Identification of very low-risk acute chest pain patients without troponin testing

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ABSTRACT

Background The HEART Pathway combines a History ECG Age Risk factor (HEAR) score and serial troponins to risk stratify patients with acute chest pain. However, it is unclear whether patients with HEAR scores of ≤1 require troponin testing. The objective of this study is to measure the major adverse cardiac event (MACE) rate among patients with ≤1 HEAR scores and determine whether serial troponin testing is needed to achieve a miss rate <1%.

Methods A secondary analysis of the HEART Pathway Implementation Study was conducted. HEART Pathway risk assessments (HEAR scores and serial troponin testing at 0 and 3 hours) were completed by the providers on adult patients with chest pain from three US sites between November 2014 and January 2016. MACE (composite of death, myocardial infarction (MI) and coronary revascularisation) at 30 days was determined. The proportion of patients with HEAR scores of ≤1 diagnosed with MACE within 30 days was calculated. The impact of troponin testing on patients with HEAR scores of ≤1 was determined using Net Reclassification Improvement Index (NRI).

Results Providers completed HEAR assessments on 4979 patients and HEAR scores<1 occurred in 9.0% (447/4979) of patients. Among these patients, MACE at 30 days occurred in 0.9% (4/447; 95% CI 0.2% to 2.3%) with two deaths, two MIs and 0 revascularisations. The sensitivity and negative predictive value for MACE in the HEAR ≤1 was 97.8% (95%CI 94.5% to 99.4%) and 99.1% (95% CI 97.7% to 99.8%), respectively, and were not improved by troponin testing. Troponin testing in patients with HEAR ≤1 correctly reclassified two patients diagnosed with MACE, and was elevated among seven patients without MACE yielding an NRI of 0.9% (95%CI −0.7 to 2.4%).

Conclusion These data suggest that patients with HEAR scores of 0 and 1 represent a very low-risk group that may not require troponin testing to achieve a missed MACE rate <1%.

Trial registration number
NCT02056964

Key messages

What is already known on this subject

► Chest pain is a common presenting complaint in emergency departments. Overuse of cardiac troponin testing in certain low-risk chest pain populations leads to unnecessary resource utilisation and patient harm.

What this study adds

► The HEART Pathway can be used to objectively identify and safely streamline care for certain low-risk chest pain patients by avoiding unnecessary cardiac troponin testing.

INTRODUCTION

Chest pain is a common symptom that accounts for 7–9 million annual emergency department (ED) visits in the USA.[1] Over half of these visits incur a lengthy evaluation to rule out acute coronary syndrome (ACS), but less than 10% of these patients are ultimately diagnosed with ACS.[2] This pattern of excessive testing results in over US$3 billion of avoidable cost spent on non-therapeutic evaluations annually, and subjects low-risk patients to harm from false-positive testing, radiation exposure and anxiety with no improvement in clinical outcomes.[2 3]

Previous studies have shown that up to 46% of cardiac troponin (cTn) testing in the ED is deemed inappropriate and results in significant wasted costs and unnecessary procedures.[4–6] More robust clinical guidelines are needed to direct cTn testing to populations at higher risk for ACS. The HEART Pathway combines a History, ECG, Age, Risk factor (HEAR) score and serial cTn to risk-stratify patients with acute chest pain and identify those suitable for early discharge from the ED without stress testing or coronary angiography.[7–10] While the HEART Pathway has proven successful at safely reducing hospitalisations and cardiac testing, it is unclear if a subpopulation of low-risk patients can be objectively identified for discharge without cTn testing.

The objective of this study was to measure the major adverse cardiac event (MACE) rate among very low-risk chest pain patients, as defined by a HEAR score ≤1, and determine whether cTn testing is needed to achieve a missed adverse cardiac event rate <1%0.[9] We hypothesise that this very low-risk patient population does not benefit from cTn testing and can be safely discharged home with no cardiac testing beyond an ECG.

METHODS

Study design

This was a preplanned secondary analysis of the Heart Pathway Implementation Trial, funded by

the Donaghue Foundation and the Association of American Medical Colleges, and conducted between November 2013 and January 2016. Details of the study methods have been previously published.[9 10] While there was no patient involvement in this study's design or analysis, patient representatives were involved in dissemination methods.

