hs-cTnT thresholds. The primary outcome was the diagnostic performance for the rule-out of AMI at the index event; the secondary the composite of AMI or all-cause death at 90 days.

Results Among 1711 patients, 61 (3.6%) were diagnosed with AMI, and 569 (33.3%) patients were assigned to single rule-out (<5 ng/L). With no AMIs in this group, the negative predictive value (NPV) and sensitivity were both 100.0% (95% CI 99.4% to 100.0% and 94.1% to 100.0%, respectively), and the specificity 34.5% (32.2% to 36.8%). The original HEART score triaged more patients as low risk (n=871), but missed five AMIs (NPV 99.4% (98.7% to 99.8%); sensitivity 91.8% (81.9% to 97.3%) and specificity 52.5% (50.0% to 54.9%)). The modified HEART score increased the low-risk sensitivity to 98.4% (91.2% to 100.0%), with specificity 38.7% (36.3% to 41.1%). The 90-day incidence of AMI or death in the single rule-out and the original and modified low-risk HEART groups were 0.0%, 0.7%, and 0.2%, respectively.

Conclusion In a primary care emergency setting, a single hs-cTnT strategy was superior to the HEART score in ruling out AMI. This rapid and safe approach may enhance the assessment of patients with chest pain outside of hospitals.

Trial registration number NCT02983123.

Strengths and limitations of this study

- The diagnostic ability to rule-out acute myocardial infarction by a single high-sensitivity cardiac troponin T was investigated and compared with the History, ECG, Age, Risk factors and Troponin (HEART) score in a primary care population.
- The observational cohort comprised a low-risk population enroled in a primary care emergency setting with few missing data.
- The study was embedded in the daily routine at the clinic, reducing bias and increasing the internal validity of the results.
- The study may not be adequately powered, as the total number of events was low.
- The HEART score was calculated retrospectively.

INTRODUCTION

Non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is an important differential diagnosis in patients presenting with acute chest pain in primary care.[1 2] Patients with chest pain or other symptoms suggestive of NSTE-ACS are often admitted to hospitals for further examination due to limited reliable diagnostic decision tools.[3–5]

The last decade has seen an increased focus on the diagnostic assessment with troponins outside of hospitals. Point-of-care (POC) troponin assays, used in general practice[6 7] or by emergency medical services (EMS),[8 9] are useful in identifying high-risk patients. Still, they may not be sufficiently safe to rule-out acute myocardial infarction (AMI).[9 10] The History, ECG, Age, Risk factors and Troponin (HEART) score,[11 12] initially developed for the emergency departments (EDs), has proven to be a valuable decision aid for the EMS, identifying low-risk and high-risk patients in the prehospital setting.[13 14] The diagnostic

parameters of the HEART score were improved when the conventional troponin assay was replaced with a high-sensitivity cardiac troponin (hs-cTn) assay.[15 16] In addition, high diagnostic performance has recently been demonstrated for novel hs-cTn POC assays in hospital cohorts, but these are not yet validated for primary care.[17 18] Therefore, a strategy that safely excludes AMI outside the hospital ED is still needed.[10 14]

We recently found a high rule-out safety for AMI in a primary care emergency setting using the European Society of Cardiology's (ESC) 0/1 hour algorithm for hs-cTnT.[19] As serial hs-cTnT measurements represent a logistic challenge in many primary care settings,[20] it was of interest to investigate the diagnostic and prognostic performance of a single hs-cTnT measurement. For the hospital setting, high rule-out safety has been demonstrated for an undetectable (<5 ng/L) hs-cTn measurement in patients presenting to the ED more than 3 hours after symptom onset.[21 22] However, evidence of the safety of a single hs-cTnT rule-out approach remains sparse for the primary care setting. Further, to the best of our knowledge, the single hs-cTnT rule-out approach has not yet been validated and compared with the HEART score in a primary care emergency setting, where patients have a low pretest probability for acute coronary syndrome (ACS).

The aim of this study was, therefore, to investigate whether the single hs-cTnT strategy was safe to rule-out AMI in patients presenting with non-specific symptoms in a primary care emergency setting, and compare it with the HEART score.

METHODS

Study design and population

This study was a planned secondary analysis of the prospective, observational One hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome (OUT-ACS) study,[19] conducted from November 2016 to October 2018 at the Oslo Accident and Emergency Outpatient Clinic (OAEOC); the main primary care emergency clinic in Oslo, Norway.

The OAEOC is staffed by general practitioners (GPs) and nurses and offers serial hs-cTnT sampling to rule-out AMI at the OAEOC observation unit 24 hours a day, all year. Patients (18 years and older) with acute non-traumatic chest pain or other non-specific symptoms admitted at the clinic for hs-cTnT, were consecutively enroled. Patients with potential atypical AMI presentation, for example, acute dyspnoea, acute fatigue or diaphoresis, were also eligible. In cases of a highly suspected ACS, including ST-segment elevation myocardial infarction, patients were directly hospitalised and not available for study enrolment. Patients with chronic kidney disease (estimated glomerular filtration rate of <30 mL/min/1.73 m^2) were excluded (figure 1). Further details regarding the study setting and participants have been described previously.[19]

Clinical assessment and measurement of hs-cTnT

Medical history, physical examination, pulse oximetry and a 12-lead ECG were obtained by the GP for all patients presenting to the OAEOC with symptoms suggestive of ACS. If indicated, chest X-ray and capillary blood measurements (C-reactive protein, haemoglobin and blood glucose) could be performed. The standard clinical approach at the OAEOC offers hs-cTnT measurements to patients considered in need of further tests to rule-out AMI, but without the need of immediate hospitalisation (online supplemental table 1). The decision is left to the discretion of the treating GP.

Blood samples for the analyses of hs-cTnT were drawn from all included patients at 0, 1 and 4 hours. Only the first hs-cTnT was considered in this subanalysis. Presenting symptoms, risk factors and time variables were registered at a predefined study form (online supplemental table 2). The upper reference limit (URL) for hs-cTnT (Elecsys Troponin T hs STAT assay, Roche Diagnostics, Switzerland) was 14 ng/L with a coefficient of variation of <10%, limit of detection (LoD) of 5 ng/L and limit of blank of 3 ng/L (additional details in the online supplemental appendix).[23]

Single hs-cTnT strategy

According to the ESC 0/1 hour algorithm for hs-cTnT,[2] the single hs-cTnT rule-out strategy applies for patients where the first hs-cTnT is <5 ng/L, sampled 3 hours or more after symptom onset. A patient is triaged towards direct rule-in if the initial hs-cTnT is ≥52 ng/L. Patients with values between these thresholds remain in the observation group in need of repeated hs-cTnT measurements. Following the guidelines, the troponin result should always be interpreted in conjunction with the clinical assessment and the ECG.[2]

HEART score

The original HEART score stratifies the risk for a major adverse cardiac event (MACE) during the first 6 weeks following presentation to an ED with symptoms suggestive of ACS.[11 12] Each of the five components (History, ECG, Age, Risk factors and Troponin) provide a score of 0–2 points (table 1). Patients with a HEART score of 0–3 points (low risk) are considered suitable for rapid discharge, a score of 4–6 points (intermediate risk) signifies the need of further observation and patients with 7–10 points (high risk) are recommended early invasive strategies.[11 12]

In this study, the subjective History component was based on the presenting composition of non-typical and typical symptoms of ACS,[11] as defined by the study investigators (online supplemental table 3). Only typical elements scored 2 points, a combination of typical and non-typical scored 1 point and only non-typical scored 0 points. The ECG component was calculated using the ECG obtained and interpreted by the GP at presentation. ECG with ischaemic ST-segment depression scored 2 points, non-specific changes in either the ST-segment,

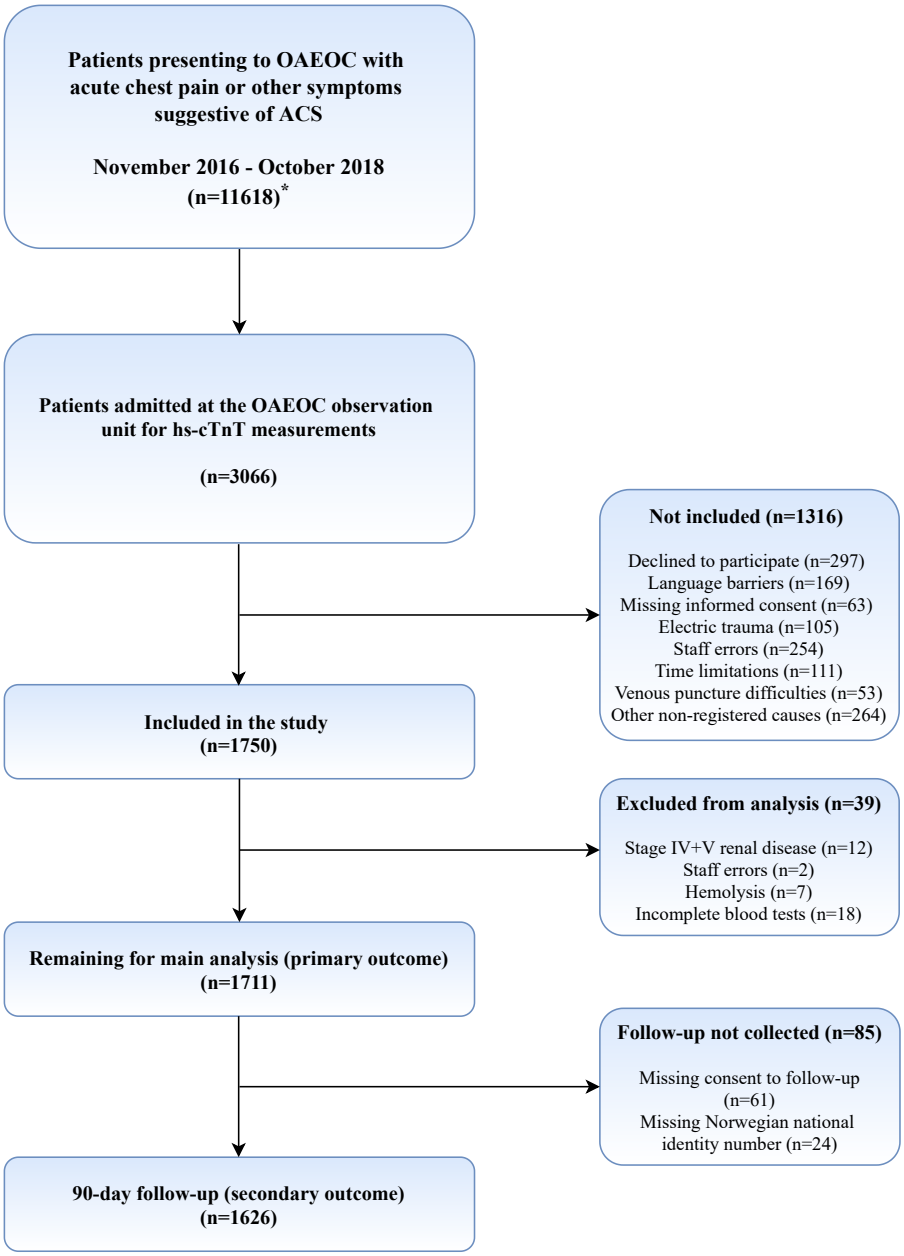

Figure 1 Patient flow chart. Study enrolment at the primary care emergency clinic during the OUT-ACS study. *Critically ill patients are brought directly to hospital by the ambulance services. ACS, acute coronary syndrome; hs-cTnT, high-sensitivity cardiac troponin T; OAEOC, Oslo Accident and Emergency Outpatient Clinic; OUT-ACS, One hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome.

T-inversions, Q-waves or left/right bundle branch block of unknown clinical significance scored 1 point and an ECG interpreted as normal scored 0 points. Among the Risk factors, obesity (BMI >30) was not systematically recorded. For the Troponin component, the first hs-cTnT sampled at the clinic was used, regardless of the time interval from symptom onset to blood draw. Hs-cTnT ≤14 ng/L scored 0 points, hs-cTnT 15–41 ng/L 1 point and hs-cTnT ≥42 ng/L 2 points.

Modified HEART score

Since the single hs-cTnT rule-out strategy is based on hs-cTnT <5 ng/L and the original HEART score operates with hs-cTnT ≤14 ng/L as the lowest cut-off value, we modified the HEART score by altering the Troponin component to more sensitive hs-cTnT thresholds. Inspired by a recent published study using a modified HEART score,[24] a hs-cTnT <5 ng/L resulted in 0 points, 1 point for hs-cTnT between LoD and URL (5–14 ng/L), and 2 points for hs-cTnT >URL (>14 ng/L). The four first components (History, ECG, Age and Risk factors) remained unchanged.

Table 1 The original HEART score for patients with chest pain

History	Highly suspicious for ACS	2 points
	Moderately suspicious	1 point
	Slightly or not suspicious	0 points
ECG	Significant ST-depression	2 points
	Non-specific changes*	1 point
	Normal	0 points
Age	≥65 years	2 points
	46–64 years	1 point
	≤45 years	0 points
Risk factors†	≥3 risk factors or previous CAD	2 points
	One or two risk factors	1 point
	No risk factors	0 points
Troponin	≥3 × URL	2 points
	>1 to <3 × URL	1 point
	≤URL	0 points
Total	Low risk	0–3 points
	Intermediate risk	4–6 points
	High risk	7–10 points

Reproduced after the original HEART score[12] with permission from the authors.
*Left bundle branch block, left ventricular hypertrophy, repolarisation changes, pacemaker.
† Risk factors: hypertension, diabetes mellitus, current or history of smoking, hypercholesterolaemia, obesity (BMI >30 kg/m²) and family history of coronary artery disease.
ACS, acute coronary syndrome; BMI, body mass index; ECG, electrocardiogram; HEART, History, ECG, Age, Risk factors and Troponin; hs-cTnT, high-sensitivity cardiac troponin T; URL, upper reference limit.

The HEART scores were applied and calculated retrospectively. During the HEART score assessments, the study investigators were blinded to patient identity, final diagnosis and other information not part of the HEART calculations.

Outcome measures

The primary outcome was the diagnostic performance for the rule-out of AMI at the index event for the three different strategies (single hs-cTnT, original and the modified HEART score).

The composite of AMI or all-cause death at 90 days was the secondary outcome, as a measure of the prognostic performance of the three different rule-out strategies. The 90-day follow-up data were collected through linkage with the Norwegian Cardiovascular Disease Registry[25] as previously described.[19]

Final adjudication of AMI

For patients discharged home from the OAEOC, the final diagnosis was made by the treating GP based on all available information, including clinical assessment, repeated ECGs, 0, 1 and 4 hours hs-cTnT and additional lab analyses. The absence of a 0–4 hour hs-cTnT delta in accordance with the *Third Universal Definition of Myocardial Infarction*(1) served as a reference standard for ruling out AMI, as previously specified.[19] For the hospitalised patients, the final diagnosis was also based on the *Third Universal Definition of Myocardial Infarction*(1) and adjudicated by two independent cardiologists with access to all collected data from the index episode, including data from the OAEOC and hospital discharge documents. In 19/227 of the cases, a third cardiologist was involved in solving disagreements.

Statistical analysis

Numbers were presented as frequencies and percentages, means and standard deviations (SDs), or medians and IQRs, as appropriate. Comparisons of baseline characteristics between the single rule-out approach and the two low-risk HEART groups were made using the Pearson χ^2 test or the Fisher exact test for categorical variables, whereas the Kruskal-Wallis test was used when comparing continuous variables. We used two-sided hypothesis testing with a significance level set at α=0.05. The sample size calculation for the main study has been described previously.[19]

The rule-out performance of the three strategies were assessed by calculating sensitivity and the negative predictive values (NPVs), with corresponding 95% CIs (online supplemental table 4). In addition, the specificity and positive predictive values (PPVs) were estimated to assess the accuracy of the rule-in and the high-risk HEART groups, and likelihood ratios were estimated for all categories. The overall diagnostic performance of the three strategies was illustrated by the area under the ROC (receiver operating characteristics) curve (AUC). To visualise the large intermediate groups in need of further testing, we used the predefined cut-off values for each group. The AUCs were compared using the 95% CIs and the McNemar's test with the single hs-cTnT strategy as the referent.

IBM SPSS V.26.0 (SPSS, IBM, Armonk, New York, USA), and Stata V.16.0 (Stata Corp, College Station, Texas, USA.) were used in the calculations.

Ethics

The study was approved by the Regional Committee North for Medical and Health Research Ethics (no. 2016/1241) and the Oslo University Hospital Information Security and Privacy Office (no. 2016/13308). Participation was based on written, informed consent. The OUT-ACS study is registered at ClinicalTrials.gov (NCT02983123) and was conducted in accordance with the STARD (Standards for Reporting Diagnostic Accuracy Studies) guidelines.[26]

Patient and public involvement

The patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research. However, we have involved users from our formalised 'patient-contributors-to-research' group established by the Medical Department of Oslo University Hospital. We received clear indications that a fast and reliable rule-out of AMI in patients with chest pain has a high

priority among users (patients). These inputs helped in the design and interpretation of the study.

RESULTS

Study participants

During the OUT-ACS study enrolment period (November 2016–October 2018), 3066 patients were transferred to the OAEOC observation unit for hs-cTnT measurements, with 1750 patients included in the study (figure 1). Thirty-nine patients were excluded from the primary analysis (figure 1), yielding 1711 participants.[19] For 1529 (89.4%) of the patients, the first hs-cTnT was measured 3 hours or more after symptom onset (table 2). The median time from OAEOC presentation to first blood sample was 136 min (IQR 100–194).

