Diagnostic accuracy of a machine learning algorithm using point-of-care high-sensitivity cardiac troponin I for rapid rule-out of myocardial infarction: a retrospective study

Betül Toprak, Hugo Solleder*, Eleonora Di Carluccio, Jaimi H Greenslade, William A Parsonage, Karen Schulz, Louise Cullen, Fred S Apple, Andreas Ziegler, Stefan Blankenberg, on behalf of the Artificial Intelligence in Suspected Myocardial Infarction Study (ARTEMIS) group†*

Summary

Background Point-of-care (POC) high-sensitivity cardiac troponin (hs-cTn) assays have been shown to provide similar analytical precision despite substantially shorter turnaround times compared with laboratory-based hs-cTn assays. We applied the previously developed machine learning based personalised Artificial Intelligence in Suspected Myocardial Infarction Study (ARTEMIS) algorithm, which can predict the individual probability of myocardial infarction, with a single POC hs-cTn measurement, and compared its diagnostic performance with standard-of-care pathways for rapid rule-out of myocardial infarction.

Methods We retrospectively analysed pooled data from consecutive patients of two prospective observational cohorts in geographically distinct regions (the Safe Emergency Department Discharge Rate cohort from the USA and the Suspected Acute Myocardial Infarction in Emergency cohort from Australia) who presented to the emergency department with suspected myocardial infarction. Patients with ST-segment elevation myocardial infarction were excluded. Safety and efficacy of direct rule-out of myocardial infarction by the ARTEMIS algorithm (at a pre-specified probability threshold of <0·5%) were compared with the European Society of Cardiology (ESC)-recommended and the American College of Cardiology (ACC)-recommended 0 h pathways using a single POC high-sensitivity cardiac troponin I (hs-cTnI) measurement (Siemens Atellica VTLi as investigational assay). The primary diagnostic outcome was an adjudicated index diagnosis of type 1 or type 2 myocardial infarction according to the Fourth Universal Definition of Myocardial Infarction. The safety outcome was a composite of incident myocardial infarction and cardiovascular death (follow-up events) at 30 days. Additional analyses were performed for type I myocardial infarction only (secondary diagnostic outcome), and for each cohort separately. Subgroup analyses were performed for age (<65 years *vs* ≥65 years), sex, symptom onset (≤3 h *vs* >3 h), estimated glomerular filtration rate (<60 mL/min per 1·73 m² *vs* ≥60 mL/min per 1·73 m²), and absence or presence of arterial hypertension, diabetes, a history of coronary artery disease, myocardial infarction, or heart failure, smoking, and ischaemic electrocardiogram signs.

Findings Among 2560 patients (1075 [42%] women, median age 58 years [IQR 48·0–69·0]), prevalence of myocardial infarction was 6·5% (166/2560). The ARTEMIS-POC algorithm classified 899 patients (35·1%) as suitable for rapid rule-out with a negative predictive value of 99·96% (95% CI 99·64–99·96) and a sensitivity of 99·68% (97·21–99·70). For type I myocardial infarction only, negative predictive value and sensitivity were both 100%. Proportions of missed index myocardial infarction (0·05% [0·04–0·42]) and follow-up events at 30 days (0·07% [95% CI 0·06–0·59]) were low. While maintaining high safety, the ARTEMIS-POC algorithm identified more than twice as many patients as eligible for direct rule-out compared with guideline-recommended ESC 0 h (15·2%) and ACC 0 h (13·8%) pathways. Superior efficacy persisted across all clinically relevant subgroups.

Interpretation The patient-tailored, medical decision support ARTEMIS-POC algorithm applied with a single POC hs-cTnI measurement allows for very rapid, safe, and more efficient direct rule-out of myocardial infarction than guideline-recommended pathways. It has the potential to expedite the safe discharge of low-risk patients from the emergency department including early presenters with symptom onset less than 3 h at the time of admission and might open new opportunities for the triage of patients with suspected myocardial infarction even in ambulatory, preclinical, or geographically isolated care settings.

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Introduction

Chest pain is the leading cause of presentation to the emergency department globally.[1] However, among patients with indicative symptoms, only 5% to 25% are finally diagnosed with an acute myocardial infarction or require immediate treatment.[2] The identification of

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*Contributed equally

†A full list of collaborators is provided at the end of this Article

Department of Cardiology (B Toprak MD, Prof A Ziegler PhD, Prof S Blankenberg MD) **and University Center of Cardiovascular Science** (B Toprak, Prof S Blankenberg) **and Department for Population Health Innovation** (B Toprak, Prof S Blankenberg), **University Heart and Vascular Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; German Center for Cardiovascular Research (DZHK), Partner Sites Hamburg/Kiel/Luebeck, Hamburg, Germany** (B Toprak, Prof A Ziegler, Prof S Blankenberg); **Cardio-CARE, Medizincampus Davos, Davos, Switzerland** (H Solleder PhD, E Di Carluccio MSc, Prof A Ziegler); **Emergency and Trauma Centre, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia** (J H Greenslade PhD, Prof L Cullen MD); **Australian Centre for Health Services Innovation, School of Public Health and Social Work, Queensland University of Technology, Brisbane, QLD, Australia** (Prof W A Parsonage MD, Prof L Cullen); **Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA** (K Schulz DC, Prof F S Apple PhD); **Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia** (Prof L Cullen); **Hennepin Healthcare Research Institute, Minneapolis, MN, USA** (Prof F S Apple); **School of**

Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, Pietermaritzburg, South Africa
(Prof A Ziegler)

Correspondence to:
Prof Stefan Blankenberg, Department of Cardiology, University Heart and Vascular Center, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany
s.blankenberg@uke.de