Study setting and population

The study was conducted at three hospitals in the Piedmont Region of North Carolina: Wake Forest Baptist Medical Center (114 000 annual ED visits), Wake Forest Lexington Medical Center (37 000 annual ED visits) and Wake Forest Davie Medical Center (12 000 annual ED visits). The study used a preimplementation and postimplementation design with a wash-in period between exposures to allow provider acclimation to the HEART Pathway. During the preimplementation period providers used 'usual care' for chest pain assessment while the HEART Pathway was used during the postimplementation period. The wash-in period limited carry-over effects from the prior treatment, while providing an opportunity to β-test the electronic health record (EHR)-based HEART Pathway clinical decision support (CDS) tool and train providers. At Wake Forest Baptist Medical Center and Wake Forest Davie Medical Center, participants were accrued into the preimplementation cohort from November 2013 to October 2014 and the postimplementation cohort from February 2015 to January 2016 with a wash-in period from November 2014 to January 2015. Wake Forest Lexington Medical Center accrued patients into the preimplementation cohort from January to July 2015 and the postimplementation cohort from August 2015 to January 2016 with a 1-month wash-in period. Wake Forest Baptist and Davie Medical Centers used the Siemens Ultra ADVIA Centaur TnI-Ultra (Siemens, Munich, Germany; URL 0.040 ng/L) troponin assay and Wake Forest Lexington Medical Center used the Beckman Coulter Access troponin assay (Beckman Coulter, Indianapolis, Indiana, USA; URL 0.030 ng/L) during this study.

Included in this analysis were adult ED patients (≥21 years of age) in the postimplementation and wash-in periods being investigated for chest pain due to possible ACS with a completed HEAR assessment. Patients presenting with chest pain and no evidence of ST-segment elevation myocardial infarction (STEMI) on ECG were eligible for the assessment if at least one cTn was ordered by the clinician. Patients with incomplete HEAR assessments such as those without a HEAR score calculation or without information on ECG or coronary artery disease (CAD) were also excluded (n=820). Patients with an acute ischaemic ECG (≥1 mm of ST depression or T wave inversion in contiguous leads) and those with known CAD (prior MI, prior coronary revascularisation or known coronary stenosis ≥70%) were considered high-risk and not included in this analysis (n=1170). Figure 1 illustrates the flow of patients into the study.

