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ORIGINAL RESEARCH

Effectiveness and Safety of the ESC-TROP (European Society of Cardiology 0h/1h Troponin Rule-Out Protocol) Trial

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BACKGROUND: European guidelines recommend the use of a 0h/1h hs-cTn (high-sensitivity cardiac troponin) protocol in patients with acute chest pain. We aimed to determine the performance of this protocol in routine care when supplemented with patient history and ECG and a recommendation to refrain from noninvasive testing in low-risk patients.

METHODS AND RESULTS: This was a pre- and postimplementation study with concurrent controls. Patients with chest pain were enrolled at 5 Swedish emergency departments (EDs) during a 10-month period in both 2017 and 2018. All hospitals used a 0h/3h hs-cTnT protocol in 2017 and 3 EDs implemented a 0h/1h hs-cTnT protocol during 10 months in 2018. The 2 coprimary outcomes were the incidence of acute myocardial infarction and all-cause death within 30 days and ED length of stay. The study included 26 040 consecutive patients. In the intervention hospitals, 21 (0.40%) of the discharged patients had an acute myocardial infarction/death event during the control period (0h/3h testing) and 22 (0.45%) in the intervention period (0h/1h testing), which met the criteria for noninferiority. There was no significant difference in ED length of stay (ratio 0.99, P=0.48) or ED discharge rate between the periods in the intervention versus the control hospitals. A total of 3142 patients met low-risk 0h/1h hs-cTnT criteria and were discharged, of whom 2 had an acute myocardial infarction/death event.

CONCLUSIONS: A 0h/1h hs-cTnT protocol incorporating patient history and ECG was as safe as using a 0h/3h protocol but did not reduce ED length of stay or increase the discharge rate. Refraining from noninvasive testing in patients identified as low risk was safe.

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Key Words: acute coronary syndrome ■ chest pain ■ diagnosis ■ myocardial infarction ■ sensitivity and specificity

Chest pain is a common complaint at the emergency department (ED)[1] and the ED evaluation is often focused on identifying or ruling out acute coronary syndrome (ACS), that is, acute myocardial infarction (AMI) or unstable angina (UA). The fear of missing patients with ACS leads to numerous investigations and high admission rates.[2] Because only a few of the admitted patients prove to have a final diagnosis of ACS,[3,4] the diagnostic evaluation needs to be improved.

The ED assessment of patients with chest pain relies primarily on the history and physical examination, ECG, and analysis of cardiac troponins.[5] With the advent of hs-cTn (high-sensitivity cardiac troponin) assays, several studies have shown that AMI can be safely ruled out using only hs-cTn testing at patient presentation

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CLINICAL PERSPECTIVE

What Is New?

- When implemented in real-life care, a 0h/1h hs-cTnT (high-sensitivity cardiac troponin T) protocol incorporating patient history and ECG was as safe and effective as using a 0h/3h protocol but did not reduce emergency department length of stay or increase discharge rate.
- The 0h/1h protocol was feasible to implement in real life, had a high interrater reliability, and was associated with a high level of physician satisfaction.
- Refraining from noninvasive testing in those identified as low risk with the 0h/1h protocol was safe.

What Are the Clinical Implications?

- Implementing a 0h/1h protocol including a recommendation to refrain from further noninvasive testing in low-risk patients was safe.
- In our setting the use of a 0h/1h protocol did not translate into lower emergency department length of stay or a higher emergency department discharge rate.

Nonstandard Abbreviations and Acronyms

ESC	European Society of Cardiology
hs-cTnT	high-sensitivity cardiac troponin T
HiSTORIC	High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction
SWEDEHEART	Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart disease Evaluated According to Recommended Therapies
UA	unstable angina

(0 hours) and 1 hour later.[6–12] This has led to a class 1 recommendation of a 0h/1h hs-cTnT protocol in the European Society of Cardiology (ESC) guidelines, and the previous recommendation of a 0h/3h protocol has now been removed.[13]

There are, however, several knowledge gaps. First, most studies evaluating the 0h/1h protocol have been observational, and the only randomized control trial showed a 30-day AMI/death rate that most physicians will likely consider too high.[14,15] Second, the ESC guidelines state that the protocol should be combined with ECG and patient history but do not specify how, and the effects of this on safety and efficacy are unknown. Third, according to the guidelines, further noninvasive testing should be considered in patients identified as low risk.[13] However, the benefit of such testing is unclear in low-risk patients identified with the 0h/1h protocol in conjunction with patient history and ECG, with observational data indicating that further testing may not be needed in these patients.[6–8,10]

The aim of this study was to determine the effectiveness and safety of the ESC 0h/1h hs-cTnT protocol, supplemented with patient history and ECG, when implemented in routine care, including a recommendation to refrain from further noninvasive testing in low-risk patients.