Triage and baseline characteristics

After a single hs-cTnT measurement, 569 (33.3%) patients were assigned towards rule-out, 1098 (64.2%) to the observation group in need of further hs-cTnT measurements, while 44 (2.6%) patients were assigned towards rule-in. The original HEART score categorised 871 (50.9%) of 1711 patients as low risk, 760 (44.4%) as intermediate risk and 80 (4.7%) as high risk. By applying the modified HEART score with more sensitive troponin thresholds, 639 (37.3%) patients were triaged towards low risk, 876 (51.2%) as intermediate risk and 196 (11.5%) towards the high-risk group. Baseline characteristics of the single hs-cTnT rule-out and the low-risk HEART groups are shown in table 2.

Diagnostic and prognostic performance

AMI was diagnosed in 61 (3.6%) of 1711 patients at the index observation. Among the 569 patients directly ruled-out by the single hs-cTnT strategy, there were no incidents of AMI during the index episode. Hence, this approach had a rule-out sensitivity and NPV of 100.0% (figure 2 and table 3). Thirty-two (5.6%) of the direct rule-out patients were hospitalised for other non-cardiac causes, whereas the remaining patients were discharged home (online supplemental table 5).

The HEART score risk-stratified more patients towards low risk (n=871) but missed five AMIs (0.6%) during the index episode (details in online supplemental table 6). This gives a sensitivity of 91.8% (95% CI 81.9% to 97.3%) and NPV 99.4% (95% CI 98.7% to 99.8%, figure 2 and table 3). By applying the modified HEART score, only one patient with AMI (0.2%) was misclassified as low risk (n=639), improving sensitivity to 98.4% (95% CI 91.2% to 100.0%) and NPV to 99.8% (95% CI 98.9% to 100.0%). The number of low-risk patients in need of hospitalisation was 66 (7.6%) and 40 (6.3%) in the original and modified HEART groups (online supplemental table 5).

The PPV in the single rule-in and the original and modified high-risk HEART scores were 77.3% (95% CI 63.8% to 86.8%), 22.5% (95% CI 15.5% to 31.5%) and 10.7% (95% CI 7.6% to 14.9%), respectively (table 3). In the single hs-cTnT rule-out group, one patient was considered high risk by both HEART scores (online supplemental table 7). The original and modified HEART score means were 3.6 (SD 1.6) and 4.2 (SD 1.8) points, respectively (online supplemental table 8).

The corresponding overall diagnostic performance, illustrated by the AUC for the three different strategies, was 0.85 (95% CI 0.81 to 0.89), 0.77 (95% CI 0.73 to 0.82), and 0.74 (95% CI 0.70 to 0.78) (figure 3). Using McNemar's two-sided test, the results demonstrated that the single hs-cTnT strategy performed better than the original and modified HEART scores ($p<0.01$).

The prognostic performance of the three rule-out approaches, as demonstrated by the composite of AMI or all-cause death at 90 days, was 0.0% for the single rule-out strategy and 0.7% and 0.2% for the original and modified low-risk HEART groups (figure 2 and table 3).

DISCUSSION

In the current secondary analysis of the OUT-ACS study, the single rule-out approach (hs-cTnT <5 ng/L in patients presenting with symptom onset ≥3 hours), had an excellent diagnostic and prognostic safety in a primary care emergency setting, with one-third of the participants triaged towards direct rule-out. Both the sensitivity and the NPV were 100.0%, with no incidents of AMI or death for the following 90 days.

The original low-risk HEART score was less safe than the single rule-out strategy. Even though more patients were triaged towards low risk and early discharge, this entailed missing five AMIs, which we consider unacceptable. The sensitivity and the NPV in the low-risk HEART group improved with the modified HEART score, with only one missing AMI. On the other hand, the modified high-risk group had more false positives than the single rule-in group, which would have contributed to more hospitalisations. Similar data were found in an ED cohort, where patients with a modified HEART score >3 points had a lower risk for MACE than the original HEART score using a conventional troponin assay.[27] All aspects considered, in our study, the simple single troponin approach was superior to both HEART scores when applied in a primary care emergency setting. In a recent hospital cohort, similar rule-out sensitivity was found after 6 weeks for the low-risk HEART group and the hs-cTnT <LoD strategy.[28] Although 6-week MACE was not reported in our study, several studies from the ED setting are in line with our results. One study demonstrated higher rule-out sensitivity for the hs-cTnI-only (<3 ng/L) strategy when compared with the modified low-risk HEART group.[24] In a 1 year low-risk cohort, the safety of the hs-cTnT <LoD strategy was not improved by the HEART score in late presenters (chest pain onset ≥3 hours).[29] And even though a direct comparison is not possible, our findings are somewhat consistent with a

Table 2 Baseline characteristics

	OUT-ACS study, total[19] n=1711 (100.0%)	Single hs-cTnT, rule-out group n=569 (33.3%)	Original HEART, low-risk group n=871 (50.9%)	Modified HEART, low-risk group n=639 (37.3%)	P value
Female sex, n (%)	816 (47.7)	340 (59.8)	384 (44.1)	306 (47.9)	<0.001
Age, median (IQR)	56 (45–68)	47 (38–56)	46 (38–55)	43 (35–51)	<0.001
Risk factors for CVD, n (%)					
Current/history of smoking	449 (26.2)	156 (27.4)	214 (24.6)	141 (22.1)	0.098
Previous coronary artery disease	317 (18.5)	40 (7.0)	9 (1.0)	5 (0.8)	<0.001
Hypertension	448 (26.2)	83 (14.6)	92 (10.6)	48 (7.5)	<0.001
Dyslipidaemia	422 (24.7)	94 (16.5)	78 (9.0)	50 (7.8)	<0.001
Other CVD*	288 (16.8)	51 (9.0)	71 (8.2)	47 (7.4)	0.59
Diabetes mellitus	171 (10.0)	44 (7.7)	42 (4.8)	21 (3.3)	0.002
COPD	80 (4.7)	7 (1.2)	10 (1.1)	5 (0.8)	0.71
Family history of CVD	691 (40.4)	253 (44.5)	333 (38.2)	245 (38.3)	0.037
Presenting acute symptoms, n (%)					
Chest pain	1486 (86.8)	525 (92.3)	791 (90.8)	588 (92.0)	0.56
Constricting	1239 (72.4)	439 (77.2)	637 (73.1)	475 (74.3)	0.23
Sharp	404 (23.6)	168 (29.5)	263 (30.2)	201 (31.5)	0.76
Tearing	64 (3.7)	19 (3.3)	39 (4.5)	30 (4.7)	0.45
Burning	208 (12.2)	81 (14.2)	127 (14.6)	99 (15.5)	0.81
Respiratory dependent	302 (17.7)	126 (22.1)	215 (24.7)	164 (25.7)	0.34
Chest wall tenderness	205 (12.0)	80 (14.1)	135 (15.5)	104 (16.3)	0.56
Movement dependent	219 (12.8)	93 (16.3)	146 (16.8)	115 (18.0)	0.72
Other pain (abdomen, back or neck)	48 (2.8)	15 (2.6)	15 (1.7)	10 (1.6)	0.34
No pain	177 (10.3)	29 (5.1)	65 (7.5)	41 (6.4)	0.20
Pain radiation	972 (56.8)	369 (64.9)	534 (61.3)	401 (62.8)	0.40
Dyspnoea	901 (52.7)	327 (57.5)	489 (56.1)	369 (57.7)	0.80
Palpitations	637 (37.2)	232 (40.8)	367 (42.1)	278 (43.5)	0.63
Syncope/presyncope	460 (26.9)	155 (27.2)	259 (29.7)	189 (29.6)	0.55
Acute fatigue	571 (33.4)	188 (33.0)	295 (33.9)	223 (34.9)	0.79
Nausea/vomiting	732 (42.8)	251 (44.1)	377 (43.3)	285 (44.6)	0.87
Diaphoresis	561 (32.8)	184 (32.3)	310 (35.6)	221 (34.6)	0.44
Symptom onset to first hs-cTnT, n (%)					
<3 hours	182 (10.6)	0 (0.0)	114 (13.1)	80 (12.5)	<0.001
3 to <6 hours	609 (35.6)	225 (39.5)	316 (36.3)	231 (36.2)	0.38
6 to <12 hours	409 (23.9)	148 (26.0)	186 (21.4)	137 (21.4)	0.081
12 to <24 hours	224 (13.1)	82 (14.4)	104 (11.9)	76 (11.9)	0.31
≥24 hours	287 (16.8)	114 (20.0)	151 (17.3)	115 (18.0)	0.42

All values are presented as n (%) and median (IQR). P values are calculated for comparisons across all three groups (single rule-out and the two low-risk HEART groups). The Pearson χ^2 test or the Fisher exact test were used for the categorical variables and the Kruskal-Wallis test for the continuous variables.
*Includes atrial fibrillation, other arrhythmias, cardiomyopathies, cerebral stroke, heart failure or valvular disease.
COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; HEART, History, ECG, Age, Risk factors and Troponin; hs-cTnT, high-sensitivity cardiac troponin T; OAEOC, Oslo Accident and Emergency Outpatient Clinic.

previous study from the High-STEACS (High-Sensitivity Troponin in the Evaluation of Patients with Acute Coronary Syndrome) investigators, where clinical risk scores did not enhance the diagnostic rule-out performance when lower cut-off values for high-sensitivity cardiac troponin I (hs-cTnI) were applied.[30]

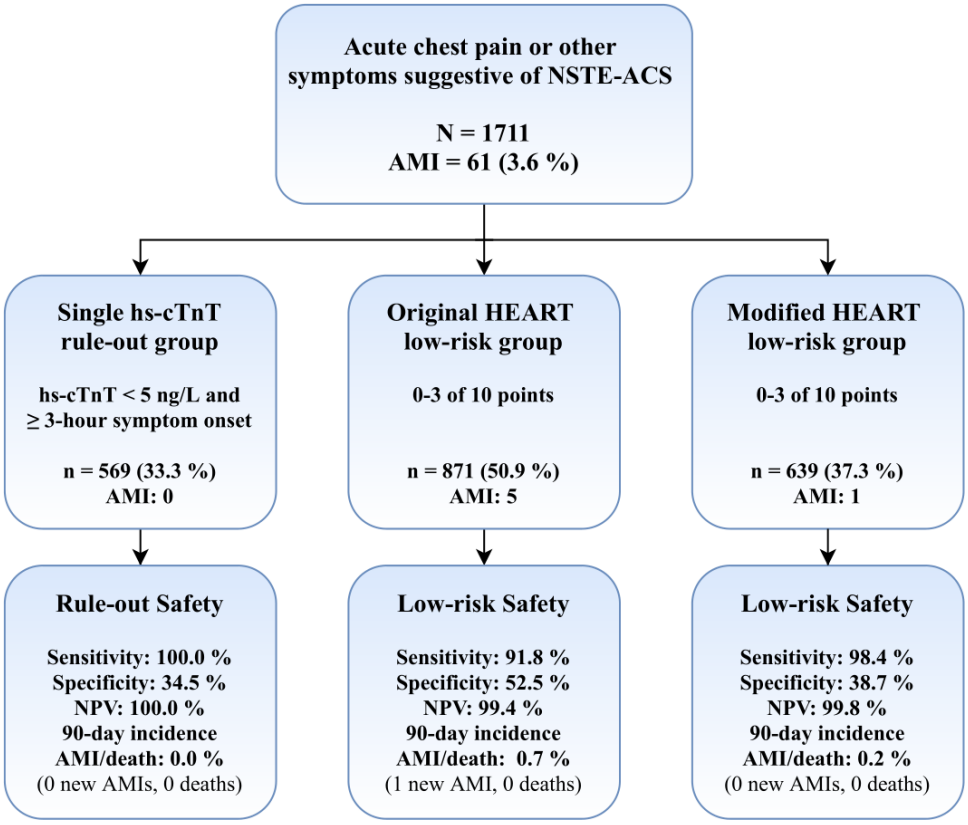

Figure 2 The diagnostic and prognostic safety of the three rule-out strategies at the primary care emergency clinic. AMI, acute myocardial infarction; HEART, History, ECG, Age, Risk factors and Troponin; hs-cTnT, high-sensitivity cardiac troponin T; NPV, negative predictive value; NSTE-ACS, non-ST-segment elevation acute coronary syndrome.

Our evaluation of the HEART score outside of hospitals differs from the previous EMS studies[13 14] by not including patients with a highly suspected ACS. This is reflected by the low mean of both the original and the modified HEART scores (online supplemental table 8). Our study population comprised patients with low-to-intermediate risk in need of additional tests for a safe AMI rule-out, but not considered in urgent need of hospitalisation. This is also apparent from the delay in time to first hs-cTnT measurement, as the low-risk patients were rarely prioritised for rapid initial assessment. Our study also included patients with atypical symptoms such as acute fatigue, diaphoresis and acute dyspnoea without chest pain. The study was embedded in the regular clinical practice at the primary care clinic, which might increase both the external and internal validity of the results.

A recent cost–benefit analysis from the Netherlands demonstrated that patients categorised as low-risk HEART incurred high hospital expenses with limited benefits for each patient.[31] Performing the initial hs-cTn workup of low-risk patients outside of hospitals might reduce unnecessary hospital admissions, healthcare utilisation and costs. Further implementation and cost–benefit studies in primary care are warranted.

Prehospital studies among paramedics have demonstrated that POC troponin assays should not be used to rule-out AMI due to low sensitivity.[9 10] However, the newer POC devices might perform better if tested at primary care emergency clinics, where they would be less subject to movement and temperature alterations. The novel hs-cTnI POC assays with diagnostic performance comparable to central lab assays may also show themselves valuable decision aids in primary care in the future.[17 18]

Some limitations need to be addressed: first, only 61 (3.6%) of 1711 patients in the OUT-ACS study were diagnosed with an AMI. Hence, the calculations on the diagnostic performance are based on few events and should be interpreted with care.

Second, the AMI diagnoses might be subject to verification bias, as the adjudication committee only evaluated hospitalised patients. For all patients discharged home, the final diagnosis was made by the discharging GP at the OAEOC. It would not have been ethical or feasible to admit all 1711 patients to the hospital for a similar diagnostic workup.

Third, there is no current consensus on how the subjective History component in the HEART score should be assessed.[32] We based this component on the presenting symptoms registered at index and retrospectively categorised them as typical or non-typical for NSTE-ACS, as defined in online supplemental table 3.

Fourth, by assessing the HEART score retrospectively, the Risk factor 'obesity' was missing for all participants, as body mass index (BMI) was not systematically reported.

Table 3 Diagnostic and prognostic performance of the single hs-cTnT strategy and the two HEART scores

		Index episode		Diagnostic performance				Prognostic performance
N (%)	Classification	Total n=1711	AMI n=61	Sensitivity (95% CI)	Specificity (95% CI)	NPV or PPV (95% CI)	LR (95% CI)	n=1626 90-day AMI or death
Single hs-cTnT *	**Rule-out** *(<LoD)*	569 (33.3%)	0	100.0% (94.1% to 100.0%)	34.5% (32.2% to 36.8%)	NPV: 100% (99.4% to 100.0%)	LR–: 0.0	0/541 (0.0%)
	Observation	1098 (64.2%)	27	–	–	–	LR: 0.7 (0.5 to 0.9)	36/1042 (3.5%)
	Rule-in	44 (2.6%)	34	55.7% (42.5% to 68.5%)	99.4% (98.9% to 99.7%)	PPV: 77.3% (63.8% to 86.8%)	LR+: 92.0 (47.7 to 177.4)	34/43 (79.1%)
The original HEART score †	**Low risk** *(0–3 points)*	871 (50.9%)	5	91.8% (81.9% to 97.3%)	52.5% (50.0% to 54.9%)	NPV: 99.4% (98.7% to 99.8%)	LR–: 0.2 (0.1 to 0.4)	6/829 (0.7%)
	Intermediate risk *(4–6 points)*	760 (44.4%)	38	–	–	–	LR: 1.4 (1.2 to 1.7)	43/722 (6.0%)
	High risk *(7–10 points)*	80 (4.7%)	18	29.5% (18.5% to 42.6%)	96.2% (95.2% to 97.1%)	PPV: 22.5% (15.5% to 31.5%)	LR+: 7.9 (5.0 to 12.4)	21/75 (28.0%)
The modified HEART score ‡	**Low risk** *(0–3 points)*	639 (37.3%)	1	98.4% (91.2% to 100.0%)	38.7% (36.3% to 41.1%)	NPV: 99.8% (98.9% to 100.0%)	LR–: 0.04 (0.0 to 0.3)	1/611 (0.2%)
	Intermediate risk *(4–6 points)*	876 (51.2%)	39	–	–	–	LR: 1.3 (1.0 to 1.5)	42/827 (5.1%)
	High risk *(7–10 points)*	196 (11.5%)	21	34.4% (22.7% to 47.7%)	89.4% (87.8% to 90.8%)	PPV: 10.7% (7.6% to 14.9%)	LR+: 3.3 (2.2 to 4.7)	27/188 (14.4%)

The three different diagnostic strategies applied in the study population (n=1711). The 2×2 tables used in the calculations of the diagnostic performance are listed in online supplemental table 4.
*Single hs-cTnT strategy with hs-cTnT criteria—<LoD rule-out: hs-cTnT <5 ng/L and ≥3 hours symptom onset; single rule-in: hs-cTnT ≥52 ng/L.[2]
†The original HEART score with hs-cTnT criteria—0 point: ≤14 ng/L, 1 point: 15–41 ng/L and 2 points: ≥42 ng/L.[11 12]
‡The modified HEART score with hs-cTnT criteria—0 point: <5 ng/L, 1 point: 5–14 ng/L and 2 points: >14 ng/L.
AMI, acute myocardial infarction; HEART, History, ECG, Age, Risk factors and Troponin score; hs-cTnT, high-sensitivity cardiac troponin T; LoD, limit of detection; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