Research in context

Evidence before this study

Myocardial infarction is a major global health issue. International guidelines recommend standardised triage pathways to diagnose and rule-out myocardial infarction in emergency departments. These conventional pathways rely on fixed assay-specific high-sensitivity cardiac troponin (hs-cTn) concentrations and require central laboratory structures. In addition, they are not applicable to patients with early symptom onset, and neglect clinical variables. A global application including a personalised and universal approach for clinical decision making is lacking. Machine learning is increasingly used to address these limitations by combining distinct variables to achieve high diagnostic accuracy. We systematically searched PubMed for studies published from database inception up to April 5, 2024, using the keywords: "machine learning", "myocardial infarction", "diagnosis", and "troponin" without any language restrictions. We identified three machine learning algorithms for suspected myocardial infarction that were validated after derivation: myocardial-ischaemic-injury-index (MI^3), Collaboration for the Diagnosis and Evaluation of Acute Coronary Syndrome (CoDE-ACS), and Artificial Intelligence in Suspected Myocardial Infarction Study (ARTEMIS). Among them, the personalised ARTEMIS algorithm that combines hs-cTn values with routinely available clinical variables to estimate the individual probability of myocardial infarction is the first to be applicable with numerous available hs-cTn assays and to specifically allow for the integration of point-of-care (POC) hs-cTn. In contrast to other machine learning-based diagnostic algorithms for suspected myocardial infarction, the ARTEMIS algorithm does not require measurement of further biomarkers and can be flexibly and universally applied with most available hs-cTn assays including POC tests.

Added value of this study

By combining the previously derived, validated, and generalised ARTEMIS algorithm with POC hs-cTn, our study provides the first (to our knowledge) retrospective application of a patient-tailored algorithm in conjunction with a single POC high-sensitivity cardiac troponin I measurement and its suggested threshold for rapid rule-out of myocardial infarction in two geographically distinct cohorts. The ARTEMIS-POC algorithm yields doubled efficacy with maintained high safety compared with guideline-recommended pathways. Further, it performs consistently well across clinically challenging subgroups, including patients with early symptom onset.

Implications of all the available evidence

Our study builds upon previous work within the ARTEMIS framework and extends the concept of machine learning for rule-out of myocardial infarction to its use in conjunction with POC hs-cTn. The ARTEMIS-POC algorithm can be calibrated and customised according to local care priorities (eg, rural areas) by providing flexibility of the selection of diagnostic thresholds. Further, it has the potential to reduce rule-out time to only a few minutes even in patients with early symptom onset, safely redirect low-risk patients away from the emergency department, and allow for an extension of rule-out of suspected myocardial infarction from high-resource emergency departments with access to a central laboratory 24 h a day towards alternative health-care settings, including preclinical or ambulatory care. The current application of the ARTEMIS algorithm in existing study cohorts allows for its calibration to multiple clinical and local settings. To achieve real-world clinical implementation, investigation of outcomes such as feasibility, sustainability, and cost-effectiveness of the ARTEMIS algorithm is still warranted. Overall, the integration of POC hs-cTn into an easy to use, calibrated algorithm for suspected myocardial infarction may allow for its uniform clinical application in any setting.

individuals at low risk of myocardial infarction who will not benefit from hospital admission or who qualify for early discharge has gained growing interest.

Together with the introduction of high-sensitivity cardiac troponin (hs-cTn) assays, a continuous evolution of diagnostic pathways towards rapid rule-out protocols has emerged to achieve this goal.[3–5] Such clinical decision pathways (ie, as endorsed by the European Society of Cardiology [ESC][6] or the American College of Cardiology [ACC])[7] rely on fixed assay-specific hs-cTn thresholds and are limited by turnaround times of laboratory-based hs-cTn testing. Additionally, these clinical decision pathways do not systematically account for important clinical variables that are known to influence hs-cTn concentrations and pretest probability of myocardial infarction, such as age, sex, symptom onset, electrocardiographic findings, and cardiovascular risk factors.[8–11] In addition, both guideline-recommended pathways do not allow for direct rule-out of myocardial infarction in early presenters based on a single hs-cTn measurement.

To address these limitations, the Artificial Intelligence in Suspected Myocardial Infarction Study (ARTEMIS) algorithm was developed and externally validated in two German cohorts, including patients with symptoms suggestive of an acute myocardial infarction, and most importantly, was shown to be generalisable in 13 international cohorts across four continents. This personalised diagnostic algorithm estimates the individual probability of myocardial infarction by integrating routinely available clinical variables of interest, using single or serial concentrations of six different hs-cTn assays, and allowing for flexible timing of serial blood testing.[12] The algorithm is optimised for the identification of both non-ST-elevation myocardial infarction type 1 (T1MI) and type 2 (T2MI).

If this patient-tailored algorithm is used in connection with modern hs-cTn point-of-care (POC) assays fulfilling the requirements of high sensitivity based on whole blood assessment,[13,14] it has the potential to improve immediate and safe rule-out of patients not only in the emergency department, but also in ambulatory and pre-clinical care including rural settings in which hospital infrastructure is insufficiently available.

We therefore aimed to retrospectively apply the ARTEMIS algorithm and the guideline-recommended pathways in conjunction with a single POC hs-cTn level at presentation and compare their safety and efficacy for immediate rule-out in two geographically distinct cohorts of patients with suspected myocardial infarction.

Methods

Study cohorts

Individual-level data from two prospective observational cohort studies, the US-based Safe Emergency Department Discharge Rate (SEIGE; registered with ClinicalTrials.gov, NCT04772157; registration date: Feb 26, 2021) and the Australian Suspected Acute Myocardial Infarction in Emergency (SAMIE; registered with ACTRN, ACTRN12621000053820; date of registration: Jan 21, 2021) cohort, were jointly and retrospectively analysed. The STARD checklist for this study is provided in the appendix (p 10). Study protocols for each cohort were approved by the respective institutional review boards (IRBs) under numbers HHRI 20–4828 and LNR/2020/QRBW/65773. All participants provided written informed consent. Based on the study-specific IRBs, the need for additional ethical approval to conduct the current analyses was waived.