METHODS

Study Design and Patient Inclusion

ESC-TROP (Effectiveness and Safety of a Clinical assessment and 0h/1h Troponin Rule-Out Protocol; clinicaltrials.gov NCT03421873) was a pragmatic implementation study with a pre- and postimplementation phase as well as concurrent controls, and the methods have been described in detail elsewhere.[16] Briefly, all patients seeking care due to nontraumatic chest pain were enrolled at 5 EDs in southern Sweden during a 10-month period (February to November) in both 2017 and 2018. The patients were identified through the electronic ED patient log and screened for eligibility (flow diagram presented in Figure 1). Only the first visit due to chest pain during the study period was included. Exclusion criteria were (1) a diagnosis of ST-segment–elevation AMI during the index visit; (2) no hs-cTnT ordered; (3) patient leaving the ED against medical advice; (4) patient with no Swedish personal ID number, as these patients cannot be followed up via national registries; and (5) patient declining participation. This study was approved by the Regional Ethics Review Board without the need for active patient consent. Posters in the EDs informed the patients about the study and that they could withdraw from participation at any time by contacting a study nurse.

All 5 hospitals used a 0h/3h hs-cTnT protocol during the 10-month period from February to November in 2017, which was the "control period" before implementation. The new 0h/1h hs-cTnT protocol was implemented during a 2-month run-in period from December 2017 to January 2018 at 3 volunteering EDs (intervention hospitals), and this was followed by a 10-month period from February to November 2018 where the 0h/1h protocol was part of routine care at the same hospitals ("intervention period"). The remaining 2 EDs wanted to continue with the 0h/3h protocol also during 2018 and acted as concurrent controls. Intervention hospitals thereby acted as their own controls, but to

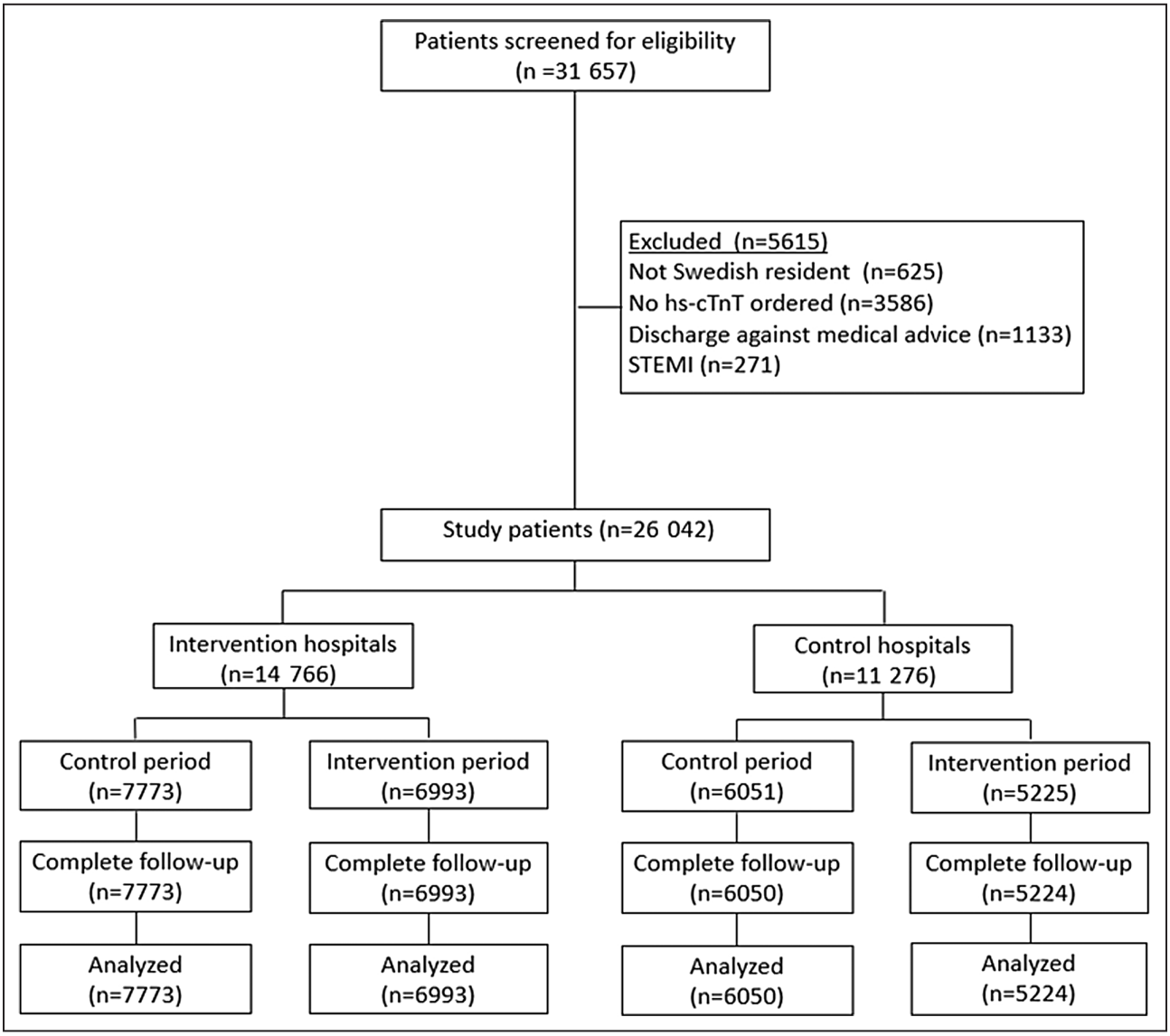

Figure 1. Patient flow.
hs-cTnT indicates high-sensitivity cardiac Troponin T; and STEMI, ST-segment–elevation myocardial infarction.

