

Potential performance of a 0 h/1 h algorithm and a single cut-off measure of high-sensitivity troponin T in a diverse population: main results of the IN-HOPE study

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Aims

Chest pain is a major cause of medical evaluation at emergency department (ED) and demands observation to exclude the diagnosis of acute myocardial infarction (AMI). High-sensitivity cardiac troponin assays used as isolated measure and by 0- and 1-h algorithms are accepted as a rule-in/rule-out strategy, but there is a lack of validation in specific populations.

Methods and results

The IN-Hospital Program to systematize Chest Pain Protocol (IN-HOPE study) is a multicentre study that prospectively included patients admitted to the ED due to suspected symptoms of AMI at 16 sites in Brazil. Medical decisions of all patients followed the standard approach of 0 h/3 h protocol, but, in addition, blood samples were also collected at 0 and 1 h and sent to a central laboratory (core lab) to measure high-sensitivity cardiac troponin T (hs-cTnT). To assess the theoretical performance of 0 h/1 h algorithm, troponin < 12 ng/L with a delta < 3 was considered rule-out while a value ≥ 52 or a delta ≥ 5 was considered a rule-in criterion (the remaining were considered as observation group). The main objective of the study was to assess, in a population managed by the 0 h/3 h protocol, the accuracy of 0 h/1 h algorithm overall and in groups with a higher probability of AMI. All patients were followed up for 30 days, and potential events were adjudicated. In addition to the prospective cohort, a retrospective analysis was performed assessing all patients with hs-cTnT measured during the

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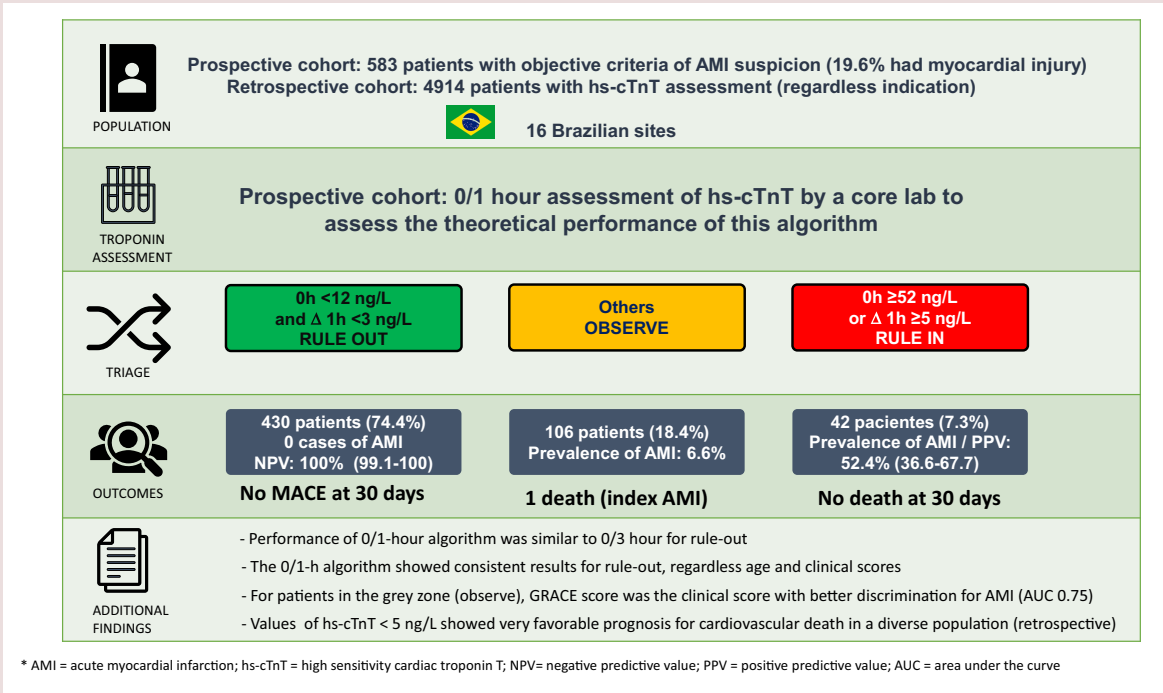
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year of 2021 but not included in the prospective cohort, regardless of the indication of the test. A total of 5,497 patients were included (583 in the prospective and 4,914 in the retrospective analysis). The prospective cohort had a mean age of 57.3 ($\pm$ 14.8) and 45.6% of females with a mean HEART score of 4.0 ± 2.2 . By the core lab analysis, 74.4% would be eligible for a rule-out approach (45.3% of them with a HEART score > 3) while 7.3% would fit the rule-in criteria. In this rule-out group, the negative predictive value for index AMI was 100% (99.1–100) overall and regardless of clinical scores. At 30 days, no death or AMI occurred in the rule-out group of both 0/1 and 0/3 h algorithms while 52.4% of the patients in the rule-in group (0 h/1 h) were considered as AMI by adjudication. In the observation group (grey zone) of 0 h/1 h algorithm, GRACE discriminated the risk of these patients better than HEART score. In the retrospective analysis, 1,091 patients had a troponin value of < 5 ng/L and there were no cardiovascular deaths at 30 days in this group. Among all 4,914 patients, the 30-day risk of AMI or cardiovascular death increased according to the level of troponin: 0% in the group < 5 ng/L, 0.6% between 5 and 14 ng/L, 2.2% between 14 and 42 ng/L, 6.3% between 42 and 90 ng/L, and 7.7% in the level ≥ 90 ng/L.

Conclusion In this large multicentre study, a 0 h/1 h algorithm had the potential to classify as rule-in or rule-out in almost 80% of the patients. The rule-out protocol had high negative predictive value regardless of clinical risk scores. Categories of levels of hs-cTn T also showed good accuracy in discriminating risk of the patients with a very favourable prognosis for cardiovascular death in the group with value < 5 ng/L.