The SEIGE study includes consecutive patients aged 21 years or older presenting to the emergency department in whom high-sensitivity cardiac troponin I (hs-cTnI) measurements were obtained upon clinical indication between October, 2020 and January, 2021 at the Hennepin Healthcare/Hennepin County Medical Center (Minneapolis, MN, USA). Patients undergoing investigation for suspected myocardial infarction were included if they had serial cTnI measurements at minimum at baseline and 2 h after presentation and at least one 12-lead electrocardiogram (ECG) available. Patients were excluded if they had ST-segment elevation myocardial infarction, were pregnant, declined to participate, or were unable to provide informed consent.

The SAMIE study includes consecutive patients aged 18 years or older who presented to one of five Australian hospitals between November, 2020 and September, 2021. Blood samples for hs-cTn measurements were collected at presentation and 2–3 h later in all patients per protocol. Patients were excluded if they had ST-segment elevation myocardial infarction, were pregnant, transferred from another hospital, previously enrolled within 30 days, or were unable or unwilling to provide informed consent. Further details about both cohorts are provided in the appendix (p 2).

Patients from both cohorts in whom the treating physician performed investigation for ruling out or ruling in an acute myocardial infarction upon clinical indication were included in the analyses of this current study. Patients with a symptom onset of less than 3 h were considered early presenters.

Procedures

Cardiac troponin assays

In SEIGE, fresh ethylene diamine tetraacetic acid plasma was sampled for hs-cTnI measurement using the Architect hs-cTnI assay (Abbott, IL, USA). In SAMIE, the Access hs-cTnI assay (Beckman Coulter, Brea, CA, USA) was used in routine clinical practice. Hs-cTnI measurements used in routine care (Abbott or Beckman) were considered for adjudication of diagnoses in both cohort studies.

In SEIGE, lithium-heparinised whole blood was used to concurrently measure Siemens POC Atellica VTLi hs-cTnI. In SAMIE, lithium-heparinised plasma samples were taken at the same time as the samples for the standard-of-care hs-cTnI assay and stored at –80°C. These samples were later thawed and tested in a single batch on the POC Atellica VTLi platform at the end of July, 2021. The POC Atellica VTLi assay, which is the investigational assay in both cohorts, has a limit of detection of 1·24 ng/L. The lower limits of quantification are 3·7 ng/L for whole blood and 2·1 ng/L for plasma. Further assay-specific analytical information is provided in the appendix (p 2).

See Online for appendix

Adjudication of index diagnoses

In each cohort, adjudication of diagnoses was performed independently by two local specialists (cardiologists, emergency medicine specialists, or both) in a blinded fashion. For adjudication, all available medical records were reviewed, including 12-lead ECG, findings from echocardiography and angiography if available, hs-cTnI concentrations as measured by the clinically applied assay, and other clinical data. The Fourth Universal Definition of Myocardial Infarction was used for the diagnosis of myocardial infarction. Patients with myocardial infarction were further classified as having T1MI or T2MI; T2MI required objective evidence or documentation of oxygen supply–demand imbalance as the underlying pathogenesis of myocardial ischaemia.[15,16]

Follow-up data at 30 days

Follow-up information (ie, incident myocardial infarction excluding the index myocardial infarction event, and cardiovascular death) was collected at 30 days after index presentation to the emergency department using medical and social security records.

ARTEMIS diagnostic algorithm

The summary concept with all steps related to derivation, validation, and generalisation of the ARTEMIS algorithm

has been previously described.[12] Details are provided in the appendix (pp 3–6). In brief, feature selection for the ARTEMIS models was initially performed using different learning machines and 10-fold cross-validation across all available hs-cTn assays and a total of 18 available candidate features. Eight clinical variables, including age, sex, symptom onset greater than 3 h, ischaemic signs in the ECG in line with guideline-recommended definitions[7] (details are provided in the appendix [p 4]), heart rate, smoking status (including current and former smoking), hyperlipoproteinaemia, and family history of coronary artery disease were kept after variable selection in the single hs-cTn ARTEMIS model. This model estimates the individual myocardial infarction probability as a number between 0% and 100%. A myocardial infarction probability threshold of less than 0·5% was previously proposed as the applicable direct rule-out threshold.[12] Relevant information regarding all modelling steps is provided in an executive summary in the appendix (p 4). No modifications were made to the model in the current study.

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Among all available hs-cTn assays, the current analyses focus on the application of the POC VTLi hs-cTnI assay in conjunction with the single hs-cTn measurement-based ARTEMIS algorithm and the pre-specified probability threshold.

Guideline-recommended pathways

According to the ESC 0 h pathway, immediate rule-out was allowed if symptom onset was greater than 3 h and hs-cTnI was very low. A rapid rule-out threshold of less than 4 ng/L was previously derived and validated for the POC VTLi assay.[14] This threshold was used to apply the ESC 0 h pathway in our present study. According to the ACC 0 h pathway (ie, the modified ESC 0 h pathway), immediate rule-out was possible with the presence of a non-ischaemic ECG, symptom onset 3 h or greater, and hs-cTnI below the respective limit of quantification. Following the recommendations of the International Federation of Clinical Chemistry and Laboratory Medicine–Committee of Clinical Applications of Cardiac Bio-Markers (IFCC C-CB), hs-cTnI values were rounded to the nearest integer before applying the pathway rules. Further details are provided in the appendix (p 7).

Outcomes

The primary diagnostic outcome was defined as the adjudicated final diagnosis of non-ST-elevation myocardial infarction (T1MI or T2MI) at index presentation to the emergency department. The secondary diagnostic outcome comprised the adjudicated diagnosis of T1MI only. The safety outcome was a composite of incident myocardial infarction and cardiovascular death at 30 days, excluding events that occurred during index presentation.