exclude that a possible difference between the control and intervention periods was due to temporal trends alone, this difference was compared with the difference between control and intervention period in the control hospitals (difference in difference). The study design is outlined in Figure S1. Data management and statistical analyses were performed by Clinical Studies Sweden Forum South, which is an independent research support facility within the Scania region (Region Skåne) administration. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Intervention

The 0h/1h hs-cTnT protocol (Figure 2) used in this study is based on the ESC guidelines,[17] with the addition of clinical assessment and ECG. This reflects real-life practice and has been shown to improve the performance of the protocol.[6] In addition, the protocol provides clear suggestions for management, which is an important feature of clinical decision rules.[18] A 1-hour hs-cTnT was defined as a second hs-cTnT sample drawn 45 to 90 minutes after the 0-hour sample drawn at patient presentation. Before the start of the intervention period, physicians and nurses at the intervention hospitals were given a standard lecture and pocket cards detailing the protocol. Posters and written guidance to the ED personnel were also distributed. According to the protocol, patients with chest pain were stratified into 3 categories: low, intermediate, or high risk of ACS. A detailed description of the protocol is provided in Data S1.

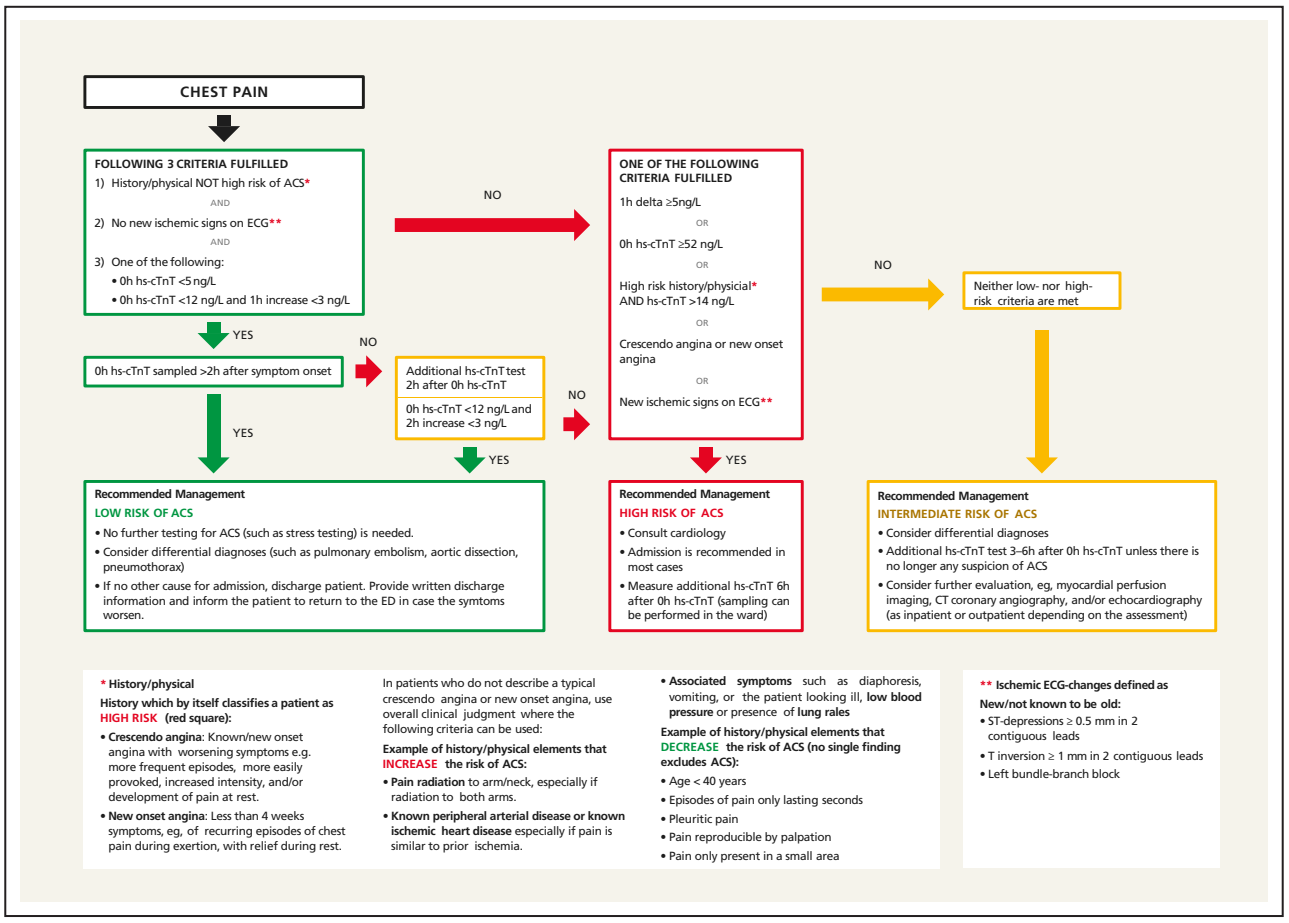

Figure 2. 0h/1h protocol.
ACS indicates acute coronary syndrome; CT, computed tomography; ED, emergency department; and hs-cTnT, high-sensitivity cardiac troponin T.