ClinicalTrials.gov NCT04756362

Graphical Abstract



Keywords Chest pain • Troponin • Diagnosis

Introduction

About 100 million people seek emergency care every year in the USA, and the most common clinical reason for this type of evaluation is chest pain.^{1,2} Given the possibility of life-threatening diagnoses, especially acute myocardial infarction (AMI), patients with chest pain are not routinely discharged at the beginning of the evaluation and remain under observation.³⁻⁶ Thus,

the combination of high volume of patients with chest pain who seek emergencies and the requirement to keep these subjects under observation generates a great burden of patients using emergency care resources and, consequently, increasing costs for the health system.¹⁻⁶ Methods of rapid risk stratification have been developed to ensure safe and early discharge of these patients evaluated in emergency department (ED) due to chest pain.^{1,4-7} The fastest method recommended by guidelines

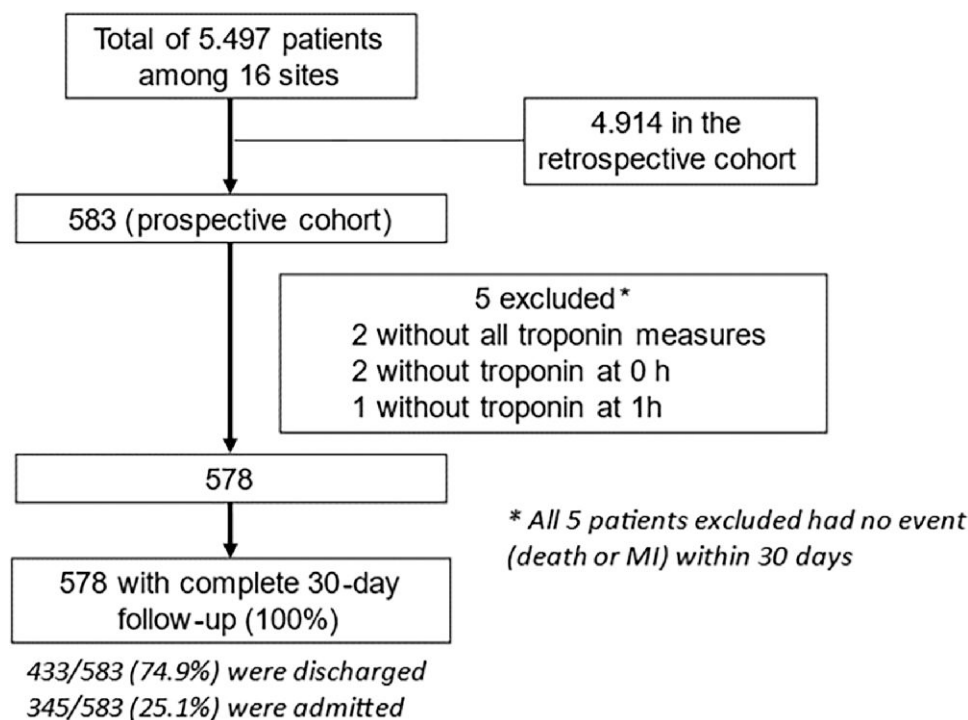


Figure 1 Study flowchart. MI, myocardial infarction.

is the 0- to 1-h algorithm with high-sensitivity troponin.^{4,6} In addition, recent publications^{8,9} have reinforced the prognostic value (death and AMI within 30 days) of an isolated measure of high-sensitivity troponin in selected patients. However, the approaches for risk stratification of these patients still have great variability, even in services with high-sensitivity troponin. This variation could be related to limited information of the performance of these fast-track algorithms among elderly patients and groups with higher values of clinical scores such as TIMI, GRACE, HEART, and EDACS. Current guidelines³⁻⁶ recommend the use of different risk scores, but there are also statements in the same documents indicating that the use of high-sensitivity troponin could be sufficient to stratify risk without the need for clinical scores.^{1,5-10} In addition to the variability in risk stratification, studies that validated these early assessment strategies were carried out mostly with patients with chest pain in Europe, the USA, and Oceania, with the population of patients with other suspected symptoms beyond chest pain¹¹ and/or Latin American patients being under-represented.^{1,7-13}

Thus, a prospective multicentre study was developed to assess the accuracy and efficiency of a strategy to early rule out the diagnosis of infarction in a Brazilian population, with and without chest pain, using high-sensitivity troponin associated or not with clinical scores. In addition, a retrospective analysis was performed using real-world evidence of patients assessed by troponin to identify the prognostic value of isolated values of this biomarker regardless clinical indication of the test.

Methods

IN-Hospital Program to systematize Chest Pain Protocol (IN-HOPE) was an investigator-initiated study with financial support from Roche Diagnostics and coordinated by Americas Institute that included patients in 16 sites in Brazil.

Study objectives

IN-HOPE was designed to evaluate two main questions: (i) the theoretical performance of an early exclusion protocol (0- /1-h algorithm) for the

diagnosis of index myocardial infarction using high-sensitivity cardiac troponin T (hs-cTnT) with or without traditional risk scores (TIMI, GRACE, HEART, and EDACS) in a Latin American population admitted due to pre-specified criteria (with or without chest pain) and (ii) the prognostic value (death and AMI within 30 days) of an isolated measure (single cut-off) of high-sensitivity troponin T test for patients in ED or hospitalized, regardless of the indication of the test.

Additionally, the performance of risk scores was assessed overall and in the observation group (grey zone) of the 0 h/1 h algorithm. Finally, the standard approach based on the 0 h/3 h algorithm was also evaluated regarding resource utilization (e.g. non-invasive and invasive cardiac procedures) and diagnostic performance (of index AMI and also AMI/death in 30 days).