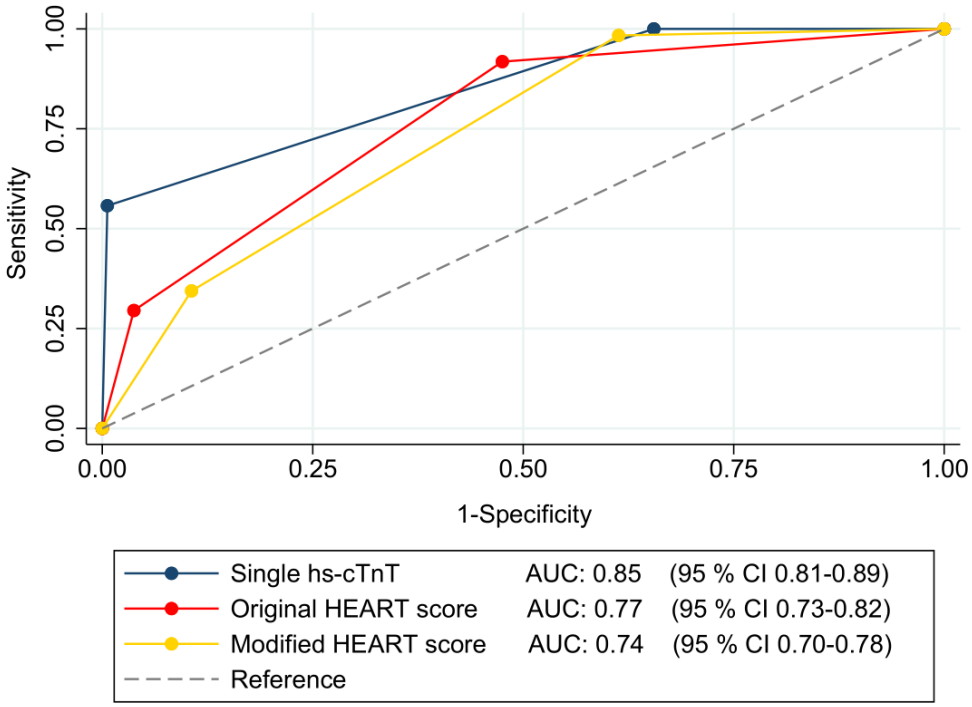

Figure 3 The overall diagnostic performance of the single hs-cTnT strategy, the original HEART score and the modified HEART score were illustrated by the AUC, which was achieved using the predefined cut-off values for the three different strategies. The single hs-cTnT rule-in and high-risk HEART groups are shown in the lower-left corner, the single hs-cTnT rule-out and low-risk HEART groups in the upper right. The large intermediate groups represent the patients in need of further tests. AUC, area under the curve; HEART, History, ECG, Age, Risk factors and Troponin; hs-cTnT, high-sensitivity cardiac troponin T.

Finally, the T component was based on the first hs-cTnT sample collected, regardless of symptom onset. Two of the five missed AMIs in the original low-risk HEART group had a symptom onset less than 3 hours before blood draw (online supplemental table 6). By using 3 hour onset as a prerequisite before rapid discharge, the diagnostic performance would have been improved. The onset of symptoms should, therefore, be taken into consideration if implemented in clinical practice.

In conclusion, when applying a hs-cTnT assay, the single hs-cTnT strategy (<5 ng/L with symptom onset ≥3 hours) was superior to the original HEART score in ruling out AMI in a primary care emergency setting. The rule-out safety of the HEART score was improved when lower troponin thresholds were used but at the cost of a low PPV. The single hs-cTnT strategy might have a great potential for simplifying and accelerating the triage of patients presenting with acute non-specific AMI symptoms in primary care, hence reducing unnecessary advanced testing, crowding in the EDs, and overall expenses.

Author affiliations
[1]Department of General Practice, University of Oslo, Oslo, Norway
[2]Department of Emergency General Practice, Oslo Accident and Emergency Outpatient Clinic, Oslo, Norway
[3]Department of Cardiolgy, Oslo University Hospital, Ullevaal, Oslo, Norway
[4]Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[5]Section of Cardiovascular and Renal Research, Oslo University Hospital, Ullevaal, Oslo, Norway

Twitter Tonje R Johannessen @tonjerj

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Contributors TRJ, OMV, DA and SH contributed in the conception and design of the study. TRJ supervised the data collection and collated the data. TRJ and IM did the statistical analyses and analysed the data with contributions from OMV, SH and DA. ACKL, DA and SH contributed in the interpretation of the laboratory results. TRJ drafted the manuscript, and all authors contributed in revising and approving the final version for publication.

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ORCID iDs
Tonje R Johannessen http://orcid.org/0000-0001-9368-1471
Dan Atar http://orcid.org/0000-0003-1513-8793
Odd Martin Vallersnes http://orcid.org/0000-0003-1213-392X
Anne Cecilie K Larstorp http://orcid.org/0000-0002-0223-9248
Ibrahimu Mdala http://orcid.org/0000-0002-5204-1934
Sigrun Halvorsen http://orcid.org/0000-0001-7561-7644

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ONLINE SUPPLEMENTARY APPENDIX

To the manuscript

Comparison of a single high-sensitivity cardiac Troponin T measurement with the HEART score for rapid rule-out of acute myocardial infarction in a primary care emergency setting: a cohort study

Tonje R. Johannessen, Dan Atar, Odd Martin Vallersnes, Anne Cecilie K. Larstorp, Ibrahimu Mdala, and Sigrun Halvorsen

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ONLINE TABLE 1 Selection of patients with chest pain or other symptoms suggestive of NSTE-ACS at the OAEOC

GP triage	**NSTE-ACS not suspected** = Other causes/disorders more likely	**NSTE-ACS mild to moderately suspected** = In need of further tests to rule-out AMI without urgent need of hospitalisation	**NSTE-ACS or STEMI highly suspected** = In need of urgent hospitalisation for more advanced testing/care
Examples	• Myalgia • Costochondritis • Tietze's syndrome • Stress • Anxiety • Panic disorder • Pulmonary infection • COPD • Pulmonary embolism • Gastric reflux • Gastritis • Gastric ulcer • Cholelithiasis • Acute pancreatitis	• Pain-free but mild to moderately suspected history/clinical presentation • Patients without classic cardiac chest pain, but concomitant symptoms of unknown origin consistent with possible CAD (e.g. single syncope, acute dyspnoea or acute fatigue) • Including the elderly, diabetics, and patients with several comorbidities	• History/clinical presentation highly suspicious *And/or* • Ongoing or recurrent cardiac-suspected chest pain *And/or* • Ischaemic suspected ECG (including significant ST-segment elevation/ depression or new LBBB) *And/or* • Haemodynamic instability *And/or* Respiratory distress
Further management	Home with/without treatment ***OR*** hospitalised due to other conditions	Admission at the OAEOCs observation unit for serial hs-cTnT measurements in order to rule-out AMI	Direct transfer to hospital by ambulance (usually within 20-60 minutes after OAEOC arrival)

AMI: acute myocardial infarction; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; GP: general practitioner; hs-cTnT: high-sensitivity cardiac troponin T; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; OAEOC: Oslo Accident and Emergency Outpatient Clinic; STEMI: ST-segment elevation myocardial infarction

ONLINE TABLE 2 Details in the predefined study form

Basics	• Norwegian personal identity number (later replaced by a study ID) • Sex and Age
Time variables (time/date)	• Onset of symptoms • Arrival at the OAEOC • Admission at the OAEOC observation unit • Hs-cTnT measurements • OAEOC discharge
Risk factors for cardiovascular disease	• Current or history of smoking last ten years • Diabetes mellitus • Chronic obstructive pulmonary disease • Previous history of CAD • Hypertension • Hypercholesterolemia • Other CVD (valvular disease, previous cerebral stroke, cardiomyopathies, atrial fibrillation other arrhythmias), • History of CAD in first-degree sibling <60 years of age

Presenting acute symptoms	• Chest pain
	  ○ Constricting
	  ○ Tearing
	  ○ Burning
	  ○ Sharp
	  ○ Respiratory-dependent
	  ○ Position-dependent
	  ○ Palpation-dependent
	• Pain radiation (arms, neck, jaws, upper abdomen, scapulae)
	• Acute dyspnoea
	• Acute fatigue
	• Syncope, pre-syncope
	• Observed or reported diaphoresis
	• Nausea or vomiting
	• Palpitations
	• Other pain: upper abdomen or upper back/scapulae only
	• No pain

ICD-10 discharge codes	• Given by GP responsible for OAEOC discharge
Further disposition after OAEOC discharge	• Home/no follow-up • Advised to contact regular GP • Referral to hospital outpatient clinic • Admitted at a municipality (primary care) short term facility • Left during observation • Admitted hospital • Direct transfer to the cath lab

CAD: coronary artery disease; CVD: cardiovascular disease; GP: general practitioner; hs-cTnT: high-sensitivity cardiac troponin T; ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision; OAEOC: Oslo Accident and Emergency Outpatient Clinic

Laboratory analysis

Venous blood samples were collected in serum tubes and stored locally at room temperature (approximately 20 °C) for a maximum of 30 minutes before centrifugation, then stored in a refrigerator before being sent to the laboratory every four hours, as per standard procedure at the primary care emergency clinic. Hs-cTnT was analysed at the Department of Medical Biochemistry at Oslo University Hospital Ullevaal on the Cobas 8000 e602 and later the Cobas 8000 e801 Module Analyzer using the Elecsys Troponin T hs STAT assay (Roche Diagnostics, Switzerland). The cTnT has a stability of 24 hours with storage at 2-8 °C,[1,2] and similar stability has previously been demonstrated for hs-cTnT samples stored under the conditions in our study.[3] EQA (external quality assessment) material from Noklus (Bergen, Norway) and Equalis (Equalis AB, Uppsala, Sweden) was regularly analysed at the central lab with good performance during the inclusion period. The coefficient of variation (CV) was 6 % at concentrations ≥ 20 ng/L and 10 % at concentrations < 20 ng/L.

ONLINE TABLE 3 The History component of the HEART score used in the OUT-ACS study

Non-typical elements for ACS	Typical elements for ACS
• Sharp or burning chest pain • Pain in the upper abdomen or upper back/scapulae only • Palpation, position or respiratory-dependent pain • Acute fatigue • Syncope/pre-syncope • Palpitations	• Constricting or tearing retrosternal chest pain • Radiation of pain to arms, neck or jaws • Diaphoresis (observed or reported) • Vomiting, nausea • Acute dyspnoea

Following the original HEART score,[4] the History is considered highly suspicious and given 2 points if only typical elements are reported, 1 point if the medical history contains a combination of both non-typical and typical elements, and 0 points if all elements in are considered non-typical.

The following classification of which elements are considered non-suspicious or suspicious are defined by the OUT-ACS study investigators in this table, based on symptoms reported at the initial examination.

ACS: acute coronary syndrome; HEART: History, ECG, Age, Risk factors and Troponin; OAEOC: Oslo Accident and Emergency Outpatient Clinic

ONLINE TABLE 4 Separate 2x2-tables used in the calculation of the diagnostic performance for the three different strategies

	Single hs-cTnT		Original HEART score		Modified HEART score	
	Rule-out group	**Rule-in group**	**Low-risk group**	**High-risk group**	**Low-risk group**	**High-risk group**
True positive	61	34	56	18	60	21
False positive	1081	10	784	62	1012	175
False negative	0	27	5	43	1	40
True negative	569	1640	866	1588	638	1475
Total	**1711**	**1711**	**1711**	**1711**	**1711**	**1711**

The diagnostic performance for each rule-out, rule-in, low-risk, and high-risk groups were calculated separately.

HEART: History, ECG, Age, Risk factors and Troponin; hs-cTnT: high-sensitivity cardiac troponin T

ONLINE TABLE 5 Disposition after ended observation at the OAEOC

n (%)	Single hs-cTnT			Original HEART score			Modified HEART score		
	Rule out	**Obser-vation**	**Rule in**	**Low risk**	**Inter-mediate**	**High risk**	**Low risk**	**Inter-mediate**	**High risk**
No follow-up	163 (28.6)	230 (20.9)	1 (2.3)	247 (28.4)	141 (18.6)	6 (7.5)	190 (29.7)	180 (20.5)	24 (12.2)
Contact regular GP	344 (60.5)	631 (57.5)	1 (2.3)	513 (58.9)	431 (56.7)	32 (40.0)	374 (58.5)	512 (58.4)	90 (45.9)
Admitted municipal short term facility	0 (0.0)	21 (1.9)	2 (4.5)	2 (0.2)	17 (2.2)	4 (5.0)	2 (0.3)	16 (1.8)	5 (2.6)
Referral to hospital outpatient clinic	20 (3.5)	47 (4.3)	0 (0.0)	27 (3.1)	35 (4.6)	5 (6.3)	20 (3.1)	31 (3.5)	16 (8.2)
Left during observation	10 (1.8)	15 (1.4)	0 (0.0)	16 (1.8)	9 (1.2)	0 (0.0)	13 (2.0)	12 (1.4)	0 (0.0)
Admitted hospital	32 (5.6)	153 (13.9)	37 (84.1)	66 (7.6)	124 (16.3)	32 (40.0)	40 (6.3)	122 (13.9)	60 (30.6)
Direct coronary angiography	0 (0.0)	1 (0.1)	3 (6.8)	0 (0.0)	3 (0.4)	1 (1.3)	0 (0.0)	3 (0.3)	1 (0.5)
Total N = 1711	**569 (33.3)**	**1098 (64.2)**	**44 (2.6)**	**871 (50.9)**	**760 (44.4)**	**80 (4.7)**	**639 (37.3)**	**125 (51.2)**	**196 (11.5)**

GP: general practitioner; HEART: History, ECG, Age, Risk factors, Troponin; hs-cTnT: high-sensitivity cardiac troponin T; OAEOC: Oslo Accident and Emergency Outpatient Clinic

ONLINE TABLE 6 Misclassification in the original low-risk HEART score group

Sex	Age	HEART score	Symptom onset to first hs-cTnT, hours	hs-cTnT at the OAEOC			Disposition after OAEOC	Adjudicated final diagnosis
				0-hour	1-hour	4-hour		
Female	40	3	1.8	30	69	X	Hospital	AMI
Male	59	3	2.3	9	12	37	Hospital	AMI
Female	57	3	5.7	13	X	X	Hospital	AMI
Male*	32	3	9.5	378	481	X	Hospital	AMI
Female	70	3	18.1	5	6	13	Home	AMI

*Also misclassified by the modified low-risk HEART score.

AMI: acute myocardial infarction; HEART: History, ECG, Age, Risk factors and Troponin; hs-cTnT: high-sensitivity cardiac troponin T; OAEOC: Oslo Accident and Emergency Outpatient Clinic; X: not measured due to hospitalisation

ONLINE TABLE 7 Classification of the HEART scores compared to single hs-cTnT approach and the 0/1-hour algorithm for hs-cTnT

		HEART Classification	Original HEART score n	Original HEART score %	Modified HEART score n	Modified HEART score %
Single hs-cTnT (n=1711)	**Rule-out (n=569)**	Low risk	430	75.6	430	75.6
		Intermediate	138	24.3	138	24.3
		High risk	1	0.2	1	0.2
	Observation (n=1098)	Low risk	440	40.1	208	18.9
		Intermediate	595	54.2	711	64.8
		High risk	63	5.7	179	16.3
	Rule-in (n=44)	Low risk	1	2.3	1	2.3
		Intermediate	27	61.4	27	61.4
		High risk	16	36.4	16	36.4
0/1-hour algorithm (n=1711)[5]	**Rule-out (n=1311)**	Low risk	815	62.2	617	47.1
		Intermediate	490	37.4	658	50.2
		High risk	6	0.5	36	2.7
	Observation (n=334)	Low risk	50	15.0	19	5.7
		Intermediate	231	69.2	178	53.3
		High risk	53	15.9	137	41.0
	Rule-in (n=66)	Low risk	6	9.1	3	4.5
		Intermediate	39	59.1	40	60.6
		High risk	21	31.8	23	34.8

The total HEART scores were stratified into three risk groups; low-risk (0-3 points), intermediate-risk (4-6 points), and high-risk (7-10 points), and further classified according to the single hs-cTnT strategy and the ESC 0/1-hour algorithm.

ESC: European Society of Cardiology; HEART: History, ECG, Age, Risk factors and Troponin; hs-cTnT: high-sensitivity cardiac troponin T

ONLINE TABLE 8 Distribution of the calculated HEART scores

Classification	Points	Original HEART score		Modified HEART score	
		n	%	n	%
Low risk	0	4	0.2	3	0.2
	1	110	6.4	74	4.3
	2	305	17.8	239	14.0
	3	452	26.4	323	18.9
Intermediate risk	4	377	22.0	350	20.5
	5	242	14.1	302	17.7
	6	141	8.2	224	13.1
High risk	7	60	3.5	130	7.6
	8	16	0.9	53	3.1
	9	4	0.2	13	0.8
	10	0	0.0	0	0.0
Total		**1711**	**100.0**	**1711**	**100.0**
Mean (SD)		3.64 (1.568)		4.22 (1.785)	

SD: standard deviation; HEART: History, ECG; Age; Risk factors; Troponin

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IV

Paper IV

Cost-effectiveness of a rule-out algorithm of acute myocardial infarction in low-risk patients: Emergency primary care versus hospital setting

Authors

Tonje R. Johannessen, MD[a,b], Sigrun Halvorsen, MD, PhD[c,d], Dan Atar, MD[c,d], John Munkhaugen MD, PhD[e,f], Anne Kathrine Nore, MD[b], Torbjørn Wisløff, PhD[g,h], and Odd Martin Vallersnes, MD, PhD[a,b]

Affiliations

a Department of General Practice, University of Oslo, Oslo, Norway
b Oslo Accident and Emergency Outpatient Clinic, City of Oslo Health Agency, Oslo, Norway
c Department of Cardiology, Oslo University Hospital Ullevaal, Oslo, Norway
d Institute of Clinical Medicine, University of Oslo, Oslo, Norway
e Department of Medicine, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway
f Department of Behavioural Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
g Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway
h Health Services Research Unit, Akershus University Hospital, Lørenskog, Norway

Corresponding author

Tonje R. Johannessen, Department of General Practice, Institute of Health and Society, University of Oslo, 1130 Blindern, NO - 0318 Oslo, Norway
E-mail: t.r.johannessen@medisin.uio.no

ABSTRACT

Aims

Hospital admissions of patients with chest pain considered as low risk for acute coronary syndrome contribute to increased costs and crowding in the emergency departments. This study aims to estimate the cost-effectiveness of assessing these patients in a primary care emergency setting, using the European Society of Cardiology (ESC) 0/1-hour algorithm for high-sensitivity cardiac troponin T, compared to routine hospital management.