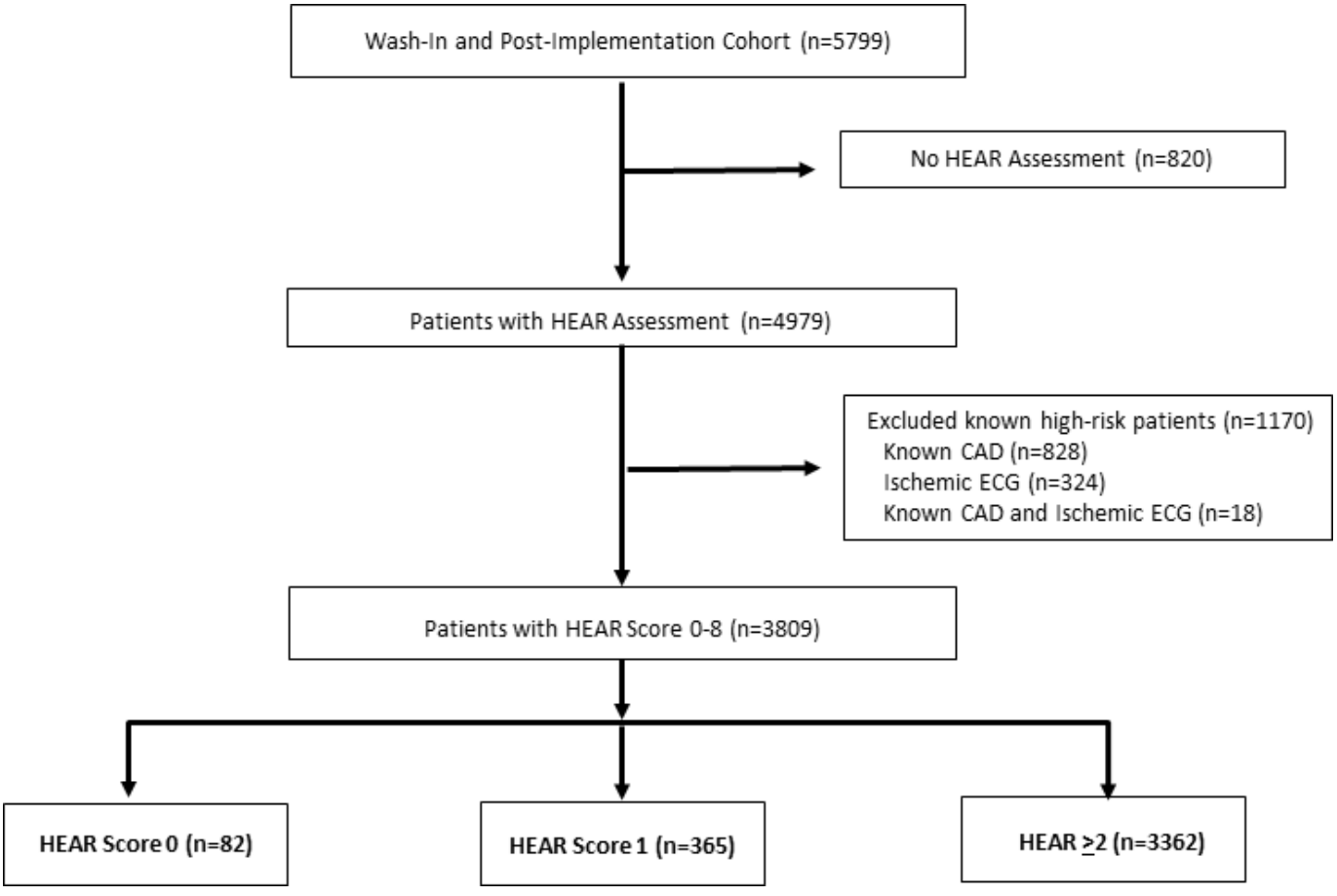

Figure 1 Participant flow diagram. A total of 4979 patients were accrued in the postimplementation and wash-in periods. A total of 820 patients were excluded for not having HEART pathway assessments. A total of 1170 patients were excluded for being obviously high risk, leaving 3809 patients who were eligible for hear score calculation using the HEART pathway CDS tool. CAD, coronary artery disease; CDS, clinical decision support; HEAR, History ECG Age Risk factor.

Study protocol

HEAR scores (without troponin) incorporating only the history, ECG, age and risk factor aspects of the HEART Pathway Assessment were calculated as part of the HEART Pathway accelerated diagnostic protocol using an interactive CDS tool that was fully integrated into the EHR. ED providers saw an interruptive pop-up alert for the HEART Pathway tool as a Best Practice Advisory in the EHR for any adult patient with chest pain and at least 1 cTn ordered in the postimplementation and wash-in periods. Providers were prompted to answer a series of objective, binary questions about the clinical features of the chest pain and ECG abnormalities to prospectively risk-stratify eligible patients in real time while identifying as non-low-risk those patients with STEMI, known CAD, or acute ischaemic changes on ECG such as new ST-segment depression in contiguous leads. The CDS calculated the history, ECG, age and risk factor components of the HEART Pathway assessment based on the provider's responses to a validated algorithm within the software.[9 10] Key differences between the HEART score and HEART Pathway assessment are summarised in online supplementary appendix 2. cTn measurements were then incorporated through a direct link to the laboratory orders and the complete HEART Pathway Assessment was automatically calculated from the HEAR score and 0 and 3 hours cTn measures. Patients deemed low risk were those with HEAR scores≤3 and without elevated cTn values, while patients with HEAR scores≥4, elevated cTn, known CAD or ischaemic ECG changes were classified as non-low risk. Low-risk patients were targeted for early discharge without objective cardiac testing and non-low-risk patients were recommended for further testing or admission. For this analysis, patients with a HEAR score of ≤1 were considered very-low-risk.