Study population

In the absence of an exclusion criterion, patients with age ≥ 18 years old who signed an informed consent form within 1 h of admission and had one of the following two criteria were eligible to the trial: (i) acute chest pain (last episode of pain with onset < 6 h from enrollment) or (ii) syncope, dyspnoea, or epigastric pain without an obvious cause at baseline (last episode of one of these symptoms with onset < 6 h from enrollment) associated with at least one of the following: age ≥ 65 years, history of arterial disease, and history of diabetes mellitus.

Since patients included in the prospective cohort were managed locally by the 0 h/3 h protocol (while blood samples were sent to a central lab to evaluate the potential performance of a 0 h/1 h protocol), patients with more than 6 h would not be considered for a two-measurement protocol using high-sensitivity troponin (a single negative measurement was the standard for cases with more than 6 h). Thus, these patients were not eligible to the IN-HOPE prospective study.

Exclusion criteria included situations that would not be applicable an early rule-out algorithm as any medical condition requiring hospitalization identified within 1 h of assessment (e.g. thrombolytic therapy, primary angioplasty, cardiac arrest, and haemodynamic instability). Dialysis and trauma patients as well as subjects with myocardial revascularization or AMI in the last month were not included due to relevant confounding factors in the

analysis of troponin. Finally, pregnant and breastfeeding women and patients unable to be followed up for 30 days were also excluded from criteria.

Patient inclusion and variables collected in the prospective analysis

The study was approved by institutional review board in accordance with local regulations and was carried out in accordance with ethical principles consistent with the Declaration of Helsinki, Good Clinical Practices of International Conference on Harmonisation and in compliance with national resolutions (CNS/MS 466/2012).

In the prospective cohort, after signature of informed consent and study enrolment, all the clinical data were collected at the initial consultation as baseline data (index visit) and at 30-day follow-up (see [Supplementary material online, Figure S1](#)). All the data were inserted in an electronic case report form (eCRF). At baseline, the patient was assessed by symptoms, physical examination, medical history, electrocardiogram, and risk scores (TIMI, GRACE, HEART, and EDACS), which were calculated.^{5,9} The initial blood sample (0-h) was analysed both in local laboratory (for medical decision in the ED) and in a central laboratory (for study purposes). After 1 h from the initial blood sample collection, a second sample was collected and sent exclusively to the central laboratory. Despite the use in the local practice of all sites of highly sensitive assay formats of troponin, the investigation of the patient in the ED followed a conservative 0- to 3-h approach (see [Supplementary material online, Table S1](#))³⁻⁵ since this was the algorithm mainly accepted in our local clinical practice in Brazil at the time of the study. Decisions regarding hospitalization, discharge, and subsequent interventions were made at physician's discretion (the study protocol did not change the routine of the chest pain protocol, which was based on international guidelines for diagnosis and treatment decisions).³⁻⁵ Data of patient's symptoms, medical history, electrocardiogram, and laboratory results were collected from admission to discharge. After discharge, all patients were followed with a telephone contact at 30 days ($\pm$ 7 days) and electronic medical records were also assessed by study coordinator and medical adjudicators. On-site monitoring and remote monitoring were performed to ensure data quality.

Troponin analysis

The central laboratory (Hospital Israelita Albert Einstein) received, from all study sites, two blood samples of each patient (0 and 1 h) and analysed the levels of high-sensitivity troponin T (Roche Elecsys hs-cTnT) for study purposes (this analysis was performed *a posteriori* and the result was not used for medical decision). All the samples analysed by the central laboratory were frozen at -20°C and were processed weekly. The laboratory is accredited by the College of American Pathologists (CAP). Samples with technical problems in the analysis (e.g. haemolysis) were included in the study database with a note regarding the limitation of the analysis.

Retrospective analysis

Data from medical records and administrative databases were analysed, and information on readmissions and deaths was obtained from the health plan's administrative databases. The analysis included all patients with available values of high-sensitivity troponin T (Roche Elecsys hs-Tnt) from local laboratory during the year of 2021 at the participant sites.

Study outcomes

Performances of an early exclusion algorithm (0 h/1 h) and also of a traditional protocol (0-/3- h approach) were evaluated according to the diagnosis of myocardial infarction by the fourth universal definition of myocardial infarction.¹² These algorithms were also evaluated in terms of risk of myocardial infarction and death at 30 days. The 0 h/1 h protocol⁴⁻⁶ was used in the analysis to categorize patients in the following groups according to the central laboratory result: rule-out ($<12\text{ ng/L}$ with a $\Delta < 3\text{ ng/L}$), rule-in (value $\geq 52\text{ ng/L}$ and/or a $\Delta \geq 5$), or observation (others values of high-sensitivity troponin T). These categories were used only for study purposes but not in medical decision which used the 0- to 3-h approach (see [Supplementary material online, Table S1](#))³⁻⁵ as the standard. Hospitalization and medical procedures (for diagnosis or intervention) were collected, but all these decisions were based on medical judgment.