Methods

A cost-effectiveness analysis was conducted. For the primary care estimates, costs and health care expenditure from the observational OUT-ACS (One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome) study were compared with anonymous extracted administrative data on low-risk patients at a large general hospital in Norway. Patients discharged home after the hs-cTnT assessment were defined as low risk in the primary care cohort. In the hospital setting, the low-risk group comprised patients discharged with a non-specific chest pain diagnosis (ICD-10 codes R07.4 and Z03.5). Loss of health related to a potential increase in acute myocardial infarctions the following 30-days was estimated. The primary outcome measure was the costs per quality-adjusted life-years (QALYs) of applying the ESC 0/1-hour algorithm in primary care. The secondary outcomes were health care costs and length of stay in the two settings.

Results

Differences in costs comprise personnel and laboratory costs of applying the algorithm at primary care level (€192) and expenses related to ambulance transports and complete hospital costs for low-risk patients admitted to hospital (€1986). Additional diagnostic procedures were performed in 31.9 % (181/567) of the low-risk hospital cohort. The estimated healthcare cost reduction when using the 0/1-hour algorithm outside of hospital was €1794 per low-risk patient, with a mean decrease in length of stay of 18.9 hours. These numbers result in an average per-person QALY gain of 0.0005. Increased QALY and decreased costs indicate that the primary care approach is clearly cost-effective.

Conclusion

Using the ESC 0/1-hour algorithm in low-risk patients in emergency primary care appears to be cost-effective compared to standard hospital management with an extensive reduction in costs and length of stay per patient.

Abbreviations and acronyms

ACS: acute coronary syndrome

AMI: acute myocardial infarction

CHEERS: Consolidated Health Economic Evaluation Reporting Standards statement

DRG: diagnosis-related groups

ECG: electrocardiogram

ED: emergency department

EMS: emergency medical services

ESC: European Society of Cardiology

GP: general practitioner

hs-cTnT: high-sensitivity cardiac troponin T

ICD-10: International Statistical Classification of Diseases and Related Health Problems, 10th Revision

LOS: length-of-stay

NSTE-ACS: non-ST-segment elevation acute coronary syndrome

OAEOC: Oslo Accident and Emergency Outpatient Clinic

OOH: Out-of-hours

OUT-ACS: One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome

QALY: quality of life-adjusted years

INTRODUCTION

Primary care serves as a gatekeeper to the specialist healthcare system in order to reduce healthcare expenditure and unnecessary hospital admissions in many countries.[1] Chest pain and other symptoms suggestive of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) represent a major challenge for primary care physicians due to a lack of sensitive diagnostic decisions aids outside of hospital.[2, 3] Although the prevalence of acute myocardial infarction (AMI) in a primary care setting is usually below 5 %,[4-6] diagnostic uncertainty results in increased risk of more defensive practice with hospital referrals to exclude an acute cardiac event.[7-10] Still, as recently demonstrated by Vester et al., more than 80 % of the referrals end up with a non-cardiac diagnosis at discharge.[11]

There is a growing international awareness to address issues related to overdiagnosis,[12-16] where extensive hospital admission of low-risk patients with chest pain and screening with high-sensitivity cardiac troponins (hs-cTn) are highlighted examples of overuse of care.[14-16] Studies from the Netherlands have shown that hospital admissions of patients considered as false-positive ACS[6] or as low-risk by the HEART (History, Electrocardiogram (ECG), Age, Risk factors and Troponin) score[17] yield few additional health benefits despite substantial use of healthcare expenditure. Both studies further elaborated on the potential reduction in overall expenses if these low-risk groups were offered improved risk stratification outside the emergency departments (ED).[6, 17]

High efficacy and subsequent reduction in costs, length of stay, and patient crowding in the EDs, have been demonstrated for patients triaged towards AMI rule-out by the European Society of Cardiology (ESC) 0/1-hour algorithm for hs-cTn.[18-21]. The 0/1-hour algorithm was also listed as the preferred biomarker strategy in the *2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.*[22] In previous work from the observational OUT-ACS study (*One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome*),[23] we demonstrated high rule-out performance for AMI (sensitivity 98.4 %, negative predictive value 99.9 %) by using the ESC 0/1-hour

algorithm for hs-cTnT in an emergency primary care setting. In addition, 80.5 % of the patients were conclusively triaged by the algorithm, and only 13.2 % of 1711 patients required hospitalisation.[23] With these results in mind, we hypothesise that initial triage with the 0/1-hour algorithm of low-risk patients with chest pain outside the hospital EDs would substantially reduce additional advanced testing, unnecessary hospitalisations, and overall expenses. To the best of our knowledge, the potential reductions in health care expenditure by applying the ESC 0/1-hour algorithm in emergency primary care has so far not been studied.

Objectives

This study aimed to explore the cost-effectiveness of assessing low-risk patients with chest pain using the ESC 0/1-hour algorithm for hs-cTnT in emergency primary care compared to routine hospital management. In addition, the differences in direct costs and length of stay per low-risk patient between the two settings were investigated.

MATERIAL AND METHODS

Study design

In this cost-effectiveness analysis, we compared a cohort of low-risk patients with chest pain managed with the 0/1-hour algorithm in emergency primary care to a comparable low-risk cohort in a hospital ED. Data from the prospective, observational OUT-ACS study,[23] conducted at the Oslo Accident and Emergency Outpatient Clinic (OAEOC) from November 2016 to October 2018, were used to calculate direct costs and additional length-of-stay for the emergency primary care setting. These estimates were compared with patients considered as low risk for NSTE-ACS at Drammen Hospital in 2018. The chosen analytical method combines empirical data from the OUT-ACS study and a simulation model.

Study settings and locations

The OAEOC is the main primary care emergency clinic in Oslo, Norway, which serves the entire city of Oslo 24/7 all year, with approximately 200 000 consultations a year. Unlike most Norwegian out-of-hours (OOH) clinics, the clinic has available chest x-ray service, facilities for observation of patients for up to 24 hours, and a possibility of having venous blood samples sent to hospital for analysis. Otherwise, the OAEOC is a standard primary care emergency clinic with limited diagnostic and therapeutic options, staffed by general practitioners (GPs) and nurses.

Drammen Hospital was chosen as the comparator to the OAEOC, as the primary care emergency clinics in the region of Drammen do not offer hs-cTn measurements. Hence, all patients in need of a safe exclusion of AMI are hospitalised. Drammen Hospital is a large general hospital in Vestre Viken Hospital Trust, with a total catchment area of 168 000 inhabitants.[24]

Clinical assessment of low-risk patients

In Norway, all patients with acute chest pain are advised to call the emergency services. As the vast majority will have an ambulance dispatched, patients with STEMI or patients considered critically ill generally bypass primary care. All others are initially assessed in primary care, either by their regular GP during office hours or by GPs at out-of-hours/primary care emergency clinics. In most cases, standard assessment comprises medical history, focused clinical examination, vital signs, and a 12-lead ECG. If NSTE-ACS is suspected or cardiac troponins are considered necessary to exclude an AMI, the patient is transferred to a hospital ED. This is also the setting in Drammen (Figure 1A and Online Figure S1; standard care). Some GPs do have access to prehospital point-of-care troponin assays, but these do currently not provide adequate sensitivity for a safe AMI rule-out.[3, 25, 26]

At the OAEOC, a third diagnostic option is available. Patients considered clinically stable, pain-free and without urgent need for hospital transfer may be offered serial hs-cTnT measurements at the clinic. This group comprises patients with resolved pain but increased cardiovascular risk profile, non-specific findings at the ECG of unknown clinical relevance, or patients with atypical symptom presentation (acute

fatigue, dyspnoea, or diaphoresis). While these patients wait at the clinic, the blood samples are sent to the central laboratory at Oslo University Hospital Ullevaal by courier transport (approximately 4 kilometres). The hs-cTnT measurements were sampled at 0, 1, and 4 hours during the OUT-ACS study.[23]

At Drammen Hospital ED, a complete clinical examination, repeated ECGs, a standard blood test panel, and a chest x-ray is obtained from all patients admitted with chest pain or other symptoms suggestive of NSTE-ACS. Additional diagnostic workup and treatment are offered if considered necessary by the treating physician. The ESC 0/1-hour algorithm was not implemented at Drammen hospital, and hs-cTnI was measured at admission and approximately six hours later. The non-specific ICD-10 (*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*)[27] codes R07.4 (*chest pain, unspecified*) or Z03.5 (*observation for other suspected cardiovascular diseases*) are set in the absence of a more specific diagnosis at discharge. Patients registered with R07.4 and Z03.5 were considered as low risk for NSTE-ACS in this study. In the following analyses, we assume that this low-risk group would not have been hospitalised if the 0/1-hour algorithm for hs-cTn had been available at the primary care emergency clinic in Drammen. Details regarding the ESC 0/1-hour algorithm is described in Online Figure S2, and the two management strategies and levels of care are illustrated in Figure 1 and Online Figure S1.

Outcome measures

The primary outcome measure was the costs per quality-adjusted life-years (QALYs) of applying the ESC 0/1-hour algorithm in emergency primary care compared to routine hospital management. The secondary outcome measures were the estimated healthcare cost and length of stay per patient in the two settings.

For estimation of QALYs, potential health loss due to the estimated length of stay was multiplied by estimates of health-related quality of life among patients with AMI,[28] when considering the potential of a minimal increase in AMIs in the primary care cohort. The OUT-ACS study[23] reported 0.2 % AMIs (2/1232) the following 30 days among those ruled out by the algorithm and discharged home (one AMI at index

and another on day 5), and three events (2 AMIs; 1 death) among the non-hospitalised patients in the observation group (n=243). Therefore, total events after 30-days were 0.3 % (5/1485) (Table 1), which was applied to estimate the lifetime health-related quality of life lost by not being hospitalised. As the low-risk hospital cohort comprises administrative data only, we applied numbers from a comparable Norwegian hospital cohort to assess the 30-day event rate at hospital level. In the 2019 publication by Bjørnsen et al., there were two events (1 death; 1 ACS) the following 30 days among 862 patients discharged with a non-specific chest pain diagnosis (R07.4).[29] In addition to the 0.2 % incidence rate,[29] we assumed an average age of 56 years and quality of life weights as reported by Wisløff et al.[28] and in official Norwegian guidelines for economic evaluations.[30]

Estimating healthcare resources

Initial resources spent in emergency primary care, comprising patient registration, triage, clinical examination, and ECG, were assumed similar in Oslo and Drammen regardless of the availability of hs-cTn in primary care. Similar assumptions apply to costs related to service, administration, buildings, and the initial use of emergency medical services (EMS) to the primary care emergency clinics. Cost estimates at the OAEOC also comprise hs-cTnT measurements, additional diagnostic tests and procedures, personnel resources applied per patient assessed by the 0/1-hour algorithm and potential referrals to outpatient cardiac testing after OAEOC discharge. Personnel resources (minutes spent per patient) were estimated by consulting experienced senior personnel at the OAEOC. Data on the probabilities of using a specific test or procedure was calculated by investigating patient records from a random selection of the OUT-ACS study cohort (n=171 of 1711; 10 %). We also assume that making hs-cTnT measurements available in primary care would lead to some overuse of care (estimated 10-15 %) with more patients made subject to triage by the algorithm. These patients were already part of the OUT-ACS cohort (Figure 1B, dark green).

For the hospital setting, anonymous, aggregated data from Drammen hospital were extracted from the hospital records for all patients discharged with a final non-specific cardiac ICD diagnosis (R07.4 and Z03.5) from January to December 2018.

Patients with elevated hs-cTn measurements were most likely not part of the low-risk hospital cohort, as these patients would be discharged with a more specific diagnosis. The variables extracted were age, sex, length of stay, procedure codes and Diagnosis-Related Group (DRG) codes. DRG is a patient classification system that standardises all charges associated with an inpatient stay from admission to discharge.[30, 31] Experienced senior personnel were consulted to estimate the use of additional diagnostic tests and procedures not encompassed by the procedure codes.

Estimating costs

All costs were based on 2020 averages and fees (2020 EUR 1.00 = NOK 10.73). According to Norwegian guidelines, prices and health estimates during future years were discounted at a 4 % discount rate.[30]

At the OAEOC, average personnel costs (per hour) were delivered by the finance consultant at the City of Oslo Health Agency. Chest x-ray and venous blood samples were calculated as outpatient radiological and laboratory services. According to *The Norwegian Medicines Agency's Guidelines for the submission of documentation for single technology assessment of pharmaceuticals*,[30] the costs of the personnel used were based on average pay multiplied by 1.3 to include payroll taxes and other social charges. Hospital services were estimated as if financed by full reimbursements from *The Norwegian Health Economics Administration* (HELFO). Services provided by GPs and primary care emergency clinics were calculated by multiplying the HELFO reimbursements by two to cover other financing sources. Outpatient radiological and laboratory services were estimated as the reimbursed sum from HELFO plus the fee paid by the patient, multiplied by two, also to include personnel costs at the radiology and lab units.[30] The estimated reduction in low-risk ED admissions with the 0/1-hour algorithm at the primary care emergency clinic is visualised by the missing yellow square at hospital level in Figure 1B.

At Drammen Hospital, the overall costs were based on the reported DRG codes for the low-risk cohort. In addition, the total number of diagnostic tests, procedures, and length of stay were reported separately. Estimated mean costs related to the use of

ambulances, including personnel and equipment, were reported by the Prehospital Division at Oslo University Hospital, Ullevaal.

Analytical methods

The health economic evaluation was performed using a decision-analytic model incorporating a simple Markov model taking long-term differences between interventions into account.[32] The structure of the decision model is illustrated in Online Figure S1. The analysis included the Markov model to provide long-term insights into impacts beyond the first year after presenting with ACS symptoms. To include potential differences in rates of ACS, the model was constructed to consist of the three health states: non-CVD, CVD and dead. One year cycle length was chosen, and a half-cycle correction was applied to account for events occurring on average halfway through cycles. Living with CVD was assumed to have a hazard ratio of 1.6 compared to living without, based on data from two analyses of Norwegian data.[33, 34] Details on other inputs are included in Online Tables S1-S4.

In addition to a base case (i.e., most likely) model, separate analyses were conducted to evaluate a conservative scenario. Four inputs were chosen, not based on what is considered most likely, but as a worst-case scenario for managing these patients in primary care. These were: 1) Costs of time spent on the 0/1-hour algorithm based on tariffs instead of personnel wages as reported in Online Table S1. 2) Incorporating a potential increase in AMIs at the OAEOC, as reported under outcome measures. 3) Costs related to a lower probability of ambulance transport for hospital admissions from primary care in Drammen. 4) Additional length of stay at the OAEOC, where the upper range of uncertainty was selected as the estimate. Probabilistic sensitivity analysis of the parameters in the base case model was also conducted and presented in the Supplementary appendix and Figures S2 and S3. Current Norwegian assumptions regarding the threshold for cost-effectiveness are cited to be between Norwegian Kroner (NOK 275,000 and 825,000 per QALY, i.e., between Euro (EUR) 25,600 and EUR 76,900 per QALY).[35]

RESULTS

Baseline description of the low-risk patients

Baseline characteristics of patients from the OUT-ACS study not being hospitalised by using the 0/1-hour algorithm (n=1485, 86.8 %) are described in Table 1. The median age was 55 (IQR 44-66) years, and 51.4 % were males. The low-risk patients admitted to Drammen hospital (n=567 admissions) had a median age of 57 (IQR 46-69) years, and 54.3 % were males.

Estimated health care expenditure

The additional costs of implementing the ESC 0/1-hour algorithm at the primary care emergency clinic were estimated to be either EUR 230 or EUR 192 for each low-risk patient in need of hs-cTnT measurements. DRG tariffs are not used for cost calculations in primary care. The estimate, therefore, comprises direct costs of laboratory and additional procedures (EUR 41), personnel costs, either by tariffs (EUR 137) or by wages (EUR 99), and estimated costs related to increased referrals to outpatient cardiac testing (EUR 52) (Table 2 and Table S1-2). The estimated reduction in health care expenditure for each low-risk patient assessable by the 0/1-hour algorithm outside of hospital was EUR -1672 per patient with the most conservative scenario and EUR -1794 with the base case scenario (Table 2).

For the low-risk cohort (n=567) at Drammen hospital, the total DRG was calculated to EUR 840,664, with a mean cost for one low-risk patient of EUR 1483 (Table 2 and Online Table S1). ECG, standard blood panel (Online Table S1) and chest x-ray were obtained from all patients on admission. Additional advanced procedures (e.g., stress ECG and echocardiogram), were performed in 31.9 % (n=181) of the low-risk group (Online Table S3). In addition, by following standard prehospital routine, most patients hospitalised with chest pain suggestive of NSTE-ACS are transported from emergency primary care by ambulance, with an estimated cost per transport of EUR 559 (Online Table S1).