Control Group

The control group were patients with chest pain at the intervention hospitals during the control period (ie, during 2017; intervention hospitals acting as their own controls) and patients with chest pain during both control and intervention periods at the control hospitals (ie, 2017 and 2018; concurrent controls). The 0h/3h hs-cTnT testing, which was previously recommended by the ESC since 2011,[19] was the standard of care during the control period at the intervention hospitals, and during the entire study at the control hospitals. The 0h/3h protocol used was a modification of the ESC recommended algorithm where patients were considered low risk for AMI if they had both a 0-hour and a 3-hour hs-cTnT ≤14 ng/L, or a 0-hour hs-cTnT ≤14 ng/L more than 6 hours after symptom onset.[20,21]

Study Outcomes and Data Collection

There were 2 coprimary outcomes:

1. Safety: The incidence of AMI and all-cause death within 30 days from ED presentation (not including the index visit) in patients discharged from the ED
2. Effectiveness: The ED length of stay (LOS) in patients discharged from the ED.

The main secondary outcome was proportion of patients discharged from the ED. Additional secondary outcomes outlined in the study protocol will be presented in separate publications.

All discharged patients with a possible event defined as a diagnosis of AMI, UA, ventricular arrhythmia, atrioventricular block, cardiac arrest, or revascularization within 30 days were identified using data from the regional electronic health records, the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) quality register,[22] and the Swedish national patient register[23] to attain close to 100% nationwide coverage. AMIs were then adjudicated by 2 independent cardiologists, using the fourth universal definition of MI,[24] and blinded to the index visit protocol assessment (0h/1h or 0h/3h). In case of disagreement, patient cases were reviewed by an adjudication committee and resolved

by majority vote. Deaths and dates of death were retrieved from the Swedish population register, which provides 100% nationwide coverage.[25]

Data on ED LOS were obtained from the electronic ED logs. All hospitals in Region Skåne use the same electronic medical records system, and this was used to analyze hospital admission rates. All noninvasive testing as well as coronary angiographies performed in the region are recorded in the same database that was used to access the data.

Data on the final diagnosis for patients admitted to in-hospital care were obtained from SWEDEHEART and the national patient register. Data on patient comorbidities and current medications were obtained from regional electronic medical records and from the Swedish prescribed drug register.[26]

Laboratory data were obtained from each hospital's laboratory database. The Elecsys hs-cTnT assay on Cobas instruments (Roche Diagnostics) was used at all hospitals during both control and intervention periods and samples were analyzed in real time and used for clinical decision-making. This assay has a limit of detection of 5 ng/L, a limit of quantitation of 6 ng/L, and a coefficient of variation <10% at the 99th percentile of 14 ng/L.[27]

Data on patients who migrated to other countries during the 30-day follow-up were obtained from the Swedish population register, and these patients were considered lost to follow-up.

Statistical Analysis

Mean (95% CI) and median (interquartile range) were used to describe continuous variables and proportions to describe categorical variables. All patients not meeting exclusion criteria were included in the analyses, regardless of physician compliance with the 0h/1h protocol to reflect the true safety and effectiveness in routine care. When comparing outcomes before and after the implementation, a hierarchical testing procedure was used:

Step 1: At the intervention hospitals, 30-day AMI/death was compared in the control versus intervention period with a noninferiority approach using Newcombe 95% CI with the noninferiority margin set to 0.5% (see sample size calculations, Data S2).

Step 2: If the event rate in the intervention period was noninferior to that in the control period, the coprimary and secondary outcomes were analyzed using linear and generalized linear mixed models, considering potential confounders (age, sex, month, and time to physician contact) as fixed factors and adjusting for potential cluster of EDs as random effects. Model validation led us to perform the ED LOS analyses with the outcome as log transformed. This sequence of testing, where safety was prioritized, was chosen because we believe that if the 0h/1h protocol was not shown to be safe, then it should not be used regardless of effectiveness.

To identify and consider possible temporal trends, the median ED LOS per month at the 5 EDs during the 2 years preceding the 10-month control period was visually assessed using a graph. To identify possible trends in overall ED care, the monthly median ED LOS in patients presenting with dyspnea or abdominal pain in the control and intervention periods at the 5 EDs was compared in a graph to the ED LOS in patients with chest pain.

To evaluate the level of agreement in the use (interpretation) of the protocol, a subset of patients were assessed by 2 independent emergency physicians and kappa values were calculated. We also used kappa values to evaluate the level of adjudicator agreement for the AMI outcome.