Statistical analysis

Baseline characteristics as provided in patients' medical records are displayed as absolute numbers (percentages) for categorical variables and median (quartiles) for continuous variables. Patients with symptoms suggestive of an acute myocardial infarction were enrolled in both registries making it imperative for clinicians to either rule in or rule out a non-ST-elevation myocardial infarction. Therefore, once the patient had agreed to participate in the study, all relevant data were collected. If data were missing, this was accidental. We thus assume the data to be missing completely at random and the missing at random assumption to be implicitly fulfilled. Multiple imputation of missing data (including ECG data in SAMIE) was performed by using 12 generalisation

	All (N=2560)	No index MI (n=2394)	Index MI (n=166)
Age, years	58·0 (48·0–69·0)	58·0 (47·0–68·0)	61·5 (53·0–74·5)
Sex			
Male	1485 (58·0%)	1379 (57·6%)	106 (63·9%)
Female	1075 (42·0%)	1015 (42·4%)	60 (36·1%)
Vital parameters			
Heart rate, bpm	79·0 (68·0–94·0)	79·0 (68·0–93·0)	85·0 (72·0–104·0)
Systolic blood pressure, mm Hg	135·0 (121·0–152·0)	134·0 (121·0–151·0)	141·0 (123·0–157·8)
Cardiac history			
History of CAD	608 (23·8%)	544 (22·7%)	64 (38·6%)
History of MI	429 (16·8%)	378 (15·8%)	51 (30·7%)
History of HF*	197 (7·7%)	172 (7·2%)	25 (15·1%)
Risk factors			
Hypertension	1416 (55·3%)	1304 (54·5%)	112 (67·5%)
Hyperlipoproteinaemia	1201 (46·9%)	1098 (45·9%)	103 (62·0%)
Smoker (current or previous)	978 (38·2%)	908 (37·9%)	70 (42·2%)
Family history of CAD	899 (35·1%)	850 (35·5%)	49 (29·5%)
Diabetes	673 (26·3%)	611 (25·5%)	62 (37·3%)
Index presentation data			
Symptom onset >3 h	1243 (48·6%)	1156 (48·3%)	87 (52·4%)
Ischaemic ECG signs	39 (1·5%)	28 (1·2%)	11 (6·6%)
Atellica VTLi POC hs-cTnI at baseline, ng/L	5·0 (3·1–10·3)	4·6 (3·0–8·9)	36·7 (16·4–118·8)
Abbott hs-cTnI at baseline, ng/L†	8·0 (4·0–21·0)	7·0 (4·0–18·0)	59·5 (21·8–171·5)
Beckman hs-cTnI at baseline, ng/L‡	3·0 (2·3–6·0)	3·0 (2·3–6·0)	61·0 (22·8–193·5)
Type 1 MI§	74 (2·9%)	..	74 (44·6%)
Type 2 MI§	92 (3·6%)	..	92 (55·4%)
ARTEMIS MI probability at baseline	1·7 (0·1–7·2)	1·5 (0·1–6·6)	22·1 (7·4–49·8)
30-day outcomes			
30-day MI	12 (0·5%)	10 (0·4%)	2 (1·2%)
30-day cardiovascular death	21 (0·8%)	17 (0·7%)	4 (2·4%)
30-day composite¶	33 (1·3%%)	27 (1·1%)	6 (3·6%)

Data are n (%) for categorical variables and median (IQR) for continuous variables and are provided for the pooled dataset (SEIGE and SAMIE cohorts) according to absence or presence of an adjudicated index diagnosis of myocardial infarction (type 1 or type 2). CAD=coronary artery disease. ECG=electrocardiogram. HF=heart failure. hs-cTnI=high-sensitivity cardiac troponin I. MI=myocardial infarction. POC=point-of-care. *Known heart failure of any type. †Assay used for adjudication in SEIGE. ‡Assay used for adjudication in SAMIE. §According to the Fourth Universal Definition of MI. ¶Composite of MI and cardiovascular death at 30 days, excluding index events.

Table 1: **Baseline characteristics and 30-day outcomes in pooled cohorts**

	<0·1%	<0·2%	<0·3%	<0·4%	<0·5%	<0·6%	<0·7%	<0·8%	<0·9%	<1%
NPV	99·96 (99·67–99·97)	99·96 (99·66–99·96)	99·96 (99·67–99·97)	99·96 (99·65–99·96)	99·96 (99·64–99·96)	99·96 (99·63–99·96)	99·75 (99·64–99·85)	99·74 (99·66–99·80)	99·73 (99·69–99·76)	99·71 (99·69–99·73)
Sensitivity	99·80 (98·24–99·81)	99·75 (97·85–99·77)	99·74 (97·74–99·76)	99·70 (97·40–99·73)	99·68 (97·21–99·70)	99·65 (96·99–99·68)	98·61 (98·00–99·11)	98·45 (97·44–99·22)	98·30 (96·84–99·32)	98·14 (96·20–99·41)
Rule-out	653 (25·5%)	748 (29·2%)	809 (31·6%)	854 (33·4%)	899 (35·1%)	939 (36·7%)	964 (37·7%)	988 (38·6%)	1018 (39·8%)	1046 (40·9%)
Index MI	0·04 (0·04–0·36)	0·04 (0·04–0·39)	0·04 (0·04–0·38)	0·05 (0·04–0·41)	0·05 (0·04–0·42)	0·05 (0·04–0·43)	0·24 (0·23–0·26)	0·26 (0·22–0·30)	0·27 (0·20–0·36)	0·29 (0·17–0·43)
Follow-up event	0·05 (0·04–0·41)	0·06 (0·05–0·51)	0·06 (0·05–0·52)	0·06 (0·06–0·54)	0·07 (0·06–0·59)	0·08 (0·07–0·71)	0·09 (0·08–0·81)	0·10 (0·09–0·88)	0·10 (0·10–0·91)	0·11 (0·10–0·95)

All effect estimates were pooled across imputed datasets for the jointly analysed cohorts (2560 patients). Data are median percent (95% CI) or n (%). Performance measures for direct rule-out by ARTEMIS-POC algorithm are shown for a range of MI probabilities from <0·1% to <1%. MI=myocardial infarction. NPV=negative predictive value. POC=point-of-care.