Length of stay

In the base case scenario, the additional length of stay at the OAEOC, using the 0/1-hour algorithm, and Drammen Hospital were 3.4 hours (SD 0.740) and 22.3 hours (SD 22.010), respectively. In the conservative scenario, the upper range of uncertainty was chosen for the mean additional length of stay at the OAEOC, at 4.0 hours (SD 0.870). Subsequently, the mean difference in length of stay between the two settings was -18.9 hours in the base case scenario and -18.3 hours in the more conservative scenario (Table 2 and Online Table S4).

Base case cost-effectiveness

In our base case analysis, QALY loss related to length of stay was 0.00009 at the OAEOC and 0.00059 at Drammen Hospital, leading to 0.00050 lower QALY with standard hospital treatment than at the OAEOC (Table 2). As the 30-day event rates in both low-risk cohorts were below the potentially acceptable AMI miss rate of ≤ 1 %,[10, 36] the health loss due to missed events was estimated at 0.0 in both settings in our base case scenario. With increased health due to less time waiting and decreased costs per patient (EUR -1794), the OAEOC strategy is cost-effective regardless of the cost-effectiveness threshold, commonly referred to as a *dominant* strategy in health economics.

Conservative scenario

Among the non-hospitalised patients in the OUT-ACS cohort, the 30-day combined incidence rate for AMI and deaths was 0.3 %. The rate was assumed to be similar to Bjørnsen et al. at 0.2 % for the hospital setting[29] and included in our conservative scenario. Estimated discounted remaining QALYs for an average person at 56 years old was estimated at 13.3 QALYs, while for a person who had experienced an AMI mounted to 11.1 QALYs. An assumed increased AMI rate of 0.1% at the OAEOC compared to the hospital would result in an additional 0.0023 QALYs lost. Including QALYs saved due to shorter length of stay, health loss in the conservative scenario is reduced to -0.0019 QALYs with the algorithm at the OAEOC. With a reduction of EUR 1672, the cost per QALY lost equals EUR -1672 / -0.0019 QALYs =

EUR 880 000 per QALY. As can be seen from Figure 2, this is well below the currently assumed thresholds for cost-effectiveness in Norway, implying that the OAEOC is cost-effective in Norway also in the conservative scenario.

Potential generalisability

Thirty-two of the total 169 Norwegian OOH-/primary care emergency clinics, with a catchment area population of 1.7 million (31.4 % of the Norwegian population), are located on hospital grounds, enabling optimal use of the 0/1-hour algorithm if implemented in routine clinical practice.[37] As an example, the catchment area population expands to 4.0 million (74.7 %) if the acceptable distance to an available hs-cTn assay is set to 20 kilometers (with a mean courier drive of 11.1 minutes) (Figure 3, Online Table S5). In 2014, 16,320 patients were discharged from Norwegian hospitals with the ICD-10 code R07 (*pain in throat and chest*), the second most common diagnosis following an acute somatic hospital admission.[38, 39] Among them, 7613 were referred after an OOH assessment.[39] Based on our figures, if all patients with an OOH clinic located within 20 kilometres of an available lab (74.7 %; n=5687) were assessed at the clinic with the 0/1-hour algorithm, 13.2 % would be hospitalised (n=751), and 86.8 % (n=4936) would be discharged home (Table 1). The following cost reduction per low-risk patient of EUR 1672 to 1794 would result in an estimated reduction of EUR 8.3 to 8.6 million per year in Norway. This number is potentially larger as 3923 of the R07 admissions were directly hospitalised by the ambulance.[39] We have reasons to believe that some of these would have been brought to an OOH clinic in case of available hs-cTn assessment.

DISCUSSION

This cost-effectiveness analysis found that assessing low-risk patients with chest pain with the ESC 0/1-hour algorithm at a primary care emergency clinic appears cost-effective in Norway. This indicates that introducing the algorithm in emergency primary care would set free health care resources that would gain more health

elsewhere than health loss due to a potential minimal increase in acute AMIs. A considerable potential reduction in healthcare costs, estimated to EUR -1672 to EUR -1794 per low-risk patient, was demonstrated when serial hs-cTn measurements were offered at the primary care level rather than in a hospital ED. In addition, the total length of stay would be reduced from 22.3 hours to between 3.4 and 4.0 hours by using the 0/1-hour algorithm in emergency primary care compared to traditional hospital assessment.

Comparable numbers of ED admissions of low-risk patients with chest pain (R07.4; 876 per 300 000 inhabitants) and hospital LOS (median 22 hours) were documented by Bjørnsen et al.[29] In addition, similar costs estimates per low-risk admission, i.e. EUR 1448[6], EUR 1360,[11] and EUR 1580,[17] have been reported in recent studies from the Netherlands.

Implementation of the 0/1-hour algorithm for hs-cTn in primary care requires a short distance to hospital ED with an available hs-cTn assay. As there are significant geographical variations between urban and rural districts in Norway, broad implementation of the algorithm is not feasible. In Norway, 32 % of patients admitted with non-specific chest pain (R07) and 50 % of all AMIs (K21) bypass primary care by being directly hospitalised by the ambulance service, especially in central areas.[38, 39] By implementing the 0/1-hour algorithm in primary care, hospitalisation of low-risk patients is expected to be reduced in central areas with a short distance to an ED. Like in Norway, several European countries have merged smaller OOH clinics into larger cooperation with increased catchment areas and more centralised locations.[40] In 2014, 63 % of the OOH services in the Netherlands were located adjacent to a hospital ED but without more extensive access to diagnostics tests or troponins.[41] Therefore, the 0/1-hour algorithm approach for the primary care setting might also be transferable to other countries with a similar organisation model.

A study by Mokhtari et al. found that the performance of the 0/1-hour algorithm combined with interpretation of the ECG and medical history-taking did not change by the physician's experience.[42] Hence, implementing such an algorithm should be feasible and user-friendly for GPs on OOH rotation.

One of the main decisions made by primary care physicians is whether a patient needs to be directly hospitalised or further assessed in primary care.[1] The fear of missed AMIs would probably result in some overuse of hs-cTn measurements at the primary care level to support the decision process. At the OAEOC, overuse of hs-cTnT measurements is estimated to 10-15 % by experienced senior GPs (illustrated by the dark green area in Figure 1B). These 15 % represent patients who most likely would have been discharged home without further testing at the primary care emergency clinic in Drammen.

Implementing a diagnostic test in a low-prevalence setting may also contribute to more false-positive results and unnecessary hospitalisations. In the OUT-ACS study, the rule-in group had a specificity of 98.7 % and a sensitivity of 73.8 %.[23] Among 1000 patients with a 3.6 % AMI prevalence, 36 patients would have an AMI, and 13 patients a false-positive test in the rule-in group. Still, most patients transferred to the hospital with a false positive hs-cTnT were admitted with other acute conditions requiring a higher level of care (e.g., acute heart failure, pulmonary embolism, or peri-myocarditis). Simultaneously, none of the false positives discharged home suffered an AMI or died the following 90-days.[23] We, therefore, conclude that assessment with the 0/1-hour algorithm in emergency primary care is sufficient for the low-risk group. This is consistent with the comprehensive gatekeeper function of primary care, which is to offer patients appropriate and adequate healthcare at the lowest effective level.[1, 43] Also, by not offering hs-cTn measurements at the OAEOC, a substantial proportion of the non-hospitalised patients (n=1485; Table 1) would probably have been directly hospitalised at substantially higher costs.

Limitations

Some limitations merit consideration: First, only the theoretical cost-effectiveness of assessing low-risk patients with chest pain outside of hospital is illustrated in this analysis. The study is based on data from the observational OUT-ACS cohort and not a real-world implementation study, which would be preferable.

Second, in this economic evaluation analysis, we cannot ensure that the assessment of low-risk patients with chest pain at the primary care level is comparable to hospital.

However, the low 30-day event rate in the non-hospitalised OUT-ACS cohort (Table 1), is similar to the rate found among low-risk patients at a large Norwegian hospital.[29] Two of the four AMIs in the OUT-ACS cohort the following 30 days were assigned to the observation group by the 0/1-hour algorithm. Improved recommendations[22] and recently validated novel criteria for patients in the observation group[44] are expected to enhance the 30-day outcomes in the future.

Third, many of our estimates are based on best guesses and uncertain assumptions. For this reason, both a base case and a conservative scenario were estimated (Table 2). For the low-risk hospital cohort, only ICD-10 R07.4 and Z03.5 were extracted from the administrative database. Hospital admissions of low-risk patients were probably higher, as some may have been discharged with a more specific ICD-10 diagnosis (e.g., anxiety disorder, gastritis, or myalgia).

Fourth, even though the 2020 ESC guidelines recommend the 0/1-hour algorithm,[22] the algorithm is still not implemented at Drammen hospital. However, in a before-after-cohort from six EDs in Sweden, in-hospital length of stay and costs per patient were reduced to 4.7 hours and $1079 (=EUR 927) after implementing a rule-out strategy combining the ESC 0/1-hour algorithm and the HEART score.[21] Similar reductions would be expected for the low-risk hospital cohort in Drammen in case of implementation. However, the additional costs of applying the algorithm in primary care will still be lower (EUR 192; Table 2).

Fifth, the calculation of potential budget impact is based on a Norwegian registry on acute somatic hospital admissions in 2014, which reports numbers on the ICD-10 R07 group combined and not the R074 separately.[39] In the calculation, we also assume that the national R07 admissions were distributed equally across all the Norwegian OOH-clinics according to geographical location, which will not be the case in a real-world setting. Still, we believe the calculation may contribute to visualising potential cost reductions provided by the algorithm outside of the EDs.

Finally, implementing the 0/1-hour algorithm for hs-cTn in primary care requires a short distance to an available lab and a similar healthcare organisation model, including a gatekeeper function in primary care and referral-based access to the ED. Nevertheless, there is increased support for an initial assessment of patients considered

as low risk at a lower level of care.[6, 17] A study from the ED setting recently concluded that additional diagnostic procedures (e.g., stress test, echocardiography and coronary angiography) for patients triaged as rule-out by the algorithm had few diagnostic benefits and more false positives.[45] Hence, implementing the algorithm for assessing low-risk patients in primary care could potentially result in less advanced testing, as these procedures are not available in primary care.

Newly developed hs-point-of-care-troponin assays have shown comparable diagnostic performance as central lab assays.[46, 47] If these could be integrated within the 0/1-hour algorithm for the primary care setting in the future, broader implementation and enhanced diagnostic chest pain assessment outside of the EDs might also be possible in rural areas.

CONCLUSION

Assessment of low-risk patients with acute chest pain using the ESC 0/1-hour algorithm in emergency primary care appears cost-effective compared to routine hospital management. This approach may contribute to an extensive reduction in healthcare expenditure and potentially reduce unnecessary hospital referrals of low-risk patients with chest pain.

DECLARATIONS

Ethics approval and consent to participate

The OUT-ACS study was performed in accordance with the Declaration of Helsinki and approved by the *Regional Committee for Medical and Health Research Ethics Northern Norway (REC North; ref. 2016/1241)* and the *Oslo University Hospital Information Security and Privacy Office (no. 2016/13308)*. Study participation in the OUT-ACS study was based on written informed consent. Written informed consent was not necessary for the anonymous administrative data extracted from Drammen Hospital. The OUT-ACS study was registered at *ClinicalTrial.gov (NCT02983123)* and was carried out according to relevant regulations and guidelines. For this current cost-effectiveness analysis, the *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)* statement was followed.[48]

Consent for publication

Not applicable.

Availability of data and materials

Data underlying the analyses of this article are presented in the Supplementary Appendix. To preserve patients' privacy, raw data are not publicly available. Additional data may be shared upon reasonable request to the corresponding author.

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Authors' contributions

TRJ, OMV, DA and SH contributed to the concept and design of the OUT-ACS study. All authors contributed to the design, calculations, and cost estimates in this current analysis. For the emergency primary care setting, data was provided by TRJ, OMV and AKN, while JM provided data from the hospital setting. The health economic analyses were performed by TW, with contributions from the remaining authors. The manuscript was drafted by TRJ, where all authors contributed to revising and approving the final version for publication.

Conflict of interest

DA has received speaker and consultancy honoraria from Roche Diagnostics and Siemens Healthcare. Outside the submitted work, JM received modest lecture fees from Sanofi, Amgen, and Bayer. The remaining authors have no conflicts to declare.

Supplementary Data

Supplementary Figures S1-4 and Tables S1-5 are available in the online Supplementary Appendix.

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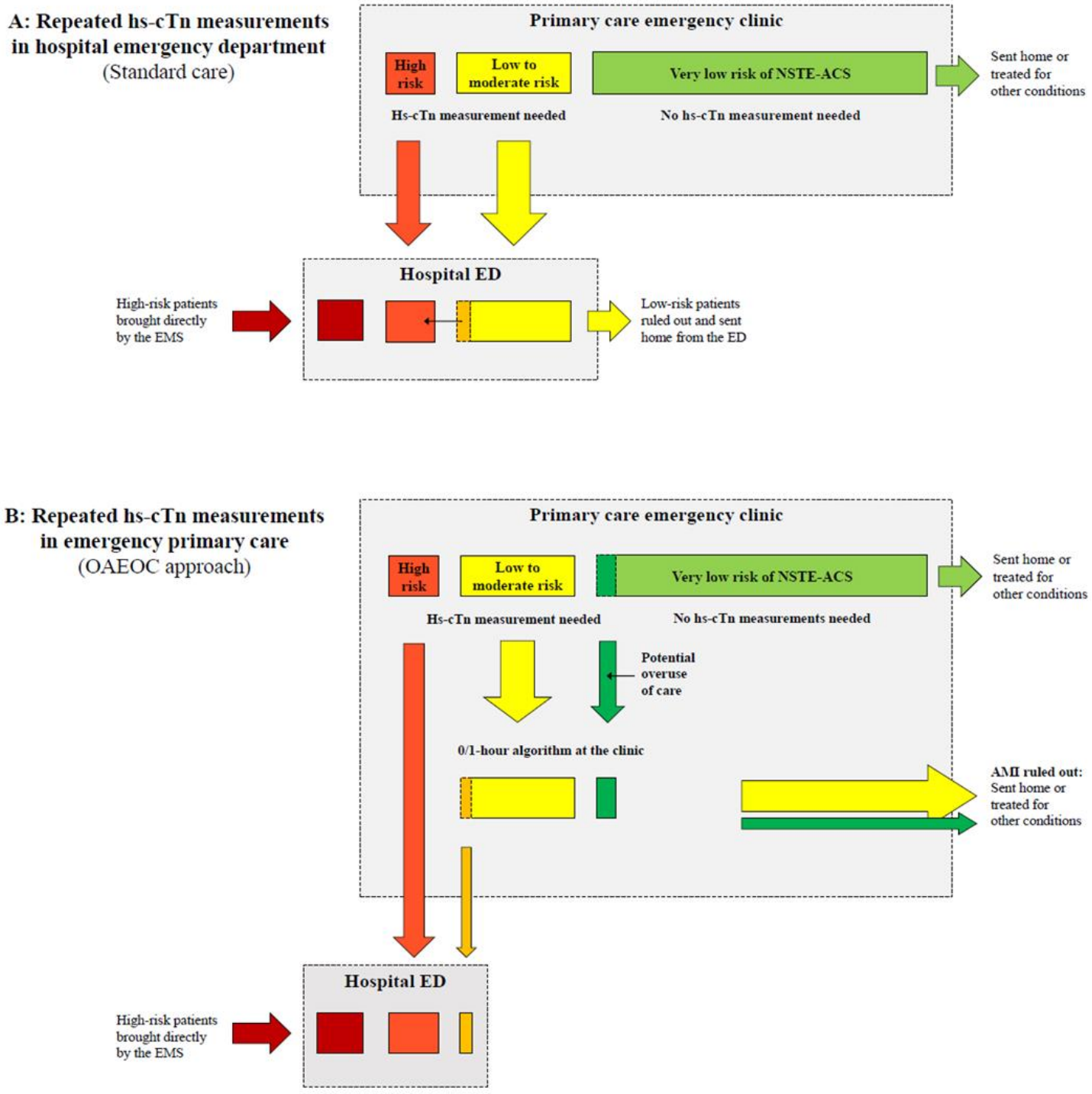

Figure 1 Management of low-risk patients at hospital versus emergency primary care

The two different assessment strategies and levels of care for patients presenting with chest pain. The estimated reduction in health care utilisation by initially assessing the low-risk group outside of the hospital ED is visualised by the missing yellow square at hospital level in Figure 1B.