Data regarding physician satisfaction with the new 0h/1h hs-cTnT protocol were collected through an electronic survey to all emergency physicians before and after implementation, and the results were analyzed using test of equality of proportions.

Data on noninvasive testing were collected in patients fulfilling low-risk hs-cTnT criteria, that is, had a 0-hour hs-cTnT <5 ng/L or a 0-hour <12 ng/L with a 1-hour increase <3 ng/L, during the intervention period in the intervention hospitals. As part of the intervention, noninvasive testing (myocardial perfusion scintigraphy, bicycle stress test, or computed tomography coronary angiography) was not recommended in low-risk patients. In the analysis, those fulfilling low-risk hs-cTnT criteria who underwent noninvasive testing during initial ED stay or as outpatients within 30 days were deemed as probable low-risk patients for whom testing should not have been performed according to the protocol. These tests were reviewed by a cardiologist and the proportion with true positive and false positive tests were assessed. Patients fulfilling low-risk hs-cTnT criteria who were admitted directly to in-hospital care were deemed to be non-low risk.

Subgroup analyses were performed for prespecified subgroups.[16]

RESULTS

A total of 31 657 patients were screened for enrollment, 5615 were excluded, and 26 040 (82.3%) patients with complete follow-up were included in the final analyses (Figure 1). Table 1 describes the patient characteristics, which seemed balanced between intervention and control hospitals and between the control and intervention periods.

In the intervention hospitals, the median hs-cTnT sampling interval between the 0-hour and the second hs-cTnT was 170 minutes (interquartile range: 120–200)

in the control period and 70 minutes (interquartile range: 60–100) in the intervention period (Table 1), indicating feasibility of implementing the 0h/1h protocol. In the control hospitals, the median sampling interval was 190 minutes in the control period and 180 minutes in the intervention period consistent with the continued use of a 0h/3h protocol. After implementation of the 0h/1h protocol at the intervention hospitals, 3142 (87.2%) patients fulfilling hs-cTnT low-risk criteria were discharged, whereas among those fulfilling hs-cTnT high-risk criteria 534 (88.9%) were admitted (Table S1) indicating good compliance with the protocol. There was also a large increase in hs-cTnT testing after implementation of the 0h/1h hs-cTnT protocol, with more patients having 2 or more hs-cTnT measurements (Table 1). After implementation of the protocol, 2270 (32.5%) patients in the intervention hospitals had a 0-hour hs-cTnT <5 ng/L. Of these 1347 (59.3%) had additional hs-cTnT sampling. The 30-day AMI/death rate was 6.2% to 7.1% in the different periods. The agreement between adjudicators for the AMI diagnosis was 96.4% with a Cohen's kappa of 0.89. In 105 patients,

Table 1. Patient Characteristics

	Intervention hospitals		Control hospitals	
	Control period (n=7773)	Intervention period (n=6993)	Control period (n=6050)	Intervention period (n=5224)
Demographics				
Mean age, y	59.7 (59.3–60.2)	59.1 (58.7–59.6)	59.5 (59.1–60.0)	58.5 (58.0–59.0)
Female sex	3717 (47.8)	3381 (48.3)	2934 (48.5)	2568 (49.1)
Arrival by ambulance	2792 (35.9)	2133 (30.5)	2261 (37.4)	1874 (35.9)
Referral	2539 (32.7)	2076 (29.7)	1943 (32.1)	1628 (31.2)
Medical history				
Diabetes	1170 (15.1)	980 (14.0)	971 (16.0)	787 (15.1)
Hypertension	1771 (22.8)	1485 (21.2)	1476 (24.4)	1221 (23.4)
AMI	940 (12.1)	611 (8.7)	724 (12.0)	498 (9.5)
Revascularization	685 (8.8)	415 (5.9)	493 (8.1)	296 (5.7)
Stroke	543 (7.0)	519 (7.4)	438 (7.2)	384 (7.3)
Heart failure	547 (7.0)	434 (6.2)	506 (8.4)	331 (6.3)
Chronic obstructive pulmonary disease	335 (4.3)	247 (3.5)	297 (4.9)	233 (4.5)
Medication				
Aspirin	1472 (18.9)	1123 (16.1)	1071 (17.7)	806 (15.4)
Beta blocker	1080 (13.9)	837 (12.0)	964 (15.9)	667 (12.8)
Angiotensin-converting enzyme inhibitor	2028 (26.1)	1695 (24.2)	1609 (26.6)	1276 (24.4)
Statin	1882 (24.2)	1441 (20.6)	1442 (23.8)	1069 (20.5)
Nitrates	523 (6.7)	377 (5.4)	424 (7.0)	291 (5.6)
Blood tests				
Median hs-cTnT sampling interval	170 (120–200)	70 (60–100)	190 (180–230)	180 (170–220)
0-h hs-cTnT<5 ng/L	2545 (32.7)	2270 (32.5)	2379 (39.3)	2088 (40.0)
0-h hs-cTnT 5-14 ng/L	3178 (40.9)	2966 (42.4)	2134 (35.3)	1851 (35.4)
0-h hs-cTnT 15-51 ng/L	1567 (20.2)	1307 (18.7)	1160 (19.2)	938 (18.0)
0-ho hs-cTnT >51 ng//L	483 (6.2)	450 (6.4)	378 (6.2)	348 (6.7)
2 hs-cTnT measured	2704 (34.8)	4460 (63.8)	1891 (31.3)	1605 (30.7)
3 hs-cTnT measured	413 (5.3)	646 (9.2)	216 (3.6)	169 (3.2)
Mean creatinine (μmol/L)	81.9 (80.9–83.0)	82.1 (81.0–83.2)	83.8 (82.4–85.1)	81.4 (79.9–82.8)
30-d AMI/death	515 (6.6)	499 (7.1)	375 (6.2)	347 (6.6)
Index visit AMI in admitted patients	437 (17.2)	418 (20.1)	300 (15.4)	289 (17.8)
Mean ED LOS*, min	346.1 (340.6–351.6)	344.6 (339.2–349.9)	302.7 (298.5–307.0)	300.2 (295.7–304.7)