Table 2: **NPVs, sensitivities, and rule-out proportions for index MI, missed index MI, and follow-up events using the ARTEMIS-POC algorithm at different MI probability thresholds**

cohorts within the ARTEMIS project. Details on these cohorts and the imputation procedure are provided in the appendix (pp 8–9). Following multiple imputation, calibration was performed across all imputed datasets. Estimates were pooled with Rubin's rule; details are again provided in the appendix (p 9).

To assess the diagnostic performance of the ARTEMIS-POC algorithm across the spectrum of probability thresholds for myocardial infarction, probabilities from 0·1% to 1% were considered in steps of 0·1%. Performance measures for rapid rule-out were negative predictive value (NPV), sensitivity, and efficacy (ie, the proportion of patients being ruled out), the proportion of missed index myocardial infarction events, and the 30-day incidence of myocardial infarction or cardiovascular death among ruled-out individuals. Corresponding 95% CIs were estimated to assess variability. Tests for statistical significance were not applicable to our analyses, especially for the comparison of the performances of the ARTEMIS algorithm, ESC, and ACC pathways, where we did not perform such tests due to the low number of events. Additional analyses were performed for T1MI only (the secondary diagnostic outcome), and per cohort (ie, for SEIGE and SAMIE separately).

Subgroup analyses were performed on non-imputed data for age (<65 years *vs* ≥65 years), sex, symptom onset (≤3 h *vs* >3 h), estimated glomerular filtration rate (<60 mL/min per 1·73 m² *vs* ≥60 mL/min per 1·73 m²), and absence or presence of arterial hypertension, diabetes, a history of coronary artery disease, myocardial infarction, or heart failure, smoking, and ischaemic ECG signs. Statistical analyses were performed in R version 4.2.0.

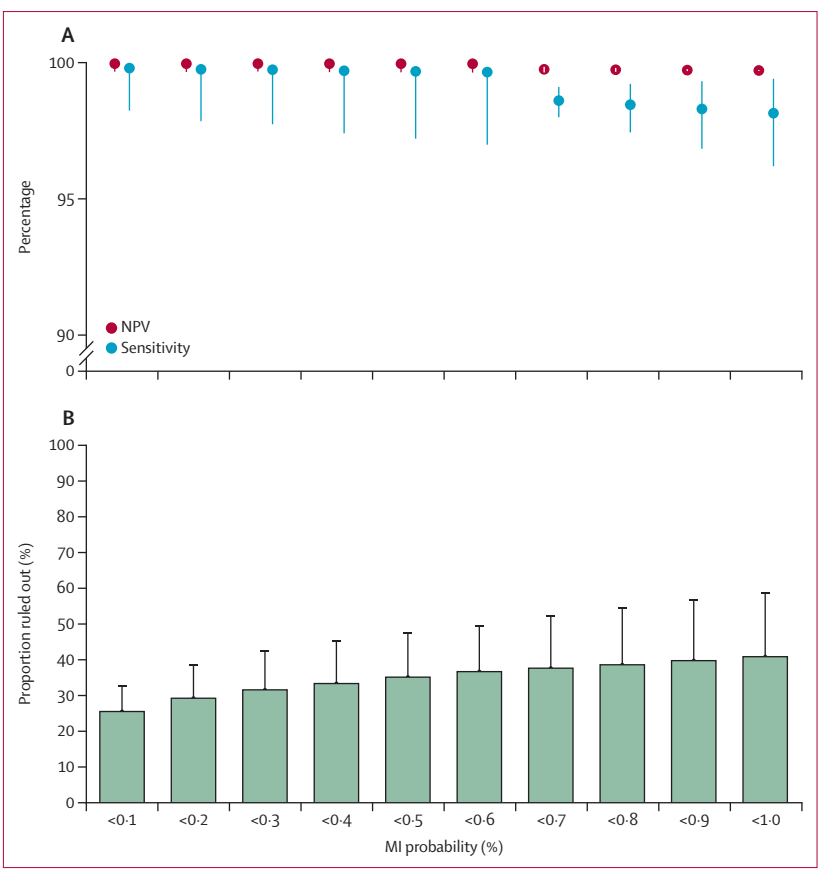

Figure 1: **NPVs, sensitivities, and rule-out proportions for index MI using the ARTEMIS-POC algorithm**
MI=myocardial infarction. NPV=negative predictive value.

Role of the funding source

Neither the funder nor any external party had a role in the data collection, analysis interpretation, writing of the manuscript, or the decision to submit for publication.

Results

Overall, 2560 patients were included from both cohorts. The median age was 58 years (IQR 48·0–69·0) and 1075 (42·0%) were women (table 1). No data on race or ethnicity were available in both cohorts. An acute myocardial infarction at index presentation was diagnosed in 166 (6·5%) of 2560 patients, of whom 74 patients (2·9%) had T1MI and 92 (3·6%) had T2MI. Individuals with an adjudicated final diagnosis of myocardial infarction were more likely to have a history of coronary artery disease, myocardial infarction, heart failure, and traditional cardiovascular risk factors. A total of 1243 (48·6%) of 2560 individuals had symptom onset greater than 3 h. Median Atellica VTLi POC hs-cTnI concentration was

5·0 ng/L (IQR 3·1–10·3; non-myocardial infarction: 4·6 ng/L [3·0–8·9]; myocardial infarction: 36·7 ng/L [16·4–118·8]). Cohort-specific baseline characteristics are displayed in the appendix (p 12).

Among all 2560 patients, 33 (1·3%) experienced either an acute myocardial infarction, cardiovascular death, or both within 30 days after index presentation (table 1). Per-cohort follow-up data are shown in the appendix (p 13).

In pooled analyses, the ARTEMIS-POC algorithm maintained its direct rule-out performance across a broad range of probability thresholds for myocardial infarction (table 2, figure 1). Respective per-cohort analyses are provided in the appendix (pp 19–20).

At a pre-specified probability threshold of less than 0·5%, the ARTEMIS-POC algorithm classified 899 patients (35·1%) of 2560 as suitable for immediate rule-out. The corresponding NPV was 99·96% (95% CI 99·64–99·96), and the sensitivity was 99·68% (97·21–99·70). For T1MI only, both NPV and sensitivity of direct rule-out reached 100% with the ARTEMIS-POC algorithm (appendix p 14). Cohort-specific performances are further displayed in the appendix (pp 14–15).