AMI: acute myocardial infarction; ED: emergency department; EMS: emergency medical services; hs-cTn: high-sensitivity cardiac troponin; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; OAEOC: Oslo Accident and Emergency Outpatient Clinic

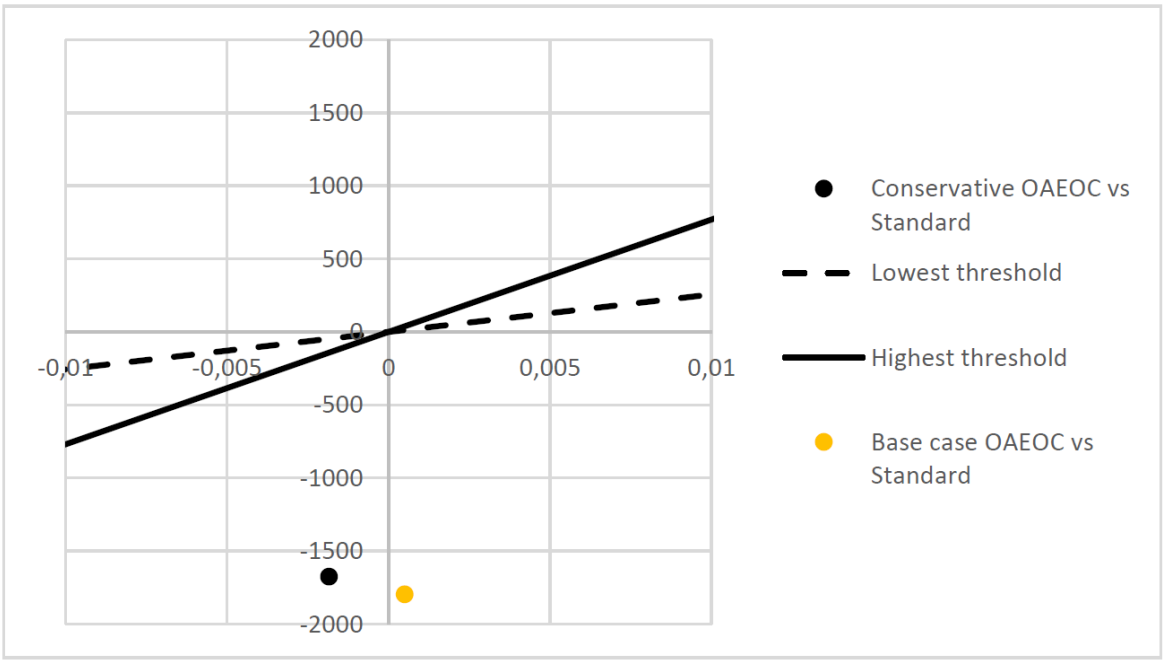

Figure 2 Cost-effectiveness of emergency primary care versus standard hospital management

The graph illustrates the difference in health on the x-axis and the difference in costs on the y-axis. The lines through the graph indicate the suggested minimum and maximum cost-effectiveness thresholds for Norway, which have been cited to be between EUR 25,600 and EUR 76,900 per QALY.[35]

The health lost due to missed AMIs at the primary care level will be bigger than the health gained by less waiting in hospital, as indicated by the negative health on the graph. Still, with a difference of EUR -1672 or -1794 per patient, the estimated QALY is well below the current assumed threshold for cost-effectiveness in Norway, implying that the primary care approach is cost-effective.

OAEOC: Oslo Accident and Emergency Outpatient Clinic; QALY: quality-adjusted life years

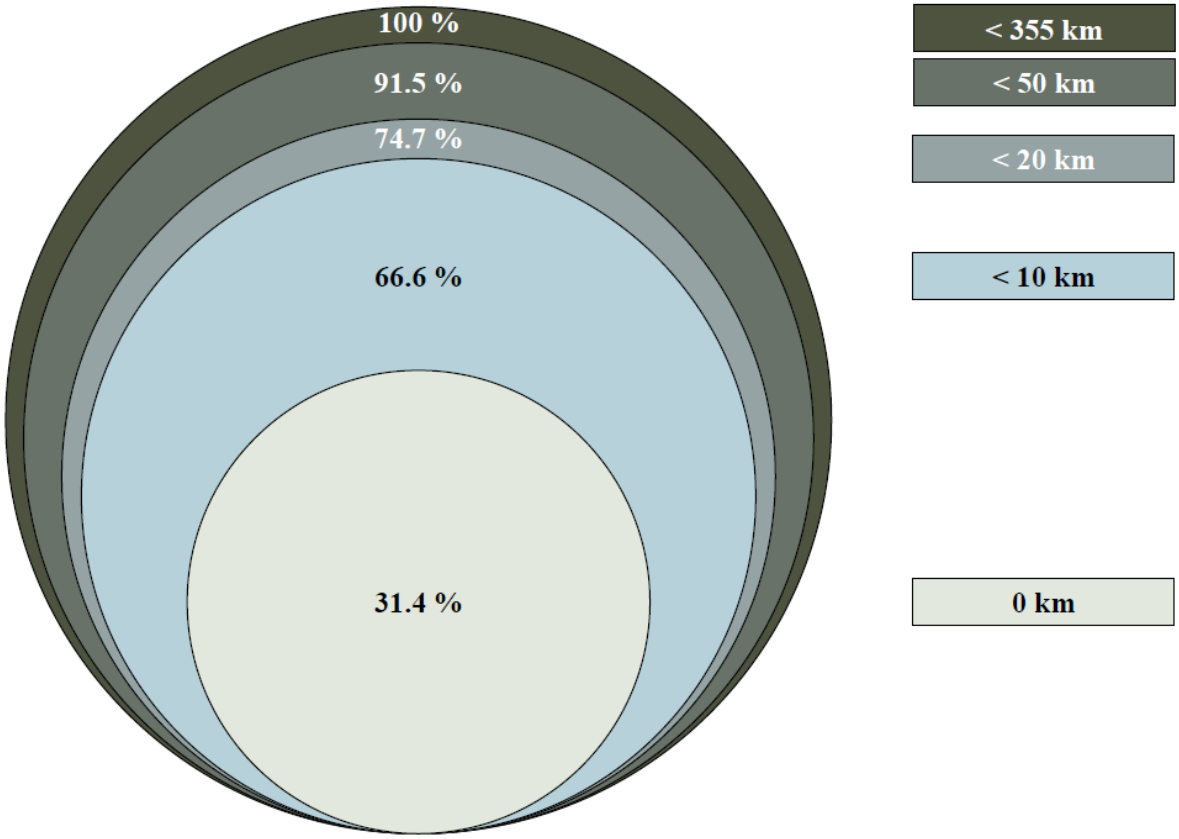

Figure 3 Distance from emergency primary care to available hs-cTn assay for the Norwegian population

Proportions of the Norwegian population (n = 5,367,580 in 2020) with emergency primary care/out-of-hours clinic located within the specified distance from the nearest available hospital hs-cTn assay.

Km: kilometres; hs-cTn: high-sensitivity cardiac troponin

Table 1 Baseline characteristics of the low-risk group at the primary care emergency clinic

	OUT-ACS total n = 1711 (100 %)	Not admitted to hospital n = 1485 (86.8 %)	Admitted to hospital n = 226 (13.2 %)
Male sex, n (%)	895 (52.3)	764 (51.4)	131 (58.0)
Age, median (IQR)	56 (45-68)	55 (44-66)	63.5 (51-73)
Risk factors for CVD, n (%)			
Current/history of smoking	449 (26.2)	387 (26.1)	62 (27.4)
Previous coronary artery disease	317 (18.5)	262 (17.6)	55 (24.3)
Hypertension	448 (26.2)	379 (25.5)	69 (30.5)
Dyslipidaemia	422 (24.7)	369 (24.8)	53 (23.5)
Other CVD*	288 (16.8)	228 (15.4)	60 (26.5)
Diabetes mellitus	171 (10.0)	143 (9.6)	28 (12.4)
COPD	80 (4.7)	58 (3.9)	22 (9.7)
Family history of CVD	691 (40.4)	603 (40.6)	87 (38.5)
Presenting acute symptoms (%)			
Chest pain	1486 (86.8)	1301 (87.6)	184 (81.4)
Constricting	1239 (72.4)	1082 (72.9)	157 (69.5)
Sharp	404 (23.6)	358 (24.1)	46 (20.4)
Tearing	64 (3.7)	58 (3.9)	6 (2.7)
Burning	208 (12.2)	183 (12.3)	25 (11.1)
Respiratory dependent	302 (17.7)	251 (16.9)	51 (22.6)
Chest wall tenderness	205 (12.0)	184 (12.4)	21 (9.3)
Movement dependent	219 (12.8)	197 (13.3)	21 (9.3)
Other pain (abdomen, back, neck)	48 (2.8)	39 (2.6)	9 (4.0)
No pain	177 (10.3)	144 (9.7)	33 (14.6)
Pain radiation	972 (56.8)	865 (58.2)	135 (59.7)
Dyspnea	901 (52.7)	768 (51.7)	133 (58.8)
Palpitations	637 (37.2)	558 (37.6)	79 (35.0)
Syncope/pre-syncope	460 (26.9)	391 (26.3)	69 (30.5)
Acute fatigue	571 (33.4)	488 (32.9)	83 (36.7)
Nausea and/or vomiting	732 (42.8)	641 (43.2)	91 (40.3)
Diaphoresis	561 (32.8)	490 (33.0)	71 (31.4)
First ECG, n (%)			
Normal	1515 (88.5)	1332 (89.7)	183 (81.0)
Non-specific changes†	196 (11.5)	153 (10.3)	43 (19.0)
Symptom onset to first hs-cTnT, n (%)			
< 3 hours	182 (10.6)	161 (10.8)	21 (9.3)
3 – 5.99 hours	609 (35.6)	532 (35.8)	77 (34.1)
6 – 11.99 hours	409 (23.9)	336 (22.6)	73 (32.3)
> 12 hours	511 (29.9)	456 (30.7)	55 (24.3)

(Table 1 continued)	OUT-ACS total n = 1711 (100 %)	Not admitted to hospital n = 1485 (86.8 %)	Admitted to hospital n = 226 (13.2 %)
According to the 0/1-hour algorithm			
Rule-out (0/1h)	1311 (76.6)	1232 (83.0)	79 (35.0)
Observation group (0/1h)	334 (20.5)	243 (16.4)	91 (40.3)
Rule-in (0/1h)	66 (3.9)	10 (0.7)	56 (24.8)
HEART risk score			
Low risk (0-3 points)	871 (50.9)	805 (54.2)	66 (29.2)
Intermediate risk (4-6 points)	760 (44.4)	633 (42.6)	127 (56.2)
High risk (7-10 points)	80 (4.7)	47 (3.2)	33 (14.6)
Endpoints			
Myocardial infarction at index	61 (3.6)	1 (0.1)	60 (26.5)
Myocardial infarction at day 30	3 (0.2)	3 (0.2)	0 (0.0)
Myocardial infarction at day 90	2 (0.1)	1 (0.1)	1 (0.4)
Deaths at day 30	5 (0.3)	1 (0.1)	4 (1.8)
Deaths at day 90	4 (0.2)	1 (0.1)	3 (1.3)

All values are presented as n (%) or median (IQR). As the low-risk hospital cohort was obtained from administrative data only, we do not have additional baseline characteristics for these patients. However, for the purpose of this analysis, we consider the non-hospitalised OUT-ACS cohort comparable to the low-risk patients at Drammen hospital.

* Includes atrial fibrillation, other arrhythmias, cardiomyopathies, cerebral stroke, heart failure, or valvular disease
† Non-specific changes in either the ST-segment, T-inversions, Q-waves, atrial fibrillation, pacemaker, or left/right bundle branch block of unknown clinical significance

COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; ECG: electrocardiogram; hs-cTnT: high-sensitivity cardiac troponin T; IQR: interquartile range; One hoUr Troponin in a low-prevalence of Acute Coronary Syndrome

Table 2 Cost estimates per low-risk patient with chest pain in the two settings

	0/1-hour algorithm at emergency primary care *OUT-ACS cohort, Oslo (n=1485)*		**All hs-cTn measurements at hospital ED** *Low-risk cohort, Drammen (n=567)*		**Difference**
	Conservative scenario	**Base case scenario**	**Conservative scenario**	**Base case scenario**	
EMS to emergency primary care *(costs per transport)*	**€ 162** *(€ 559 * 29 %)*	**€ 162** *(€ 559 * 29 %)*	**€ 162** *(€ 559 * 29 %)*	**€ 162** *(€ 559 * 29 %)*	**€ 0** *(assumed similar)*
Primary care emergency clinic					
General costs/ consultation[*]	**€ 166**	**€ 166**	**€ 166**	**€ 166**	**€ 0** *(assumed similar)*
Additional costs with a 0/1-hour algorithm	**€ 230** • *Diagnostics € 41* • *Personnel, tariffs € 137* • *Cardiac outpatient testing € 52*	**€ 192** • *Diagnostics € 41* • *Personnel, wages € 99* • *Cardiac outpatient testing € 52*	**(none)**	**(none)**	**€ 230 *or* 192**
EMS to hospital *(costs per transport)*	**(none)**	**(none)**	**€ 419** *(€ 559 * 75 %)*	**€ 503** *(€ 559 * 90 %)*	**€ -419 *or* -503**
Hospital (*DRG tariffs**)	**(none)**	**(none)**	**€ 1483**	**€ 1483**	**€ -1483**
TOTAL	**€ 558**	**€ 520**	**€ 2230**	**€ 2314**	**€ -1672 *or* -1794**
LOS	**Mean: 4.0 hours**	**Mean: 3.4 hours**	**Mean: 22.3 hours**	**Mean: 22.3 hours**	**-18.3 hours** ***or*** **-18.9 hours**
QALYs	**-0.00760** *LOS: -0.00011* *AMI: -0.00749*	**-0.00009** *LOS: -0.00009* *AMI: -0.0*	**-0.00574** *LOS: -0.00059* *AMI: -0.00515*	**-0.00059** *LOS: -0.00059* *AMI: -0.0*	**-0.00186** ***or*** **+0.00050**

Table 2 Details regarding cost estimates, probabilities and calculations are listed in Online Tables S1, S2, and S4. All numbers are adjusted to 2020 figures.

* General costs by standard consultation per patient encompass service costs, building, personnel, administration, which are assumed to be similar at the primary care emergency clinics in Oslo and Drammen.

DRG: diagnosis-related groups; EMS: emergency medical services; ED: emergency department; EUR: euro; LOS: length of stay; OUT-ACS: One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome; QALY: quality-adjusted life years

Supplementary appendix to the manuscript:

Cost-effectiveness of a rule-out algorithm of acute myocardial infarction in low-risk patients: Emergency primary care versus hospital setting

By

Tonje R. Johannessen, Sigrun Halvorsen, Dan Atar,
John Munkhaugen, Anne Kathrine Nore, Torbjørn Wisløff,
and Odd Martin Vallersnes

Oslo, Norway, 2022

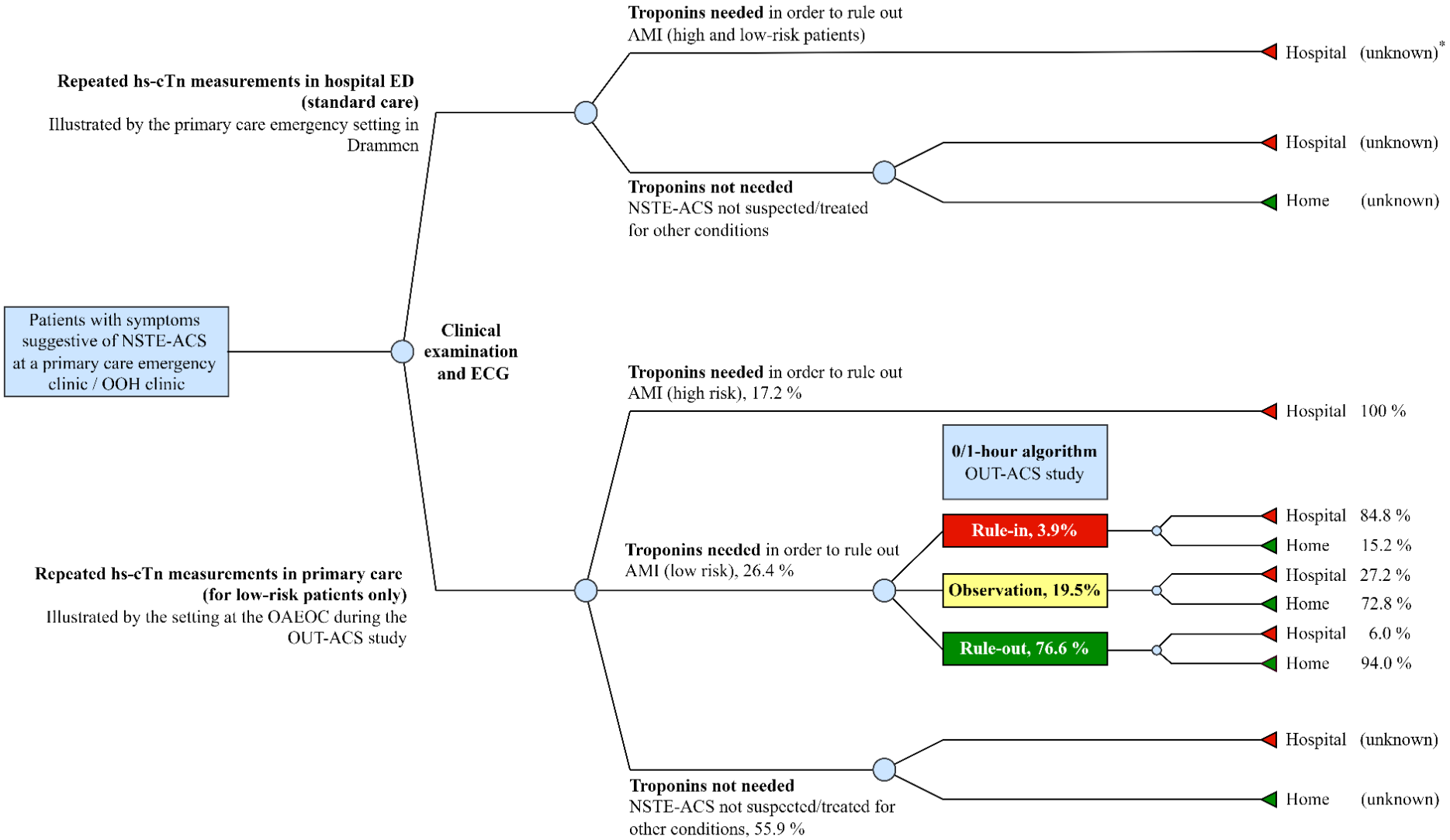

Figure S1 Decision tree

* The proportion of patients hospitalised for troponins in the standard care pathway is probably 10-15 % lower (estimated by experienced senior GPs at the OAEOC) than found at the OAEOC due to increased risk of overuse of troponins if implemented in primary care.