Data are median (interquartile range), mean (95% CI) or n (%). AMI indicates acute myocardial infarction; ED, emergency department; hs-cTnT, high-sensitivity cardiac troponin T; and LOS.

*Overall ED LOS including both discharged and admitted patients.

2 physicians evaluated the patients in the ED blinded to each other's assessment and ranked the patients as low, intermediate or high risk in accordance with the 0h/1h protocol. The agreement between the physicians was 93.3% with a Cohen's kappa of 0.84.

Safety Outcome; Discharged Patients With AMI or Death Within 30 Days

In the intervention hospitals, 21 (0.40%) of the discharged patients had an AMI (n=4) or died (n=17) within 30 days during the control period with 0h/3h testing (Table 2). In the intervention period (0h/1h testing), 22 (0.45%) of the discharged patients had an AMI (n=5) or died (n=17), which met the criteria for noninferiority (difference 0.05 percentage points [95% CI, −0.21 to 0.31], noninferiority margin 0.5%). Among the 22 missed cases during the intervention period, only 2 patients had low risk according to hs-cTnT criteria, that is, a 0-hour hs-cTnT <5 ng/L or a 0-hour hs-cTnT <12 with a 1-hour increase <3, and 5 patients fulfilled high-risk hs-cTnT criteria.

In the control hospitals, 0.54% of the discharged patients had a 30-day AMI/death during the control period versus 0.61% during the intervention period (0h/3h testing during both periods), with a difference of 0.08 percentage points between the periods. This difference was not significantly different from the corresponding 0.05 percentage points difference between the control and intervention period in the intervention hospitals and met the criteria for noninferiority (95%CI, −0.45 to 0.39 percentage points).

When all periods where 0h/3h testing was used were pooled (control period in intervention hospitals and control and intervention period in control hospitals), the 30-day AMI/death rate was 0.50% (95% CI, 0.38–0.62).

Effectiveness Outcomes: ED Length of Stay and Proportion of Discharged Patients

In the intervention hospitals, the mean ED LOS in discharged patients was 319 minutes in the control period and 314 minutes in the intervention period (−5 minutes), and the corresponding times in the control hospitals were 310 and 297 minutes (−13 minutes; Table 2). The difference in ED LOS between the control and intervention periods was not significantly different in the intervention versus the control hospitals (ratio 0.99 [95% CI, 0.97–1.02]; *P*=0.48).

There was also no apparent difference in ED LOS trends in the control versus intervention hospitals in the years before study start (2015–2016, Figure S2A). In the intervention hospitals, the trend for patients with chest pain during 2017 to 2018 was similar to that of patients with dyspnea or abdominal pain where there also was a small decrease in ED LOS during 2018 (Figure S2B).

In the intervention hospitals, 67% of patients were discharged in the control period and 70% in the intervention period (difference 3 percentage points). In the control hospitals the corresponding numbers were 68% and 69% (difference 1 percentage point), with no significant difference between the groups (ratio 1.06, [95% CI, 0.95–1.20]; *P*=0.30).

Noninvasive Testing

During the intervention period in the intervention hospitals, 3602 patients met low-risk hs-cTnT criteria, that is, had a 0-hour hs-cTnT <5 ng/L or a 0-hour <12 ng/L with a 1-hour increase <3 ng/L of whom 5 (0.1%) were

Table 2. Main Results

	Intervention hospitals			Control hospitals			
	Control period (n=7773)	Intervention period (n=6993)	Difference	Control period (n=6050)	Intervention period (n=5224)	Difference	DiD* 95% CI
AMI or all-cause death†, % (95% CI)	0.40 (0.23 to 0.57)	0.45 (0.26 to 0.63)	0.05 (−0.21 to 0.31)	0.54 (0.31 to 0.76)	0.61 (0.36 to 0.87)	0.08 (−0.27 to 0.44)	−0.03 (−0.45 to 0.39)
AMI	4 (0.1)	5 (0.1)		5 (0.1)	11 (0.3)		
All-cause death	17 (0.3)	17 (0.3)		17 (0.4)	11 (0.3)		
Emergency department length of stay, min	318.8 (313.1 to 324.6)	314.1 (308.9 to 319.3)	−4.8	310.0 (305.0 to 315.0)	296.8 (291.8 to 301.9)	−13.2	0.99 (0.97 to 1.02)‡ *P*=0.48
Proportion discharged, %	67.3 (66.3 to 68.4)	70.3 (69.2 to 71.4)	3.0	67.9 (66.7 to 69.1)	68.8 (67.6 to 70.1)	1.0	1.06 (0.95 to 1.20)‡ *P*=0.30