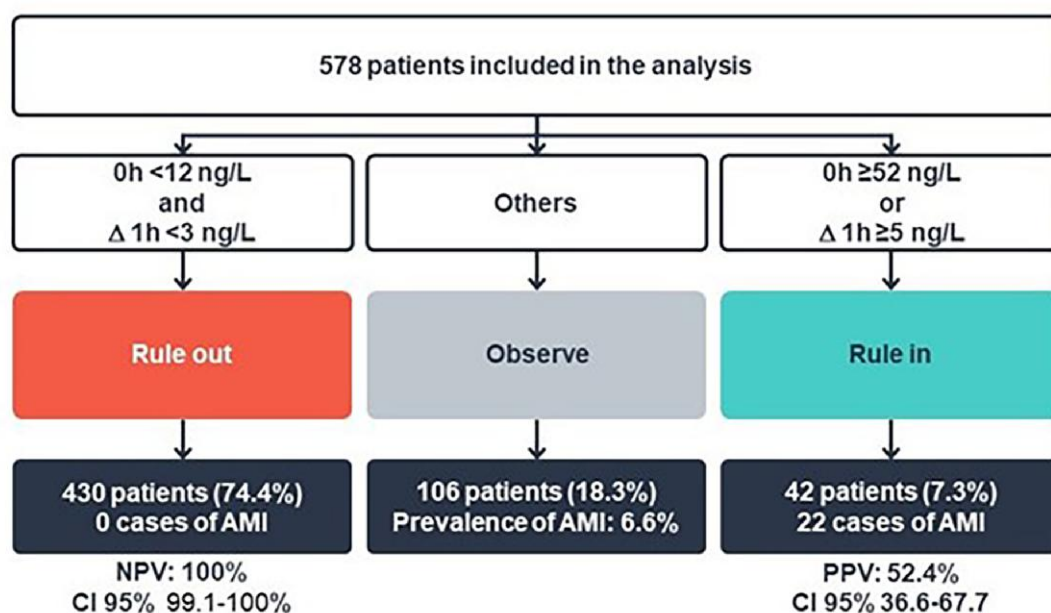
Table 1 Baseline characteristics

Variables	N = 583
Demography and lifestyle	
Age (years), mean $\pm$ SD	57.3 $\pm$ 14.9 (n = 583)
N° people > 65 years, n/N (%)	189/583 (32.4%)
Female, n/N (%)	266/583 (45.6%)
Smoking, n/N (%)	
Smoker (current or less than 1 year)	62/583 (10.6%)
Former (more than 1 year)	127/583 (21.8%)
No smoker	394/583 (67.6%)
Exercise at least three times a week	118/583 (20.2%)
Medical history	
No comorbidity	109/583 (18.7%)
Hypertension	344/583 (59.0%)
Dyslipidaemia	209/583 (35.8%)
Diabetes mellitus	131/583 (22.5%)
Obesity (BMI > 30)	85/583 (14.6%)
Heart failure	26/583 (4.5%)
Atrial fibrillation	17/583 (2.9%)
Chronic kidney disease (creatinine clearance < 60)	12/583 (2.1%)
History of acute coronary syndrome	89/583 (15.3%)
History of chronic coronary syndrome	35/583 (6.0%)
History of myocardial revascularization	81/583 (13.9%)
History of stroke or transient ischaemic attack	7/583 (1.2%)
History of non-coronary atherosclerotic disease (carotid, aortic, and peripheral arterial)	13/583 (2.2%)
Family history (first degree) of coronary heart disease < 65 years	155/572 (27.1%)
Medication	
No chronic medication	146/583 (25.0%)
Aspirin	162/583 (27.8%)
P2Y12 inhibitors	69/583 (11.8%)
Beta blocker	164/583 (28.1%)
ACE inhibitor	216/583 (37.0%)
Anticoagulant	18/583 (3.1%)
Statin	219/583 (37.6%)
Insulin	27/583 (4.6%)
Physical exam	
Systolic blood pressure	141.4 $\pm$ 22.7 (n = 583)
Diastolic blood pressure	81.9 $\pm$ 14.9 (n = 583)
Heart rate, b.p.m.	78.7 $\pm$ 15.9 (n = 583)
Respiratory rate, b.p.m.	17.2 $\pm$ 2.0 (n = 582)
Oxygen saturation	98.0 $\pm$ 1.6 (n = 583)
Temperature	36.3 $\pm$ 3.6 (n = 581)
Signs of heart failure	6/583 (1.0%)

ACE, angiotensin-converting enzyme; BMI, body mass index.

All the patients were evaluated by two independent reviewers to adjudicate potential study outcomes if they met one of the following criteria: (i) hospitalization (index or re-hospitalization), (ii) ED visit (after discharge from index event), (iii) report of a cardiac event, (iv) positive cardiac test

In Hope Results (prospective cohort)



Sensitivity 100% (81.5-100); Specificity 95.6% (93.1-97.2); Accuracy 95.8% (93.4-97.3)

Figure 2 A 0 h/1 h algorithm in the overall population. AMI, acute myocardial infarction; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

(invasive or non-invasive), and (v) local troponin result > 99th percentile. This committee was blinded to the results of frozen samples and did not include patients in the IN-HOPE sites. The reviewers used the following definition to confirm the diagnosis of AMI¹⁴: increase or decrease in troponin with at least one level above the 99th percentile associated with one additional criterion of myocardial ischaemia (symptoms compatible with myocardial ischaemia; electrocardiogram with diagnostic changes of ischaemia or development of new pathological Q waves; and coronary angiography or non-invasive testing with sign of thrombotic coronary obstruction or recent loss of viable myocardium). Autopsy confirmatory analysis could also be considered to diagnosis of AMI. Unstable angina was considered when the patient had no acute myocardial injury but had objective evidence of myocardial ischaemia (positive stress test and coronary obstruction > 50% in a main epicardial coronary artery and/or coronary revascularization). All the cases with troponin values above the 99th percentile (upper reference limit) without criteria for AMI were considered as non-ischaemic myocardial injury and categorized as acute or chronic if the variation between samples was above 20% or not, respectively.

Additional clinical secondary outcomes included rate of myocardial infarction, cardiac arrest, and death at 30 days.