AMI: acute myocardial infarction; ECG: electrocardiogram; hs-cTn: high-sensitivity cardiac troponin; NSTE-ACS: acute coronary syndrome; OAEOC: Oslo Accident and Emergency Outpatient Clinic; OUT-ACS: One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome

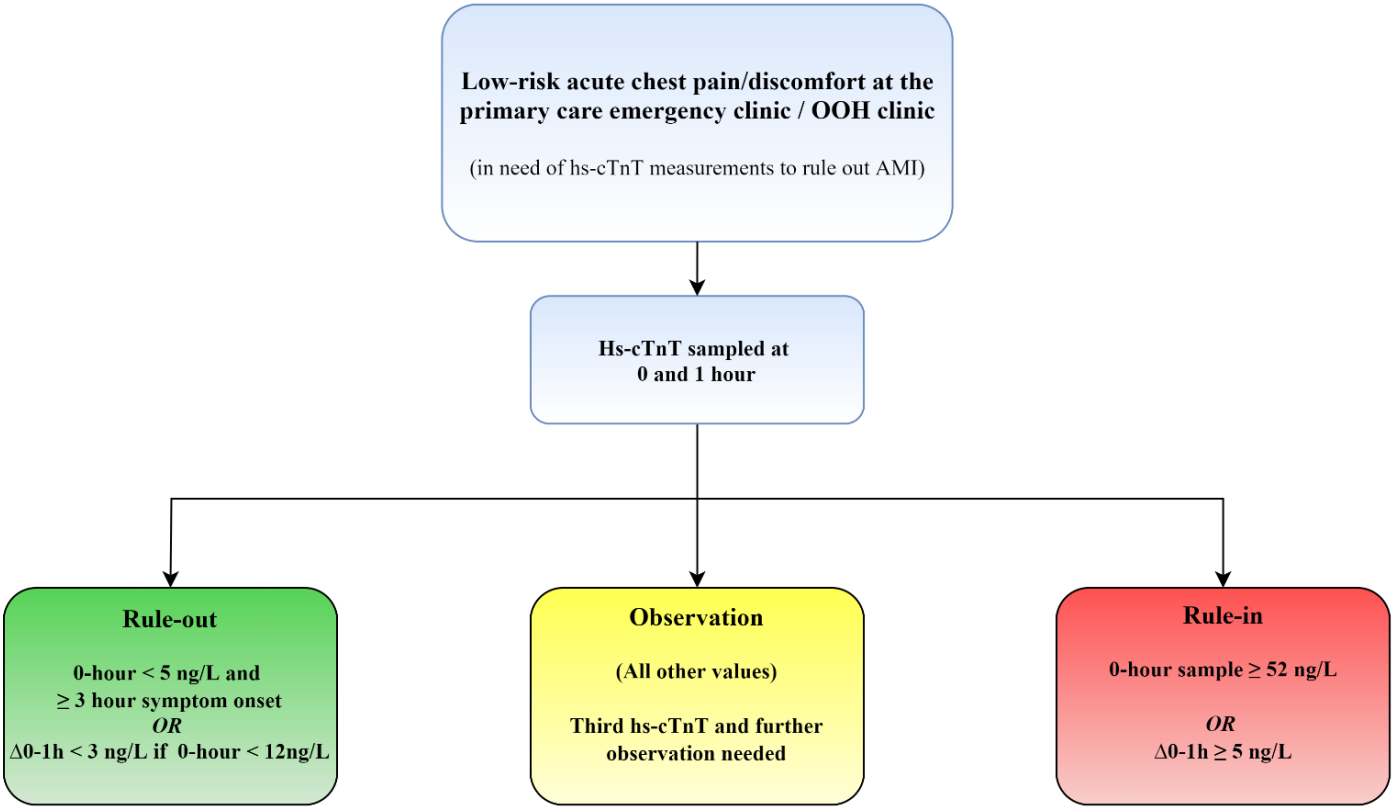

Figure S2 The ESC 0/1-hour algorithm for hs-cTnT

The ESC 0/1-hour algorithm for hs-cTnT presented according to the recent 2020 ESC guidelines on NSTE-ACS.[1] The algorithm uses assay-specific cut-off values and should always be interpreted in conjunction with the clinical assessment and the electrocardiogram.

AMI: acute myocardial infarction; ESC: European Society of Cardiology; hs-cTnT: high-sensitivity cardiac troponin T; ng/L: nanogram per litre; NSTE-ACS: non-ST-segment elevation acute coronary syndrome

Table S1 Estimating health care expenditure

Costs and resources	Estimates and calculations	Total costs (EUR)
Ambulance transport EUR 559 per transport (2020 figures)	**Transport to primary care emergency clinic:** • 29 % of the low-risk OUT-ACS cohort **Transport from primary care emergency to hospital** (recommended for all patients admitted with a suspected NSTE-ACS) • Probability 0.90 (0.75-1.00)	**EUR 162** **EUR 503**
Primary care emergency clinic, Oslo (2017 figures) Standard costs per patient	**Direct costs per patient** (including wages triage, doctors, nurses, staff, service, consultation, diagnostics, treatment) = EUR 119 **Other costs per patient** (including administration, safety, cleaning services, building) = EUR 37 Total costs per patient: EUR 157 Adjusted to 2020 figures:	**EUR 166**
Additional costs at the primary care emergency clinic Personnel resources and costs (2 models)	**Model 1: Personnel wages** (2020 figures) Additional time spent with the 0/1-hour algorithm x personnel costs per hour: **Nurses: 20 min (0.3333)** x • Day: 0.238 x NOK 393 per hour = NOK 93,534 • Other: 0.762 x NOK 569 per hour = NOK 433,578 Total: NOK 175.70 **GPs: 50 min (0.8333) x** Registrar (85 %): • Day: 0.238 x NOK 576 per hour x 0.85 = NOK 116,5248 • Other: 0.762 x NOK 802 per hour x 0.85 = NOK 519,4554 Senior (15 %): • Day: 0.238 x NOK 685 per hour x 0.15 = NOK 24,4545 • Other: 0.762 x NOK 940 per hour x 0.15 = NOK 107,442 Total: NOK 639.90 **Total GPs and nurses x 1.3 (**to cover additional social costs) = NOK 1060.28	**Model 1: EUR 99**

	Model 2: Helfo tariffs (2020 figures) • 4 x 2cd = 4 x 211 x 0.238 = 200,872 • 4 x 2cdd = 4 x 10 x 0.238 x 0.15 = 1,428 • 4 x 2ck = 4 x 174 x 0.762 = 530,352 **Total tariffs x 2** (to cover other financing sources): NOK 732,65 x 2 = NOK 1465,304	**Model 2: EUR 137**
Additional diagnostics with the 0/1-hour algorithm (2020 figures)	**Details listed in Table S2**	**EUR 41**
Additional referrals to supplementary cardiac outpatient testing (2019 figures)	• 4.5 % of the non-hospitalised OUT-ACS group • Assumption: similar referral rate by the regular GP after OAEOC discharge = Estimated probability 0.10 * CCTA costs NOK 5490 Adjusted to 2020 figures = NOK 5559 * 0.10 = NOK 556	**EUR 52**
DRG at Drammen hospital 1 DRG = EUR 4269 (2020 figures) N = 567 patients	**DRG weight x costs per 1 DRG x patients (n):** • **DRG 112A:** 1.487 x 4269 x 1 = 6348.003 • **DRG 143:** 0.407 x 4269 x 425 = 738430.275 • **DRG 980E:** 0.159 x 4269 x 138 = 93670.398 • **DRG 981X:** 0.173 x 4269 x 3 = 2215.611 **= EUR 840 664.287 / 567 patients**	**EUR 1483**

CCTA: coronary computed tomography angiography; DRG: Diagnosis Related Groups; EUR: Euro; GP: general practitioner; NOK: Norwegian Kroner; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; OAEOC: Oslo Accident and Emergency Outpatient Clinic; OUT-ACS: One-hoUr Troponin in a low-risk population of Acute Coronary Syndrome

Table S2 Additional diagnostic tests at the primary care emergency clinic in Oslo with the ESC 0/1-hour algorithm

	N	Probability	Price (NOK) 2020 figures	Tariff codes	Unit cost (NOK)*
Venous blood samples at the clinic					
Standard blood panel with the 0/1-hour algorithm					
P-hs-cTnT x2	171/171	1.00	33.65 x 2	MB7	134.60
P-CRP	171/171	1.00	9.13	MB3	18.26
P-Creatinine	171/171	1.00	4.94	MB1	9.88
Pt-Estimated GFR	171/171	1.00	0.48	MB0	0.96
S-Potassium	171/171	1.00	4.94	MB1	9.88
B-Haemoglobin	171/171	1.00	9.13	MB3	18.26
S-Glucose	171/171	1.00	4.94	MB1	9.88
Additional venous blood samples					
Abdomen panel*	24/171	0.13	4.94 x 6	MB1	7.71
B-leukocytes	70/171	0.41	9.13	MB3	7.49
B-complete blood count	34/171	0.21	33.65	MB7	14.13
P-D-dimer	29/171	0.18	78.95	MB9	28.42
P-NT-proBNP	11/171	0.06	128.28	MB10	15.39
S-Sodium	65/171	0.37	4.94	MB1	3.66
Third hs-cTnT	334/1711	0.20	33.65	MB7	13.46
Additional diagnostics					
Additional ECG	335/1711	0.20	95 + 120	10b + 707	86.00
Chest x-ray	15/171	0.09	71 + 250	851 + 899	57.78
Total costs per low-risk patient					**NOK 435.76 = EUR 41**

Data on the probabilities of using a specific test or procedure at the OAEOC clinic was extracted from a random selection of the OUT-ACS cohort (10 %, 171/1711). Unit costs are presented in Norwegian Kroner (NOK), where 2020 Euro (EUR) 1.00 = 10.73 NOK. Outpatient radiological and laboratory services were estimated as the reimbursed sum from HELFO plus the patient's fee, multiplied by two, also to include personnel costs at the radiology and lab units.[2] Medical biochemistry (MB) tariffs were provided by The Norwegian Directorate of eHealth.[3]

*Abdomen panel: P-ASAT, P-ALAT, P-GGT, P-ALP, P-bilirubin, P-amylase; each with tariff MB1
CRP: C-reactive protein; ECG: electrocardiogram; ESC: European Society of Cardiology; GFR: glomerular filtration rate; hs-cTnT: high-sensitivity cardiac troponin T; NOK: Norwegian Kroner; NT-proBNP: N-Terminal pro-Brain Natriuretic Peptide

Table S3 Diagnostic tests and procedures at Drammen Hospital

Diagnostics	Probability
Venous blood samples at ED admission	
Standard blood panel (all patients): <u>Includes:</u> *B-Sedimentation rate, P-CRP, B-Haemoglobin, B-EVF, Ery-MCV, Ery-MCH, Red cell distribution, B-Leukocytes, B-Neutrophils, B-Lymphocytes, B-Monocytes, B-Eosinophils, B-Basophils, B-thrombocytes, S-Sodium, S-Potassium, P-Calcium, Pt-Estimated GFR, P-Creatinine, P-Cystatin C, P-ALAT, P-ALP, P-Bilirubin, P-Albumin, P-hs-Troponin I x2, B-Glucose, B-HbA1c, P-Cholesterol, P-LDL-cholesterol, P-HDL-cholesterol, P-Triglycerides, Additional serum tube, Additional citrate tube*	**1.00**
P-D-dimer	**0.20**
P-NT-proBNP	**0.30**
Diagnostics at ED admission	
ECG	**1.00**
Chest x-ray	**1.00**
Arterial blood gas	**0.07**
Advanced procedures	
Stress ECG	0.23 (129/567)
Echocardiogram	0.09 (52/567)
Long-term ECG monitoring	0.01 (7/567)
Holter ECG monitoring	0.003 (2/567)
Other procedures	0.03 (17/567)
Total:	**0.32 (181/567)***

The probabilities of diagnostic tests and procedures applied in the hospital assessment were included in the cost-driving estimates of hospital costs (Diagnosis-Related Groups).
* A total of 207 procedures among 181 of 567 patients

ECG: electrocardiogram; ED: emergency department; NT-proBNP: N-Terminal pro-Brain Natriuretic Peptide

Table S4 Estimated additional length of stay among non-hospitalised patients (n=1485) at the primary care emergency clinic

	Rule-out **n = 1232** **83.0 %**	**Observation** **n = 243** **16.4 %**	**Rule-in** **n = 10** **0.7 %**
0h + 1h sample*	67.1209 (SD 9.3652)	67.1209 (SD 9.3652)	67.1209 (SD 9.3652)
Preparation + lab transport	30 (20-40)	30 (20-40)	30 (20-40)
Central lab	75 (60-90)	75 (60-90)	75 (60-90)
Additional tests for patients in the Observation group (third hs-cTnT, repeated ECG, supplementary tests, lab preparation, transport and analysis)	-	120 (100-140)	-
Discharge by the treating GP	15 (10-20)	15 (10-20)	15 (10-20)
Total (base case scenario)	187 min (160-220) = **3.1 hours**	307 min (260-360) = **5.1 hours**	187 min (160-220) = **3.1 hours**
Total (conservative scenario)	217 min = **3.6 hours**	357 min = **6.0 hours**	217 min = **3.6 hours**

As the ESC 0/1-hour algorithm has not yet been implemented as a clinical routine at the primary care emergency clinic, the estimated additional length of stay is based on best guesses after interviewing senior personnel (GPs and nurses). Brackets illustrate the range of uncertainty in the estimates, where the upper range for each step was chosen in the conservative scenario.

* Time interval (mean) between 0- and 1-hour hs-cTnT samples in the OUT-ACS study, n=1711 patients [4]

ECG: electrocardiogram; GP: general practitioner; hs-cTnT: high-sensitivity cardiac troponin T; min: minutes; OAEOC: Oslo Accident and Emergency Outpatient Clinic; OUT-ACS: One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome; SD: standard deviation

Description of probabilistic sensitivity analysis

We also conducted a probabilistic sensitivity analysis where parameters in our base case model were incorporated as probability distributions. All distributions were incorporated according to common standards, with probabilities as beta or Dirichlet distributions and costs as gamma distributions.[5] Weights for health-related quality of life were incorporated as beta distributions due to weights not likely to be below 0 for any included health states.

Results indicate a 100% probability of the intervention being cost-effective given assumptions in the base case, as all iterations of the Monte Carlo simulation lies in the lower right quadrant of the cost-effectiveness plane (Figure S3). In health economic literature, this is often indicated as being a *dominant* strategy. With two possible strategies, all iterations in the lower right quadrant will also lead to the dominant strategy having a 100% probability of being cost-effective regardless of the variation of the cost-effectiveness threshold (Figure S4).

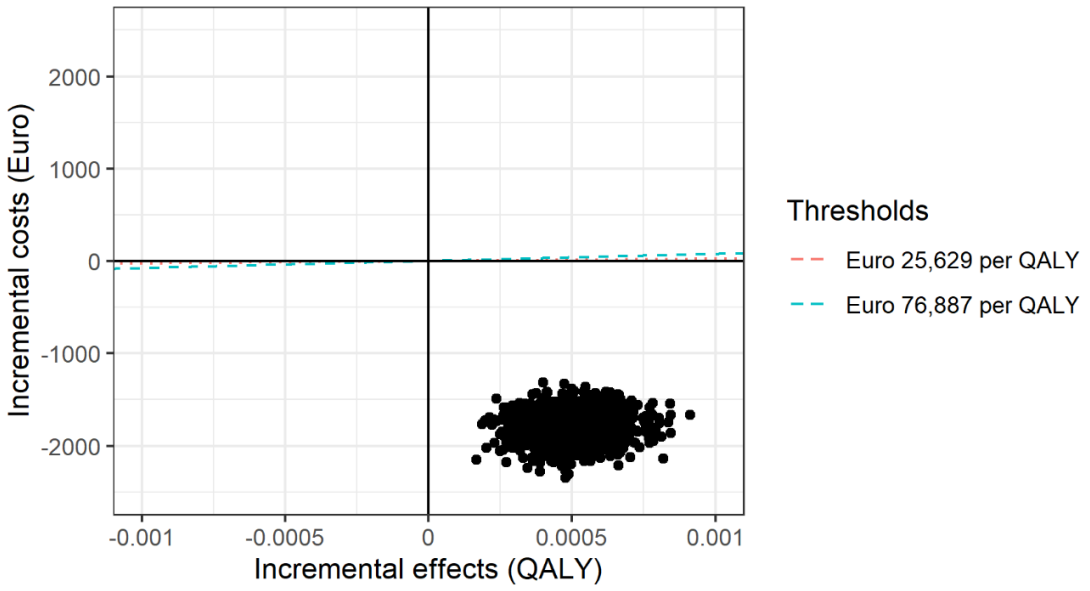

Figure S3 Scatter plot in a cost-effectiveness plane

Dots indicate each iteration from Monte Carlo simulations. Dotted lines for suggested Norwegian thresholds for cost-effectiveness.