AMI indicates acute myocardial infarction; and DiD, difference in difference.
*Difference between control vs intervention period in intervention hospitals compared with difference between the same periods in control hospitals.
†In discharged patients.
‡Ratio.

diagnosed with an AMI during the index visit and 64 (1.8%) with UA (Table S1).

A total of 3142 patients were discharged from the ED, only 2 of whom (0.06%) had a 30-day event (1 with type 2 AMI and 1 who died of pneumonia; see Data S3.)

There were 157 patients who underwent noninvasive testing during the initial ED stay (n=29) or as outpatients within 30 days (n=128). Only 1 (0.6%) patient was diagnosed with ACS. This patient underwent myocardial perfusion scintigraphy with reduced uptake in the inferior wall at rest but no reversible ischemia. He was admitted for a coronary angiography that showed a left anterior descending coronary artery stenosis and treated with a percutaneous coronary intervention. He continued to have chest pain episodes even after revascularization but was diagnosed with UA.

Nine patients (5.7%) had tests deemed as false positives, and 7 of these had a subsequent coronary angiography without significant stenoses. One patient underwent a subsequent myocardial perfusion scintigraphy that was normal, and 2 patient was asymptomatic at follow-up and not further tested. None had an event, but several were admitted solely due to the false positive test.

Two patients (1.3%) had a true positive test and shown to have obstructive coronary artery disease. Both were assessed as having stable angina by both the emergency physician and a cardiologist and were discharged from the ED. They underwent percutaneous coronary intervention after 2 and 4 months respectively and had no events during this time.

Among patients fulfilling 0h/1h hs-cTnT low-risk criteria, the 1-year all-cause death rate was only 0.5% indicating that refraining from noninvasive testing did not seem to result in poor long-term outcomes.

Physician Satisfaction

The survey showed that 54% of emergency physicians were satisfied (partially or completely on a 5-point Likert scale) with their current protocol (0h/3h) during 2017, whereas 92% were satisfied after implementation of the 0h/1h protocol (difference 38 percentage points [95% CI, 23.3–52.8]; $P<0.001$; Table S2).

Subgroup Analyses

The subgroup analyses are presented in Figure S3. Among patients managed during nightshifts, men, those ≥65 years, those with a history of coronary artery disease or diabetes, and those with a glomerular filtration rate <60, the CIs crossed the noninferiority margin. The CIs were, however, very wide in the subgroups.

Comparisons for patients who had a hs-cTnT >14 ng/L are presented in Table S3. There were no large differences between control and intervention periods in this patient group. There also did not seem to be any large differences when comparing outcomes in men and women separately (Tables S4 and S5).

DISCUSSION

In this large study we evaluated the safety and effectiveness of implementing a 0h/1h hs-cTnT protocol for ED patients with chest pain in a real-life setting. Our main findings were the following.

First, we found that the use of a 0h/1h protocol was as safe as a 0h/3h protocol. Both protocols had a miss rate that was clearly below the <1% threshold stated by the 2021 chest pain guidelines for defining low risk and safe rule-out[1] and were thus safe at a level that most emergency physicians are comfortable with.[15] The American Heart Association has the same level of recommendation (class 1) for a second hs-cTn test at 1 hour versus 3 hours,[1] whereas in the most recent ESC guidelines, the recommendation for the use of a 0h/3h protocol has been removed for fear of it being less safe.[13] Our results show that a 0h/3h protocol, when used in clinical practice in conjunction with clinical data, seems equally safe. This is also in line with the only published randomized control trial evaluating a 0h/1h hs-cTnT protocol, which showed no difference compared with 0h/3h testing, which used an equivalent of the older generation TnT.[14] However, because there is no evidence of an advantage with the 0h/3h protocol, the faster 0h/1h protocol will probably be preferred at most EDs.

Second, the ESC guidelines recommend using the 0h/1h algorithm together with patient history and ECG, and this is the first study to evaluate a standardized such combination in clinical practice. The combined evaluation was highly reproducible and both safe and effective. In the present study we also recommended no further noninvasive testing in low-risk patients because observational studies have shown that the addition of clinical findings and ECG to the 0h/1h protocol can identify patients with a very low risk of ACS.[6–8,10] There have been no prior studies that have evaluated a strategy of refraining from noninvasive testing in patients identified as low risk using the 0h/1h protocol. Consequently the ESC guidelines state that such testing should be considering in this group.[13] The use of noninvasive testing in low-risk patients is controversial, and previous American Heart Association guidelines recommended stress testing within 72 hours in low-risk patients with chest pain,[28] while the most recent American Heart Association guidelines state that there is no evidence that noninvasive testing within 30 days improves outcomes.[1] Our results support that noninvasive testing in low-risk patients is of little value and is consistent with

what has been previously published.[29,30] Among the 3142 low-risk patients discharged, only 2 had a 30-day event consisting of a patient diagnosed with a type 2 AMI and 1 patient who died of a pneumonia. Of those who underwent noninvasive testing during the initial ED stay or as outpatients, few had a positive test, and most were false positives that led to subsequent unnecessary testing. Only 1 patient was subsequently diagnosed with an ACS after noninvasive testing and he was likely misdiagnosed and did not truly have UA.