In the retrospective analysis, patients included in a database of the study sites, which provides troponin levels, were assessed for diagnosis of AMI, hospitalization, and death, based on hospital and health insurance claims. Adjudication was performed only in the cases of deaths reported in the group with at least one troponin level < 5 ng/L to confirm the cause of death using standardized criteria.

Statistical analysis

Continuous variables were described as mean (and standard deviation) or median (and interquartile range), while categorical variables as percentages. Categorical variables were compared by Fisher exact test.

Classification assessment methods (accuracy, sensitivity, specificity, and positive and negative predicted values) were presented for AMI and the composite outcome of AMI or death according to 0 h/1 h algorithm. Subgroup analyses were conducted on non-low-risk patients according to GRACE, HEART, TIMI, and EDACS scores and on elderly patients (≥65 years).

Predicted performance of the scores was evaluated with receiver operating characteristic curve for AMI or death considering the whole sample and restricted to the observation group.

All analyses were considered $\alpha = 0.05$ as the level to determine statistical significance and were performed using R software, version 3.5.2 (R Foundation for Statistical Computing).

Sample size

The predetermined sensitivity (96.7%) and 16.0% prevalence of AMI published previously⁷ were considered for the calculation to acquire 5% precision for a 95% confidence interval (CI). A minimum sample size of 294 patients was necessary for accuracy, and this calculation was based on the sensitivity of the test. A sample above 500 patients would not only provide a better precision of the accuracy of the 0 h/1 h hs-cTnT exclusion algorithm in a Brazilian population but would also provide a relevant sample for cases of particular interest (e.g. elderly and non-low-risk patients by traditional risk scores) since these are overlapping subgroups.

Regarding the retrospective analysis, the sample size was based on convenience according to the number of consecutive patients that can be analysed in the databases of the study hospitals.

Results

A total of 5,497 patients were included (583 in the prospective and 4,914 in the retrospective analysis) between July 2020 and December 2021,

Table 2 Diagnostic performance of 0 h/1 h algorithm overall and according to subgroups

Outcomes	Rule-in	Observe	Rule-out	PPV	NPV	Sensitivity	Specificity	Accuracy
Index AMI (overall)								
No	20/42 (47.6%)	99/106 (93.4%)	430/430 (100.0%)	52.4% (36.6–67.7)	100% (99.1–100)	100% (81.5–100)	95.6% (93.1–97.2)	95.8% (93.4–97.3)
Yes	22/42 (52.4%)	7/106 (6.6%)	0/430 (0.0%)					
AMI or death (overall)								
No	20/42 (47.6%)	99/106 (93.4%)	430/430 (100.0%)	52.4% (36.6–67.7)	100% (99.1–100)	100% (81.5–100)	95.6% (93.1–97.2)	95.8% (93.4–97.3)
Yes	22/42 (52.4%)	7/106 (6.6%)	0/430 (0.0%)					
Index AMI (≥ 65 years)								
No	10/22 (45.5%)	67/71 (94.4%)	94/94 (100%)	54.5% (32–75.6)	100% (96.2–100)	100% (73.5–100)	90.4% (83–95.3)	91.4% (84.7–95.8)
Yes	12/22 (54.5%)	4/71 (5.6%)	0/94 (0%)					
Index AMI (HEART^a)								
No	16/38 (42.1%)	95/102 (93.1%)	177/177 (100%)	57.9% (40.8–73.7)	100% (98.1–100)	100% (84.6–100)	92.4% (88.0–95.6)	93.1% (89.1–96.0)
Yes	22/38 (57.9%)	7/102 (6.9%)	0/177 (0%)					
Index AMI (GRACE^a)								
No	8/17 (47.1%)	46/46 (100%)	49/49 (100%)	52.9% (27.8–77.0)	100% (92.5–100)	100% (66.4–100)	85.5% (73.3–93.5)	87.5% (76.8–94.4)
Yes	9/17 (52.9%)	0/46 (0%)	0/49 (0%)					
Index AMI (TIMI^a)								
No	11/27 (40.7%)	72/75 (96.0%)	112/112 (100%)	59.3% (38.8–77.6)	100% (95.1–100)	100% (79.4–100)	87.1% (78.0–93.4)	89.1% (81.3–94.4)
Yes	16/27 (59.3%)	3/75 (4.0%)	0/112 (0%)					
Index AMI (EDACS^a)								
No	14/28 (50%)	82/88 (93.2%)	134/134 (100%)	50.0% (30.6–69.4)	100% (97.3–100)	100% (76.8–100)	90.6% (84.7–94.8)	91.4% (86.0–95.2)
Yes	14/28 (50%)	6/88 (6.8%)	0/134 (0%)					

AMI, acute myocardial infarction.

^aNon-low-risk patients by HEART (score > 3), GRACE (score ≥ 109), TIMI (score > 2), and EDACS (score ≥ 16). In all analysis of non-low-risk subjects, three patients were excluded since they did not have troponin available for 0- to 1-h algorithm (these patients were followed by the study team without death or cardiovascular events within 30 days).

but five patients were excluded from the analysis of 0 h/1 h algorithm in the prospective cohort (Figure 1).

Baseline characteristics

The prospective cohort had a mean age of 57.3 (± 14.9) with 32.4% of elderly (≥ 65 years), and 45.6% were female patients. Overall, the mean HEART score was 4.0 ± 2.2 (Table 1), chest pain was referred in 94.3% of the patients, and 25% of the ECGs were considered abnormal (see Supplementary material online, Table S2).