Across all datasets in pooled cohorts, the rate of missed index myocardial infarction events (all patients with T2MI) was 0·05% (95% CI 0·04–0·42) among patients being ruled out based on a probability threshold of less than 0·5%. Myocardial infarction, cardiovascular death, or both at 30 days after index presentation occurred in 0·07% (0·06–0·59) of patients assigned to direct rule-out (table 3). Details about missed events at index presentation and within 30 days thereafter are provided in the appendix (p 16). The ARTEMIS-POC algorithm used in conjunction with a probability threshold of less than 0·5% performed consistently well across distinct clinically relevant subgroups (figure 2).

Rapid rule-out performance measures across a range of single POC VTLi cutoff concentrations, and using the same range for the ESC 0 h and ACC 0 h pathways, are displayed in the appendix (pp 21–23). The application of the ESC 0 h pathway allowed for an immediate rule-out of an acute myocardial infarction in 390 (15·2%) of 2560 individuals. The corresponding NPV and sensitivity were 100%. Similarly, the ACC 0 h pathway assigned 352 (13·8%) of 2560 individuals to rapid rule-out with both NPV and sensitivity reaching 100%. In comparison, the ARTEMIS-algorithm identified more than twice as many individuals as eligible for rapid rule-out at the pre-specified threshold of less than 0·5% while maintaining comparable safety (NPV and sensitivity; table 3).

Among the patients of whom the ARTEMIS-POC algorithm missed an index myocardial infarction, none had a T1MI event. No index myocardial infarction event was misclassified by either guideline-recommended pathways. At the same time, 30-day event rates were comparable between the ARTEMIS-POC algorithm, and the ESC and ACC 0 h pathways (table 3). The head-to-head comparison of performance measures as compared with both guideline-recommended pathways for T1MI only is provided in the appendix (p 14). Cohort-specific performance measures are displayed in the appendix (p 15).

In all clinically relevant subgroups, the ARTEMIS-POC algorithm outperformed both guideline-recommended pathways regarding rule-out proportions while preserving high safety (figure 2, appendix pp 24–27). In patients with symptom onset greater than 3 h, the ARTEMIS-POC algorithm allowed for safe immediate rule-out of myocardial infarction in 591 (47·5%) of 1243 patients, compared with 329 (26·5%) of 1243 patients with the ESC 0 h and 294 (23·7%) of 1243 patients with the ACC 0 h pathways (appendix pp 26–27). Even in early presenters with symptom onset less than 3 h, to whom guideline-recommended pathways are not applicable, up to one fifth (153/806; 19·0%) were eligible for immediate rule-out based on a single POC measurement.

	ARTEMIS-POC algorithm (MI probability <0·5%)	ESC 0 h* pathway	ACC 0 h† pathway
Rule-out	899 (35·1%)	390 (15·2%)	352 (13·8%)
NPV	99·96 (99·64–99·96)	100 (100–100)	100 (100–100)
Sensitivity	99·68 (97·21–99·70)	100 (100–100)	100 (100–100)
Missed index MI	0·05 (0·04–0·42)	0 (0–0)	0 (0–0)
Missed follow-up events	0·07 (0·06–0·59)	0·08 (0·07–0·71)	0·08 (0·07–0·70)

All effect estimates were pooled across the imputed datasets and include T1MI and T2MI. Data are n (%) or median (95% CI). ACC=American College of Cardiology. ESC=European Society of Cardiology. MI=myocardial infarction. NPV=negative predictive value. POC=point-of-care. T1MI=type 1 myocardial infarction. T2MI=type 2 myocardial infarction. *ESC 0 h pathway; POC cut-off <4 ng/L if symptom onset >3 h. †ACC 0 h pathway; POC cut-off <4 ng/L if non-ischaemic electrocardiogram and symptom onset ≥3 h.

Table 3: **Diagnostic accuracies for index MI**

Discussion

In two geographically distinct cohorts from the USA and Australia, we clinically applied a medical decision support, machine learning-based algorithm combining clinical variables with a single POC hs-cTnI measurement to calculate the personalised risk of having an acute myocardial infarction. We specifically validated its pre-specified risk threshold for rapid rule-out of myocardial infarction and compared its performance with guideline-recommended pathways in the emergency department. The ARTEMIS-POC algorithm achieved high diagnostic accuracy and safety of immediate rule-out of myocardial infarction, yielded more than twice the efficacy compared with guideline-endorsed pathways, and maintained its robust performance across all clinically relevant subgroups, including early presenters.

The ARTEMIS algorithm allows for the estimation of an individual risk probability of myocardial infarction. It is tailored to patient-specific features, customised for use with multiple available hs-cTn assays, and does not require any specific hs-cTn cutoffs and timepoints of serial hs-cTn testing.[12] Previously, it successfully