Third, perhaps surprisingly, the implementation of a 0h/1h protocol did not result in a significantly shorter ED LOS. The reasons for the lack of an ED LOS effect are unclear, but a contributing factor could be the increase in hs-cTnT testing that the 0h/1h protocol conferred as it resulted in almost a doubling of hs-cTnT measurements. This is one of the consequences with the 0h/1h protocol as nurses will often have already performed 1-hour sampling before a physician has had time to receive/act on the results of the 0-hour test. Consequently, even among patients with a 0-hour hs-cTnT <5 ng/L, the majority still had a second hs-cTnT measurement. It is unclear whether a 0h/1h protocol based on point-of-care hs-cTn testing would have affected ED LOS more. Our results contrast with the HiSTORIC (High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction) trial where patients were managed based on a protocol that primarily relies on a 0-hour hs-cTnI value for rule-out and that resulted in a significant decrease in ED LOS.[31] In that trial however, the control arm had their second hs-cTnI measurement 6 to 12 hours after symptom onset. It should also be noted that many factors influence the ED LOS, including the turnaround time for diagnostic tests, level of ED crowding, number of ED personnel, time to seeing a physician and physician decision time, the effectiveness of transport out of the ED etc. The effects on ED LOS of an accelerated diagnostic protocol will therefore be different in every hospital.

Fourth, we found that both a 0h/1h and a 0h/3h protocol allow safe discharge of about 65% to 70% of patients with chest pain. This indicates that these protocols are effective and will allow a high discharge rate with a low miss rate in settings with an AMI/death prevalence similar to ours. In contrast to the present study, Chew et al. observed that a larger proportion of patients were discharged with a 0h/1h than a 0h/3h protocol, and with a somewhat shorter ED LOS.[14] However, the 0h/3h protocol in this study used TnT reporting equivalent of an older (non-high-sensitivity) cTnT assay, which may have increased the differences between the protocols. Also, the high discharge rate with the 0h/3h protocol in our hospitals might have been difficult to improve upon. Our discharge rates were higher than in some studies[14] and similar to others,[32,33] which is likely due to differences in patient characteristics, health care organization, and risk tolerance.

This study also addresses the concerns that have been raised regarding the feasibility of implementing a 0h/1h protocol in real-life emergency care. Our results show that it is indeed possible for nurses even in a busy ED to time the hs-cTn samples with reasonable accuracy. The use of the 0h/1h protocol was also associated with increased level of physician satisfaction.

Limitations

Although this was the largest study to date to evaluate the performance of the 0h/1h protocol when implemented in real-life ED practice, the study has several limitations. Patients were included only in centers in Southern Sweden, which may affect the generalizability of the results. We did, however, include patients at both university and community hospitals and our 30-day AMI/death prevalence was similar to that in several other ED settings.[14,34] Also, we used a hs-cTnT protocol, and the results may not be generalizable to hs-cTnI protocols.

The hospitals were not randomized but were given the option to implement 0h/1h testing or continue with 0h/3h testing, and this may have affected the results. However, the baseline characteristics of patients included at intervention and control hospitals seemed balanced.

We compared the outcomes during sequential 10-month control and intervention periods, which introduces a risk that the results were influenced by temporal trends. To mitigate this risk, we included patients during the corresponding months in both years, used concurrent control hospitals, and evaluated for trends during previous years and for other primary complaints during the study period. Our methods also enabled us to include most patients with chest pain, with very few exclusion criteria and enrollment 24/7. We believe that this minimized the risk of selection bias and increased the generalizability of the results.

We adjudicated patients discharged with suspected events, and there is a possibility that we might have missed some patients with ACS who were discharged and had no events within 30 days. If so, these patients were probably very few and equally present in control and intervention groups. Effects on the safety outcome should therefore be minimal.

The lack of difference in safety could also be due to nonadherence to the 0h/1h protocol. The median time between hs-cTnT samples, however, showed that 1-hour testing was performed in the intervention period, and compliance with the protocol was also indicated by the fact that most patients with low-risk hs-cTnT were discharged and most with high risk were admitted.

CONCLUSIONS

When implemented in real-life care, a 0h/1h hs-cTnT protocol incorporating patient history and ECG was as safe and effective as using a 0h/3h protocol but did not reduce ED LOS or increase the discharge rate. The 0h/1h protocol was feasible to implement, had a high interrater reliability, and was associated with a high physician satisfaction. It was safe to refrain from noninvasive testing in identified low-risk patients.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
Tables S1–S5
Figures S1–S3

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