Clinical outcomes

Using hs-cTnT for assessment of all patients included in the prospective cohort, 19.6% (95% CI 16.5–23.1) had a value above upper limit of normality by the core lab analysis. Based on adjudicated events, AMI was identified in 29.8% of the patients with myocardial injury (95% CI 21.6–39.1%) while non-ischaemic myocardial injury (cases of myocardial injury without criteria of AMI) was identified in 70.2% (95% CI 60.9–78.3%), which were categorized as 16% acute and 84% as chronic myocardial injury. Considering the overall population of the prospective cohort, 10.8% (95% CI 8.4–13.7) had a diagnosis of acute coronary syndrome, composed by 5.2% of AMI (95% CI 3.6–7.3) and 5.6% of cases of unstable angina (95% CI 3.9–7.9). There was only one case of death and this event occurred due to complications after coronary artery bypass graft surgery in a patient with an index non-ST elevation myocardial infarction (NSTEMI), which would be categorized as 'observation' group (grey zone) using the 0 h/1 h algorithm by the core lab analysis.

Accuracy of 0-/1-h algorithm

By the core lab analysis, 74.4% would be eligible for a rule-out approach while 7.3% would fit the rule-in criteria (Figure 2). The 0 h/1 h algorithm presented 52.4% (95% CI 36.6–67.7) of positive predictive value, 100% (95% CI 99.1–100) of negative predictive value, 100% (95% CI 81.5–100) sensitivity, 95.6% (95% CI 93.1–97.2) specificity, and 95.8% (95% CI 93.4–97.3) of accuracy for diagnosis of index AMI (adjudicated) and also for the composite outcome of AMI or death at 30 days (Figure 2 and Table 2).

Subgroup analysis of 0-/1-h algorithm

Almost one-third of the patients had age ≥ 65 years (Table 1) and more than 50% had a HEART score > 3 (see Supplementary material online, Figure S2). The 0 h/1 h algorithm showed consistent results for rule-out regardless age and clinical scores (Table 2). Comparing the area under the curve (AUC) of all four clinical scores assessed, the best was HEART score in the overall population (AUC 0.84) but, in the observation group (grey zone), GRACE score had a better performance (AUC 0.75) (Figure 3).

Resource utilization and accuracy of 0-/3-h algorithm

In the group categorized as rule-out, 81.7% were discharged from the ED by the attending physician. Regarding resource utilization, 57.1% of the patients classified as rule-in by the 0 h/3 h protocol were admitted to intensive care units while 17.9% were in the observation zone and 9.1% in the rule-out group. In the group categorized as rule-out by

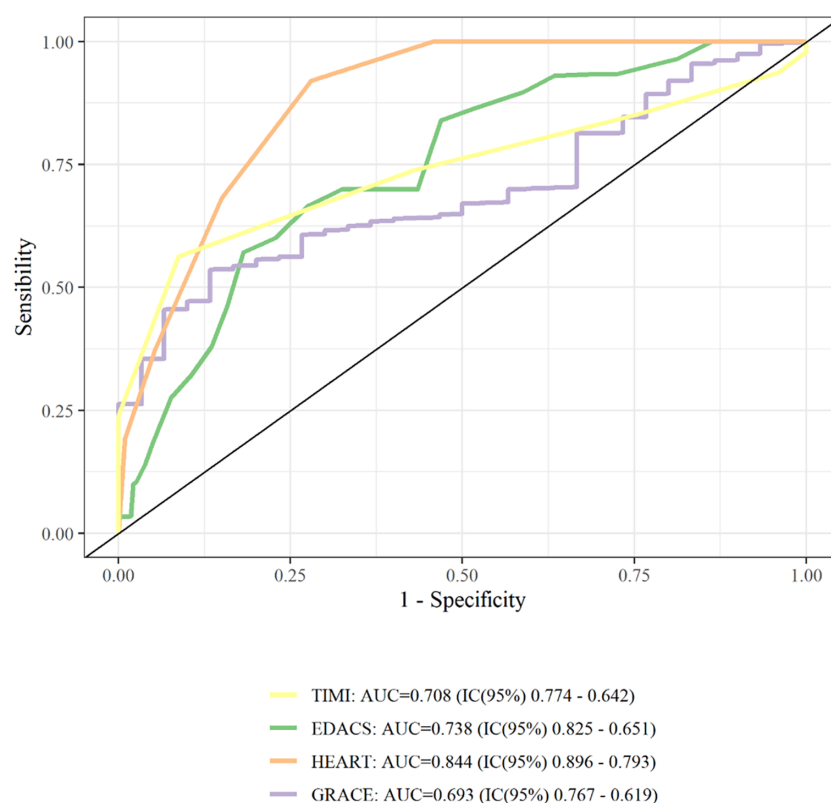
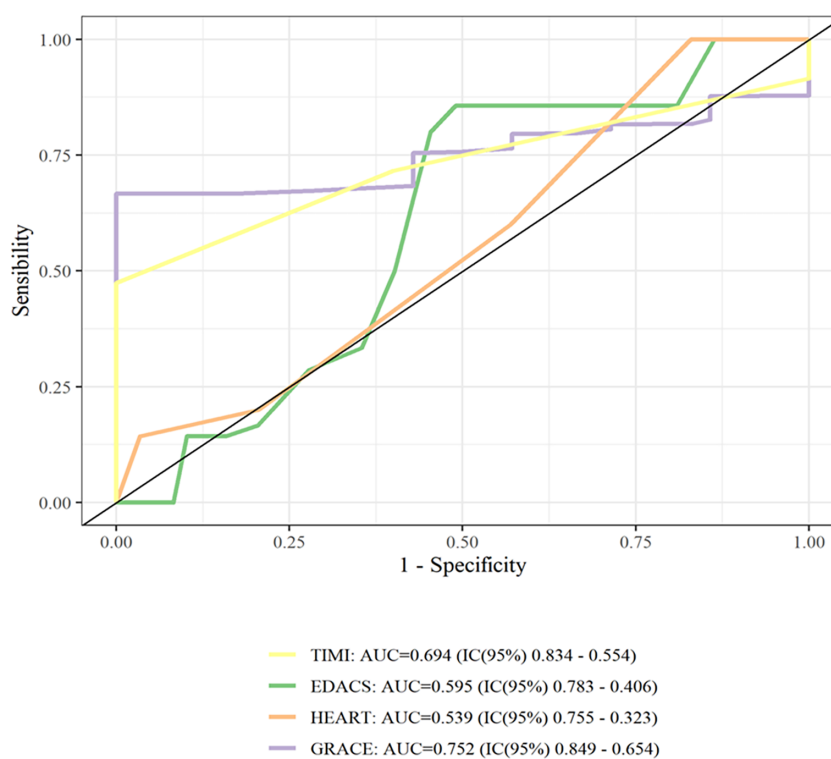
A Overall population (composed by rule-out, observe and rule-in patients)**B Observation group (grey zone)**