	Subgroup size (n)	Sensitivity (95% CI)	NPV (95% CI)	Proportion ruled out (95% CI)
Age (years)				
<65	1718	99·28 (93·82–99·34)	99·95 (99·58–99·96)	43·39 (31·25–55·94)
≥65	842	100 (100–100)	100 (100–100)	18·48 (12·02–25·97)
Sex				
Female	1072	99·99 (99·91–99·99)	100 (99·99–100)	42·42 (31·01–54·25)
Male	1485	99·53 (95·94–99·57)	99·92 (99·27–99·92)	29·97 (19·65–41·44)
Hypertension				
No	1134	99·07 (92·02–99·14)	99·94 (99·46–99·94)	49·06 (40·97–57·18)
Yes	1416	100 (100–100)	100 (100–100)	24·75 (17·42–32·89)
Diabetes				
No	1886	99·52 (95·82–99·56)	99·95 (99·61–99·96)	40·00 (30·08–50·36)
Yes	673	100 (100–100)	100 (100–100)	21·02 (18·21–23·97)
History of CAD				
No	1934	99·39 (94·71–99·44)	99·95 (99·58–99·96)	40·65 (27·78–54·21)
Yes	608	100 (100–100)	100 (100–100)	17·79 (8·88–28·95)
History of MI				
No	2115	99·43 (95·07–99·47)	99·95 (99·60–99·96)	38·59 (25·04–53·11)
Yes	429	100 (100–100)	100 (100–100)	18·20 (10·24–27·83)
History of heart failure				
No	880	100 (100–100)	100 (100–100)	32·68 (29·96–35·45)
Yes	197	100 (100–100)	100 (100–100)	14·21 (11·56–17·09)
Smoking				
No	1577	99·62 (96·70–99·65)	99·95 (99·56–99·95)	37·63 (29·39–46·24)
Yes	978	100 (100–100)	100 (100–100)	32·68 (20·77–45·86)
Symptom onset (h)				
>3	1243	99·99 (99·92–99·99)	100 (99·99–100)	47·58 (20·58–75·37)
≤3	806	99·20 (93·10–99·26)	99·74 (97·73–99·76)	18·94 (16·65–21·34)
Ischaemic ECG signs				
No	1038	100 (100–100)	100 (100–100)	29·73 (27·40–32·11)
Yes	39	100 (100–100)	100 (100–100)	17·95 (10·88–26·33)
eGFR (mL/min)				
<60	594	99·99 (99·89–99·99)	99·99 (99·93–99·99)	13·72 (12·14–15·39)
≥60	1931	99·56 (96·23–99·60)	99·96 (99·62–99·96)	41·73 (36·05–47·51)

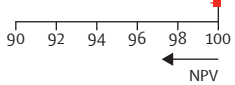

Figure 2: **Sensitivities, NPVs, and rule-out proportions using the ARTEMIS-POC algorithm (MI probability <0·5%) across patient subgroups**
CAD=coronary artery disease. ECG=electrocardiogram. eGFR=estimated glomerular filtration rate. MI=myocardial infarction. NPV=negative predictive value. POC=point-of-care.

underwent derivation and validation based on two German cohorts of patients with suspected myocardial infarction, followed by its generalisation in 13 international cohort studies. It is now applied with its pre-specified cutoffs[12] and different hs-cTn assays to various external cohorts.

Here, we presented the retrospective application of the algorithm and its suggested diagnostic threshold to observational cohorts from the USA and Australia for rapid rule-out of myocardial infarction in the context of a POC hs-cTn system. By integrating a POC hs-cTn assay which has been proven to deliver accurate results within a few minutes,[13] the algorithm further adds to its potential for the rapid triage of suspected myocardial infarction. Applying the ARTEMIS-POC algorithm on a single blood draw can potentially reduce door-to-rule-out time in the emergency department in more than one third of patients being admitted with symptoms suggestive of an acute myocardial infarction. This ability to safely tailor medical decisions in a considerable magnitude of patients in different clinical and regional settings might improve health care globally.[17]

The ARTEMIS-POC algorithm provides the opportunity to extend safe and rapid triage to pre-hospital settings with general practitioners, cardiologists in primary care, and ambulances. It might also be applied in settings without continuous access to laboratory-based testing, such as rural areas. The flexibility of selecting diagnostic thresholds (according to local priorities of different health-care providers) when using algorithms that provide continuous risk scores and probabilities for myocardial infarction harbours a clear advantage over guideline-recommended pathways that use fixed hs-cTn thresholds.[12]

The ARTEMIS-POC algorithm, including distinct patient-specific features, performed consistently across

subgroups. Importantly, in early presenters to whom recommended pathways are not applicable and second hs-cTn testing is generally advised by guidelines[6] (or even the additional measurement of biomarkers such as copeptin which is currently being discussed in the context of accelerated rule-out[18]), approximately one fifth of patients would potentially be eligible for early discharge based on the ARTEMIS-POC algorithm. If nationwide approximately 7 million patients with suspicion of myocardial infarction are evaluated in the emergency department each year,[19] the ARTEMIS-POC algorithm would (excluding approximately 750 000 annual cases of ST-segment elevation myocardial infarction[20]) potentially allow for direct rule-out of myocardial infarction in more than 1·25 million patients, even including a considerable proportion of patients who present early after symptom onset.

Previous work has already introduced machine learning concepts for the evaluation of suspected myocardial infarction (for comparison, see appendix pp 17–18);[21,22] the myocardial ischaemic injury index (MI³) was the first among them, and relies on two predefined variables, age and sex, and is restricted to one specific hs-cTnI assay. MI³ does not allow for immediate rule-out of low-risk patients as it requests serial troponin testing, and demonstrated rather poor calibration.[21] The recently published Collaboration for the Diagnosis and Evaluation of Acute Coronary Syndrome (CoDE-ACS) score was derived and validated in a large international patient population,[22] and compared with three guideline-recommended pathways.[23] Beyond its applicability with only one hs-cTnI central laboratory-based assay, it requires the addition of further biomarkers to calculate a risk score. Furthermore, the CoDE-ACS score was designed to mainly identify T1MI.[22] Another emerging concept is artificial intelligence-powered ECG analysis for detecting occlusion myocardial infarction, which is an easy-to-apply method but needs prospective validation.[24] As a future perspective, incorporating digitised ECG data into risk models might further improve triage of suspected myocardial infarction.

In contrast to guideline-based pathways, applying such algorithms in clinical practice presupposes regulatory approval, digital implementation (eg, the development of a native app or web-based interface), and devices for the algorithm to be run on, which is associated with costs and most likely translates into commercial purchase. In the case of integrated biomarker measurements, costs for measurement, including sample preparation, purchase and maintenance of systems, consumables, and quality control, have to be considered. In general, costs related to POC assays are usually higher than central laboratory-based testing and it remains unclear whether reduced turnaround times really translate into reduced length of stay in the emergency department and health-care costs, and how patient flow will be affected if used in pre-hospital settings.[13] Only prospective evaluation of clinical application and associated health-care costs will allow for adequate cost-benefit analysis.