QALY: quality-adjusted life-years

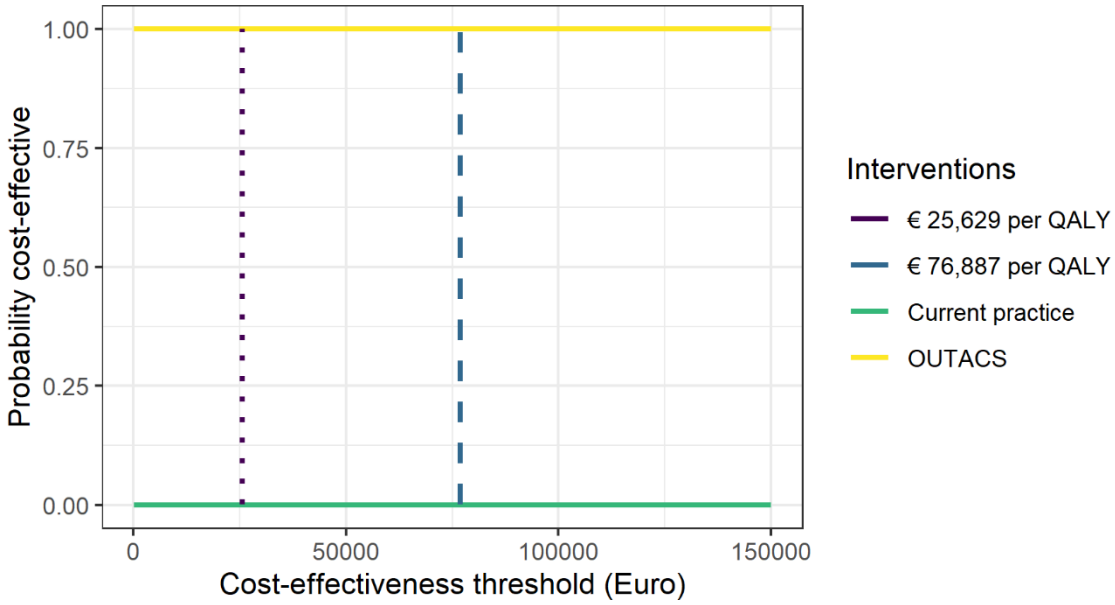

Figure S4 Cost-effectiveness acceptability curve

The curve indicates the probability of cost-effectiveness, given assumptions in the base case scenario.

OUT-ACS: One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome; QALY: quality-adjusted life-years

Table S5 Distance from emergency primary care to available hs-cTn assay according to the Norwegian population in 2020

	Norwegian emergency primary care-/OOH clinics, 2020[6]	Nearest hospital ED with an available hs-cTn assay (24/7)	Kilometres to ED	Minutes to ED (car)	OOH catchment area[6]	Cumulative population
1	Asker og Bærum OOH	Bærum hospital	0	0	127731	127731
2	Dalane (Eigersund) OOH	Stavanger University hospital	0	0	24080	151811
3	Elverum OOH	Innlandet hospital, Elverum	0	0	36475	188286
4	Flekkefjord OOH	Sørlandet hospital, Flekkefjord	0	0	25380	213666
5	Frøya OOH	Orkdal hospital	0	0	5151	218817
6	Gjøvik OOH	Gjøvik hospital	0	0	65593	284410
7	Hammerfest OOH	Hammerfest hospital	0	0	11448	295858
8	Kongsberg OOH	Kongsberg hospital	0	0	51224	347082
9	Kongsvinger OOH	Kongsvinger hospital	0	0	41468	388550
10	Kristiansand OOH	Sørlandet hospital, Kristiansand	0	0	130545	519095
11	Kristiansund OOH	Kristiansund hospital	0	0	35621	554716
12	Arendal OOH	Arendal hospital	0	0	101248	655964
13	Orkdal region OOH	Orkdal hospital	0	0	42001	697965
14	Lillehammer OOH	Lillehammer hospital	0	0	43943	741908
15	Narvik OOH	University hospital of North Norway, Narvik	0	0	22936	764844
16	Nordfjord OOH	Nordfjord hospital	0	0	16587	781431
17	Rana OOH	Helgeland hospital, Mo i Rana	0	0	30638	812069
18	Ringerike OOH	Ringerike hospital	0	0	65136	877205
19	Ryfylke OOH	Stavanger University hospital	0	0	3091	880296
20	Skien OOH	Telemark hospital, Skien	0	0	67857	948153
21	Sogn LMS OOH	Lærdal hospital	0	0	9100	957253
22	Stavanger OOH	Stavanger University hospital	0	0	181948	1139201
23	Sunnfjord-Ytre Sogn OOH	Førde Central hospital	0	0	33272	1172473
24	Sunnhordland OOH	Stord hospital	0	0	33905	1206378
25	Tinn kommunale OOH	Hospitalet Telemark, Skien	0	0	5691	1212069
26	Tromsø OOH	University hospital of North Norway, Tromsø	0	0	76974	1289043
27	Trondheim, Malvik, Melhus, Midtre-Gauldal OOH	St. Olavs hospital	0	0	242282	1531325
28	Ullensvang OOH	Odda Hospital	0	0	11048	1542373
29	Vefsn OOH	Helgeland hospital, Mosjøen	0	0	13278	1555651
30	Vesterålen OOH	Nordland hospital, Vesterålen Stokmarknes	0	0	30269	1585920
31	Voss OOH	Voss hospital	0	0	21703	1607623

	OOH clinics[6] *(Table continues)*	Nearest hospital ED with hs-cTn	Kilometres to ED	Minutes to ED (car)	OOH catchment area[6]	Cumulative population
32	Ålesund OOH	Ålesund hospital	0	0	75568	1683191
33	Innherred OOH	Levanger hospital	0.45	2	44555	1727746
34	Harstad OOH	University hospital of North Norway, Harstad	0.55	2	29576	1757322
35	Lofoten OOH	Nordland hospital, Lofoten	0.55	3	13720	1771042
36	Drammen OOH	Drammen hospital	0.6	2	128197	1899239
37	Hedmarken OOH	Innlandet hospital, Elverum	0.65	2	94875	1994114
38	Nord-Østerdal OOH	Innlandet hospital, Tynset	0.9	3	12897	2007011
39	Namsos OOH	Namsos hospital	1	3	22396	2029407
40	Bodø OOH	Nordland hospital, Bodø	1.2	3	53374	2082781
41	Molde OOH	Molde hospital	1.3	3	48755	2131536
42	Haugesund OOH	Haugesund hospital	1.5	4	55238	2186774
43	Volda, Ørsta OOH	Volda hospital	1.9	4	21298	2208072
44	Bergen OOH	Haukeland Universtiy hospital	1.9	5	283929	2492001
45	Tønsberg OOH	Vestfold hospital, Tønsberg	2.3	5	107722	2599723
46	Notodden OOH	Notodden hospital	3.3	5	25066	2624789
47	Oslo OOH	Ullevål hospital	4	12	693494	3318283
48	Nedre Romerike OOH	Akershus University hospital	4.4	7	145973	3464256
49	Sør-Varanger OOH	Kirkenes hospital	7.3	8	10158	3474414
50	Sarpsborg, Rakkestad OOH	Hospitalet i Østfold, Kalnes	7.4	11	64987	3539401
51	Porsgrunn OOH	Telemark hospital, Skien	9.8	15	36397	3575798
52	Sandnes OOH	Stavanger University hospital	13.3	14	91539	3667337
53	Bamble OOH	Telemark hospital, Skien	16.4	23	14061	3681398
54	Giske OOH	Ålesund hospital	16.7	18	8462	3689860
55	Bråset OOH (Hurum, Røyken)	Drammen hospital	16.9	23	94441	3784301
56	Nittedal OOH	Akershus University hospital	17	24	24249	3808550
57	Vennesla, Iveland OOH	Sørlandet hospital, Kristiansand	17.1	20	16105	3824655
58	Askøy OOH	Haukeland University hospital	17.2	20	29553	3854208
60	Sotra OOH	Haukeland University hospital	17.6	23	38316	3892524
59	Horten OOH	Vestfold hospital, Tønsberg	18.5	27	27351	3919875
61	Fredrikstad, Hvaler OOH	Hospitalet Østfold, Kalnes	18.7	22	87053	4006928
62	Sykkylven OOH	Ålesund hospital	20.4	47	12148	4019076
63	Klepp, Time OOH	Stavanger University hospital	23.1	24	38504	4057580
64	Karmøy OOH	Haugesund hospital	23.3	28	42186	4099766

	OOH clinics[6] *(Table continues)*	Nearest hospital ED with hs-cTn	Kilometres to ED	Minutes to ED (car)	OOH catchment area[6]	Cumulative population
65	Gloppen OOH	Nordfjord hospital	25.2	51	5854	4105620
66	Helgeland OOH	Helgeland hospital, Sandnessjøen	25.9	60	9741	4115361
67	Herøy, Dønna OOH	Helgeland hospital, Sandnessjøen	26.3	63	3148	4118509
68	Moss OOH	Østfold hospital, Kalnes	28.7	22	80559	4199068
69	Bjørnafjorden, Samnanger OOH	Haraldsplass Diakonale hospital	29.1	38	27393	4226461
70	Indre Fosen OOH	St. Olavs hospital	29.8	66	10084	4236545
71	Sandefjord OOH	Tønsberg hospital	29.8	25	63764	4300309
72	Strand OOH	Stavanger University hospital	30.4	28	12968	4313277
73	Nordhordland OOH	Haraldsplass Diakonale hospital	30.7	37	45116	4358393
74	Søndre Land OOH	Gjøvik hospital	30.8	31	5617	4364010
75	Tysnes OOH	Stord hospital	31.7	79	2869	4366879
76	Evenes-Tjeldsund OOH	University hospital of North Norway, Harstad	31.9	34	5564	4372443
77	Ørskog OOH	Ålesund hospital	32.5	32	9081	4381524
78	Sogndal OOH	Lærdal hospital	33.2	60	11847	4393371
79	Hå OOH	Stavanger University hospital	33.6	35	18991	4412362
80	Aremark og Halden OOH	Østfold hospital, Kalnes	34	29	32698	4445060
81	Værnesregionen OOH	St. Olavs hospital	35	33	31398	4476458
82	Follo OOH	Akershus University hospital	36.5	33	126330	4602788
83	Jessheim OOH	Akershus University hospital	36.9	28	63508	4666296
84	Austevoll OOH	Haukeland University hospital	36.9	85	5236	4671532
85	Ulstein-Hareid OOH	Ålesund hospital	37.3	73	13746	4685278
86	Kvinnherad OOH	Stord hospital	38.3	88	13071	4698349
87	Farsund OOH	Sørlandet hospital, Flekkefjord	40.7	41	9691	4708040
88	Larvik OOH	Vestfold hospital, Tønsberg	40.7	34	47204	4755244
89	Nesna OOH	Helgeland hospital, Sandnessjøen	42.2	72	1761	4757005
90	Grane, Hattfjelldal OOH	Helgeland hospital, Mosjøen	43	40	2779	4759784
91	Nes OOH	Akershus University hospital, Kongsvinger	43.1	38	23092	4782876
92	Steinkjer OOH	Levanger hospital	43.2	43	26420	4809296
93	Indre Østfold OOH	Østfold hospital, Kalnes	43.7	45	52192	4861488
94	Lindesnes OOH	Kristiansand hospital	44.3	45	23046	4884534
95	Herøy, Sande OOH	Volda hospital	47.4	46	11361	4895895
96	HAS OOH	Kristiansund hospital	48	116	11620	4907515
97	Indre Namdal OOH	Namsos hospital	48.4	47	5018	4912533

	OOH clinics[6] *(Table continues)*	Nearest hospital ED with hs-cTn	Kilometres to ED	Minutes to ED (car)	OOH catchment area[6]	Cumulative population
98	Seljord OOH	Notodden hospital	51.7	50	5291	4917824
99	Bremanger OOH	Nordfjord hospital	52.5	75	3629	4921453
100	Indre Salten OOH	Nordland hospital, Bodø	53.8	55	16336	4937789
101	Røros-Os-Holtålen OOH	Innlandet hospital, Tynset	55.9	53	9453	4947242
102	Vågan OOH	Nordland hospital, Vesterålen Stokmarknes	56.3	90	9608	4956850
103	Sirdal OOH	Sørlandet hospital	57.3	56	1822	4958672
104	Kragerø OOH	Skien hospital	58.5	55	10380	4969052
105	Florø OOH	Førde Central hospital	59.4	56	17207	4986259
106	Rauma OOH	Molde hospital	59.4	94	7468	4993727
107	Lunner-Gran OOH	Gjøvik hospital	59.5	50	22678	5016405
108	Luster OOH	Lærdal hospital	60.2	84	5174	5021579
109	Eidsvoll OOH	Kongsvinger hospital	62	57	25436	5047015
110	Karlsøy OOH	University hospital of North Norway, Tromsø	64.4	65	2200	5049215
111	Vanylven OOH	Nordfjord hospital	66	62	3117	5052332
112	Fronsvakta OOH	Lillehammer hospital	68.7	58	8842	5061174
113	Vega OOH	Helgeland hospital, Sandnessjøen	70.4	118	1200	5062374
114	Trysil OOH	Innlandet hospital, Elverum	71.4	58	6627	5069001
115	Vik OOH	Voss hospital	73.1	80	2635	5071636
116	Aurskog-Høland, Rømskog OOH	Akershus University hospital, Kongsvinger	73.5	65	17390	5089026
117	Bardu OOH	University hospital of North Norway, Narvik	74.2	66	16269	5105295
118	Kvam OOH	Voss hospital	75.5	80	8457	5113752
119	Lyngen OOH	University hospital of North Norway, Tromsø	79.2	107	2794	5116546
120	Vikna, Nærøy OOH	Namsos hospital	87.6	113	9623	5126169
121	Etne, Vindafjord OOH	Stord hospital	89.5	85	12776	5138945
122	Gildeskål OOH	Nordland hospital, Bodø	90.7	82	1950	5140895
123	Balsfjord-Storfjord OOH	University hospital of North Norway, Tromsø	92.2	78	7388	5148283
124	Brønnøy OOH	Helgeland hospital, Sandnessjøen	92.4	163	9892	5158175
125	Nore og Uvdal OOH	Kongsberg hospital	93.7	85	2439	5160614
126	Værøy OOH	Nordland hospital, Lofoten	96.2	175	728	5161342
127	Valdres OOH	Gjøvik hospital	97.3	88	17578	5178920
128	Fosen OOH	St. Olavs hospital	101	125	14611	5193531
129	Oppdal OOH	Innlandet hospital, Tynset	102	86	7001	5200532
130	Sunndal OOH	Kristiansund hospital	103	99	7036	5207568

	OOH clinics[6] *(Table continues)*	Nearest hospital ED with hs-cTn	Kilometres to ED	Minutes to ED (car)	OOH catchment area[6]	Cumulative population
131	Nord-Gudbrandsdal OOH	Lillehammer hospital	109	90	18262	5225830
132	Sauda OOH	Haugesund hospital	112	116	4595	5230425
133	Suldal OOH	Haugesund hospital	114	116	3804	5234229
134	Gol-Hemsedal OOH	Ringerike hospital	116	98	7094	5241323
135	Meløy OOH	Nordland hospital, Bodø	117	103	6288	5247611
136	Engerdal OOH, Trysil	Innlandet hospital, Tynset	119	98	1268	5248879
137	Vevelstad OOH	Helgeland hospital, Mosjøen	119	153	462	5249341
138	Lurøy OOH	Helgeland hospital, Sandnessjøen	122	183	1890	5251231
139	Bindal OOH	Hospitalet Namsos	127	56	1426	5252657
140	Tokke-Vinje OOH	Telemark hospital, Skien	128	124	5877	5258534
141	Solund OOH	Førde Central hospital	129	200	802	5259336
142	Stor-Elvdal OOH	Lillehammer hospital	138	128	2419	5261755
143	Rødøy OOH	Helgeland hospital, Mo i Rana	140	181	1213	5262968
144	Tana-Nesseby OOH	Kirkenes hospital	140	118	3844	5266812
145	Øvre Hallingdal OOH	Ringerike hospital	140	119	7947	5274759
146	Alta OOH	Hammerfest hospital	142	134	20789	5295548
147	Porsanger OOH	Hammerfest hospital	143	129	3998	5299546
148	Træna OOH	Helgeland hospital, Mo i Rana	143	319	435	5299981
149	Leka OOH	Namsos hospital	151	166	557	5300538
150	Finnsnes OOH	University hospital of North Norway, Tromsø	159	133	18315	5318853
151	Hol OOH	Ringerike hospital	159	135	4441	5323294
152	Måsøy OOH	Hammerfest hospital	168	153	1225	5324519
153	Vadsø OOH	Kirkenes hospital	171	144	5788	5330307
154	Kåfjord OOH	University hospital of North Norway, Tromsø	179	150	2071	5332378
155	Nordkapp OOH	Hammerfest hospital	181	167	3162	5335540
156	Bykle-Valle OOH, Hovden	Telemark hospital, Skien	194	184	2129	5337669
157	Steigen OOH	Bodø hospital	212	183	5374	5343043
158	Karasjok OOH	Hammerfest hospital	218	186	2628	5345671
159	Nordreisa OOH	University hospital of North Norway, Tromsø	224	199	4861	5350532
160	Kvænangen OOH	Hammerfest hospital	229	226	1191	5351723
161	Båtsfjord OOH	Kirkenes hospital	244	193	2221	5353944
162	Skjervøy OOH	University hospital of North Norway, Tromsø	245	217	2927	5356871
163	Vardø OOH	Kirkenes hospital	245	206	2029	5358900
164	Kautokeino OOH	Hammerfest hospital	271	239	2910	5361810
165	Berlevåg OOH	Kirkenes hospital	272	216	957	5362767
166	Hasvik OOH	Hammerfest hospital	278	318	1005	5363772

	OOH clinics[6] *(Table continues)*	Nearest hospital ED with hs-cTn	Kilometres to ED	Minutes to ED (car)	OOH catchment area[6]	Cumulative population
167	Nordkyn OOH	Kirkenes hospital	336	293	2422	5366194
168	Øksfjord OOH	University hospital of North Norway, Tromsø	355	320	888	5367082
169	Røst OOH	Nordland hospital, Bodø	?	?	498	5367580

The list of Norwegian OOH clinics in 2020 and catchment areas was obtained from the Norwegian Research Centre (NORCE).[6]
Distance and minutes by car to nearest hospital ED with available hs-cTn assay was investigated for the purpose of this study by contacting each hospital by phone and Google Maps.

ED: emergency department; hs-cTn: high-sensitivity cardiac troponin; OOH: out-of-hours

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