Figure 3 Performance of clinical risk scores: (A) overall population (composed by rule-out, observe and rule-in) and (B) observation group . AUC, negative predictive value; CI, confidence interval.

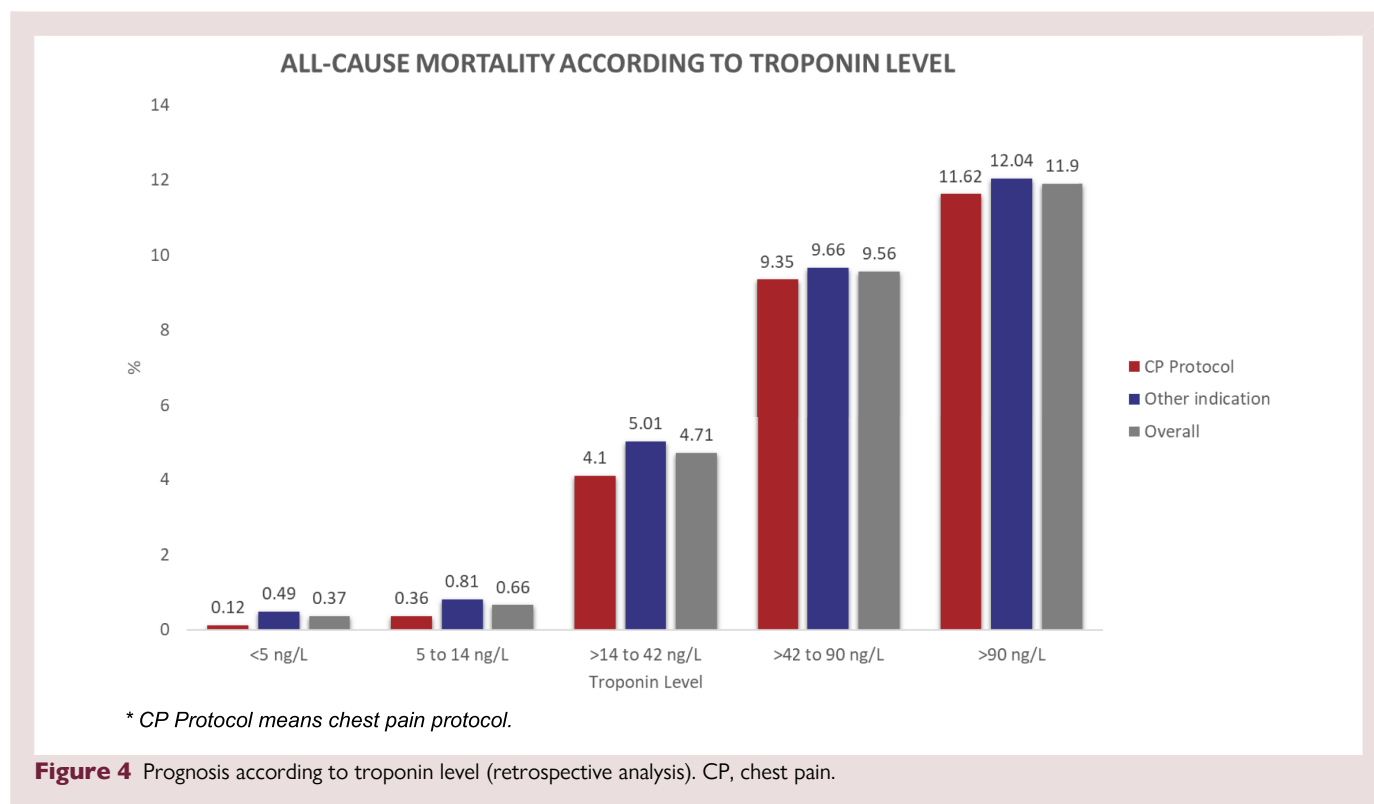


Figure 4 Prognosis according to troponin level (retrospective analysis). CP, chest pain.

the 0 h/3 h protocol, 13.4% underwent a non-invasive test for coronary disease or myocardial ischaemia and 8.6% underwent a coronary angiography (see [Supplementary material online, Table S3](#)). No case of index AMI occurred in the rule-out group (see [Supplementary material online, Table S4](#)), which represents a negative predictive value of 100% (95% CI 99.2–100).

Retrospective analysis

In the retrospective analysis, 1,091 patients had a troponin value < 5 ng/L and no cardiovascular (CV) deaths were detected ([Figure 4](#)). Among all 4,914 patients, the 30-day risk of AMI or CV death increased according to the level of troponin: 0% in the group < 5 ng/L, 0.6% (5–14 ng/L), 2.2% (14–42 ng/L), 6.3% (42–90 ng/L), and 7.7% in the level ≥ 90 ng/L ([Figure 4](#)). This risk was similar regardless the cause of troponin elevation (AMI or non-ischaemic injury) ([Figure 4](#)).