In general, the development and approval of medical decision support tools require a rigorous stepwise approach to become globally applicable. First, the development of a diagnostic algorithm should capitalise on robust approaches for integrating and weighting multiple variables (ie, by machine learning to achieve high accuracy [derivation phase]). Second, its performance needs to be validated in independent cohorts with individuals being evaluated for the investigated clinical condition (validation phase). Third, as different pre-test probabilities likely exist for the respective condition of interest across distinct regions, the diagnostic model needs to be applied in various clinical settings with methods allowing for its adaptation to local settings (ie, calibration [generalisation phase]). Fourth, pre-specified diagnostic thresholds should be applied to different cohorts to compare the algorithm's application with the current standard-of-care pathways (application phase). Fifth, the algorithm and its diagnostic cutoffs need to be tested in prospective randomised controlled trials to demonstrate clinical utility (clinical trial phase). Lastly, after the regulatory processes such as certification have been completed, real-world clinical implementation requires investigating outcomes, including feasibility, sustainability, and cost-effectiveness (implementation phase; appendix p 28).

The ARTEMIS models have not yet been prospectively tested as part of routine clinical practice. To exploit its full use case potential in different settings including in-hospital, ambulatory, and preclinical care, randomised controlled clinical trials evaluating the implementation of the ARTEMIS algorithm as a medical decision support device are warranted. We are currently in the process of obtaining certification for the ARTEMIS algorithm as a medical device, as well as developing web-based software for clinical use of the algorithm.

Some limitations should be considered. First, although the ARTEMIS-POC algorithm is potentially applicable to primary care settings with lower pre-test probability and prevalence of myocardial infarction than in the emergency department, recalibration will enable for its applicability in these settings as the algorithm was derived and validated in emergency patients clinically assessed for suspected myocardial infarction. Furthermore, the derivation and validation of ARTEMIS models were performed in German cohorts. Therefore, applying these algorithms to other countries and global regions is work in progress by using calibration methods and performing prospective randomised clinical trials. Although global generalisation was performed, data on ethnicity were not available for the derivation, validation, or generalisation cohorts, nor for the cohorts included in the current study. It remains unclear how ethnicity might impact performance. Second, the current work focused on rapid rule-out paths. We believe that the ability of POC assays to provide reliable hs-cTn results within a

few minutes is of considerable value in the context of immediate rule-out of myocardial infarction, which could translate into a rapid discharge of low-risk patients from the emergency department without the need for serial sampling. However, further investigations will follow for the ARTEMIS-POC algorithm to demonstrate its full potential, also for the triage of patients deemed intermediate-risk or high-risk. Analogous analyses are also planned for each of the central laboratory-based hs-cTn assays which are applicable with the ARTEMIS algorithm. Third, it is important to note that the ARTEMIS models were validated to estimate the risk of an acute myocardial infarction in case of clinical suspicion, which does not include other conditions that might cause similar symptoms, such as pulmonary embolism or heart failure. The estimated probabilities of myocardial infarction must always be considered in conjunction with clinical assessment and should not be used as the only basis for decision making. Fourth, central laboratory-based hs-cTnI assays that were part of routine clinical care at the time of enrolment were used for real-time clinical management of patients and post-hoc adjudication of diagnoses in both cohorts, and not the investigational POC VTLi hs-cTnI assay. Fifth, POC testing was performed by laboratory staff rather than nursing staff. If applied to routine practice in the emergency department where nursing staff are in charge of real-time bedside testing, aspects including education of the personnel, technical maintenance of the POC device, and quality control measurements on a regular basis need to be considered and integrated into the workflow.[25] Sixth, ECG data that are part of the ARTEMIS algorithm were missing in the SAMIE cohort. To account for this, we imputed missing data using a sophisticated approach based on a global dataset of 12 international cohorts. Seventh, data on quality of symptoms and symptom characteristics and the exact type of detected ischaemic ECG signs were not available. Digital or secondarily digitised ECGs were also not available in both cohorts. The integration of digital ECGs rather than dichotomised ECG data might be achieved in the future.

In conclusion, the patient-tailored ARTEMIS algorithm applied with a single POC hs-cTnI test allows for rapid, safe, but substantially more efficient direct rule-out of myocardial infarction than guideline-recommended pathways—even across distinct clinical subgroups. If implemented in clinical practice as a medical decision support tool, the ARTEMIS-POC algorithm holds promise for expediting early discharge from the emergency department, and might extend safe and rapid triage of patients with suspected myocardial infarction to diverse settings, including pre-hospital, geographically isolated, and ambulatory care settings.

Collaborators

SEIGE and SAMIE investigators: Laura Stephensen, Emily Brownlee, Ellyse McCormick, Gavin Fincher, Emma J Hall, Rebecca Hancock, Niranjan Gaikwad, Vinay Gangathimmaiah, Christian Hamilton-Craig, Andrew Hobbins-King, Gerben Keijzers, Maryam Khorramshahi Bayat, Ehsan Mahmoodi, Siegfried Perez, Isuru Ranasinghe, Andrew Staib, Anna Zournazi, and Martin Than.

Contributors

BT, AZ, and SB conceived the idea for the study, interpreted the data, and wrote the paper with input from all listed authors. HS, EDC, and AZ analysed the data. JHG, WAP, KS, LC, and FSA provided the data and were involved in data interpretation and discussion of the study results. All authors provided feedback and contributed significantly to the conducted research, analyses, and manuscript. BT and HS contributed equally to this work. All authors were permitted to access the raw datasets. BT, HS, EDC, AZ (lead statistician), and SB (corresponding author) had full direct access to the underlying data and verified them. All authors have seen and approved the final version of the manuscript and accept the responsibility to submit the manuscript for publication.

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Data sharing

All individual-level data of the included cohorts can be shared upon reasonable request to the corresponding author and completion of data transfer agreement forms. The algorithm is proprietary and subject to patent application. However, we can share it for research purposes based on a written agreement and a request made to the corresponding author.

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