Discussion

IN-HOPE study included more than 5500 patients with troponin assessment in Brazil, with almost 600 patients in the prospective cohort and near to 5000 patients in the retrospective analysis. The primary results for the theoretical performance of 0 h/1 h algorithm in the prospective cohort showed high negative predictive value for index AMI within 30 days based on the 'rule-out' criteria. This result was similar to the 0 h/3 h approach and the medical decision for 'rule-out', in theory, could be anticipated using the 0 h/1 h algorithm. Also, the retrospective analysis found very favourable prognosis for cardiac events among patients with high-sensitivity troponin T < 5 ng/L, regardless the clinical indication of the troponin (ED or during hospital stay).

Diagnostic investigation of AMI at the ED has changed significantly in the last years with the introduction of high-sensitivity cardiac troponin.^{1,3–6} This new biomarker led to the identification of more patients without diagnosis of AMI but with troponin values above the 99th

percentile (non-ischaemic injury). At the same time, this more sensitive method increased the recognition of AMI with detection of mild NSTEMI.^{1,15} Beyond a lower level of detection of isolated measures, early variations of this biomarker allowed a more rapid definition or exclusion of AMI diagnosis.^{1,3–13} The 0 h/1 h algorithm demonstrated utility in several studies^{1,3–13}; nevertheless, some questions remained. Most trials included patients only based clinical suspicion (mainly chest pain) but not using an objective inclusion criterion as used in IN-HOPE study.^{1,7–13} Also, some regions (e.g. Latin American countries) were less represented in previous trials.^{1,7–13} Finally, the performance of 0 h/1 h algorithm according to clinical risk scores had limited data using hs-cTnT.^{16,17} In the IN-HOPE study, a 0 h/1 h algorithm using hs-cTnT showed utility to define rule-in or rule-out in more than 80% of the patients. Thus, only nearly 20% of the patients would need to stay under observation after 1 h to investigate AMI. Despite the use of objective inclusion criteria, more than 90% of the prospective population were composed of patients with chest pain and the results mainly apply to this group. Since the negative predictive value was high and not different to what was observed in the 0 h/3 h protocol, an earlier assessment with the 0 h/1 h algorithm could be a safe and potentially more efficient approach for populations similar to the IN-HOPE patients.

Beyond the recommendation of using 0 h/1 h algorithm to improve efficiency, an isolated measure of troponin could be enough without the need of a second measure 1 h later.^{8,9,18} This approach showed utility for patients with more than 3–4 h of symptoms.^{3–6} An analysis of a more diverse population including all cases of troponin assessment regardless medical indication was limited.¹⁵ In the retrospective analysis performed in the IN-HOPE project with more than 5000 patients, almost 20% had very low values of hs-cTnT. This group of more than a thousand of patients showed absence of CV death at 30 days. As reported in previous publications, the risk of events increased according to the level of hs-cTnT, regardless of the clinical indication of the exam.^{1,19,20} Thus, an isolated and very low level of troponin is useful

for prognostic estimation of CV events (including CV death), regardless of the reason for ordering this exam.

IN-HOPE trial shows the applicability of 0 h/1 h algorithm in a diverse population regardless of age or the risk according to clinical tools. While HEART score still recommended,^{3–6,21,22} especially for patients with negative troponin, IN-HOPE trial did not find incremental utility of a clinical risk score for 'rule-out' patients since 45.3% of these patients had a HEART score > 3 and the negative predictive value was above 99%.²³ This observation demonstrates a safe approach using 0 h/1 h algorithm even in patients without low risk by the HEART score. Current guidelines are not clear about the need of an additional tool of stratification (e.g. clinical score), and the results of IN-HOPE trial support a more simple approach.^{3–6} Other important aspect about IN-HOPE population is that almost 20% of the prospective cohort had a troponin value above the 99th percentile (upper reference limit) but only 30% of these patients had a confirmed AMI. Among patients with intermediate value of hs-cTnT (observation group), GRACE risk score was the best model to help in the discrimination of cases with or without AMI. Since this group does not have a unique approach^{3–6} due to diverse causes for this mild to moderate elevation of troponin, the use of risk scores like GRACE could be useful in addition to other data (e.g. imaging tests) to better inform medical decision for these intermediate patients in the grey zone of 0 h/1 h algorithm (observation group).

Study limitations

The study was performed only in Brazil and some subgroups (e.g. patients without chest pain) had fewer patients than the sample size calculated for accuracy analysis. Nevertheless, elderly patients and non-low-risk patients by clinical scores had a better representation and the results are in accordance with previous data. The prospective analysis included 583 patients, which is above the sample size calculated but still has wide CIs. Also, all medical decisions (admission, discharge, and treatment) were based on local high-sensitivity troponin assays and the use of the 0 h/3 h protocol. Finally, the exploratory retrospective analysis was not exclusively for patients with suspicion of AMI and did not include adjudication beyond the cause of death among patients with very low levels of troponin.

Conclusion

In a multicentre study in Brazil, the 0 h/1 h algorithm was effective for classifying as rule-in or rule-out almost 80% of the patients. The rule-out protocol had high negative predictive value regardless of age and clinical risk scores. Troponin also showed good accuracy in discriminating the risk according to level categories with a very favourable 30-day prognosis for major cardiovascular events among patients with values <5 ng/L.

Supplementary material

[Supplementary material](#) is available at *European Heart Journal: Acute Cardiovascular Care* online.

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GlaxoSmithKline, Medtronic, Merck, Pfizer, Portola. All other authors report no conflicts of interest.

Data availability

Anonymised participant data may be made available upon requests directed to the corresponding author. Proposals will be reviewed and if approved, data can be shared through a secure online platform after signing a data access agreement.

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