Data from initial ED presentation to discharge from the ED, observation unit or inpatient ward were extracted from the health system (Clarity-Epic Systems, Verona, Wisconsin, USA). Patient demographics, medical history, cardiovascular risk factors, comorbidities, cTn results, provider's HEART Pathway assessments, disposition, diagnoses and vital status were obtained using prevalidated, structured EHR variables or diagnoses and procedure codes (Current Procedural Terminology, International Classification of Diseases, 9th revision and 10th revision).[11 12] The EHR was used for within-network return visits, along with insurers' claims data and state death index data to determine 30-day outcomes. We used claims data on patients insured by Blue Cross Blue Shield of North Carolina (the most frequent private insurer in the state), MedCost and North Carolina Medicaid. Death index data were extracted from the North Carolina State Center for Health Statistics. Patients with incomplete follow-up were considered to be free of 30-day MACE.

Measures

MACE at 30 days, a composite of death, MI and revascularisation for any reason (emergent or elective), was the primary outcome. Coronary revascularisation rate was defined as coronary artery bypass grafting, stent placement or other percutaneous coronary intervention. MI and coronary revascularisation were determined from validated diagnosis and procedure codes from prior cardiovascular trials.[11 12]

Data analysis

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative LR (−LR) for ruling out or predicting MACE during the 30-day follow-up period were calculated for patients with HEAR score 0, HEAR score ≤1 and HEAR score ≤1 with troponin. For the latter, a patient had to have a HEAR score ≤1 and 2 negative troponins to be considered low risk, so only those patients with adequate troponin measurements were included in this group (n=3278). Corresponding exact binomial 95% CIs were computed for sensitivity, specificity, PPV and NPV. For the +LR and −LR, 95% CIs were calculated using the method of Simel *et al*.[13] Consistent with prior studies, patients with incomplete follow-up (14.3%, 543/3809) were considered free of 30-day MACEs for the primary analysis.[8 14] A sensitivity analysis was performed using only those patients with complete follow-up (online supplementary appendix 1). Performance of HEAR score ≤1 and HEAR score ≤1 with troponin were compared among those patients with adequate troponin measurements using the net reclassification improvement index (NRI) which quantifies how well the addition of troponin testing improved the detection of MACE (higher NRI would indicate greater improvement with the addition of troponin testing).[15] Statistical analysis was performed using R V.3.5.1 (www.R-project.org).

Table 1 Characteristics of patients with HEAR(History ECG Age Risk factor) scores of 0, 1 and greater than 1

Characteristic	HEAR=0 (n=82)	HEAR=1 (n=365)	HEAR >1 (n=3362)	*P value
Age (year)	35±7	39±9	55±14	<0.001
Female sex	42 (51.2%)	197 (54.0%)	1937 (57.6%)	0.10
Race				<0.001
Caucasian	52 (63.4%)	200 (54.8%)	2122 (63.1%)	
Black	17 (20.7%)	117 (32.1%)	1056 (31.4%)	
Other	13 (15.9%)	48 (13.2%)	184 (5.5%)	
Ethnicity				
Hispanic	8 (9.8%)	39 (10.7%)	146 (4.3%)	<0.001
Risk factors				
Hypertension	7 (8.5%)	83 (22.7%)	2048 (60.9%)	<0.001
Diabetes	0 (0%)	19 (5.2%)	850 (25.3%)	<0.001
Hyperlipidaemia	2 (2.4%)	30 (8.2%)	1273 (37.9%)	<0.001
Family history	0 (0%)	40 (11.1%)	858 (26.3%)	<0.001
Smoking	33 (40.2%)	185 (50.7%)	1938 (57.6%)	<0.001
Obesity	9 (11.0%)	130 (35.6%)	1654 (49.2%)	<0.001
Deaths	1 (1.2%)	1 (0.3%)	12 (0.4%)	0.68
MI	0 (0%)	2 (0.5%)	151 (4.5%)	<0.001
Revascularisation	0 (0%)	0 (0%)	81 (2.4%)	<0.001

Deaths, MI (myocardial infarction), and revascularisation were measured at 30 days.
*P values compare patients with HEAR scores greater than 1 with those less than or equal to 1.

RESULTS

Cohort

During the wash-in and postimplementation study periods 5799 patients were accrued and HEAR assessments were completed in 85.9% (4979/5799) of those patients. In patients with HEAR assessments, HEAR scores of ≤1 occurred in 9.0% (447/4979) of patients with 1.6% (82/4979) and 7.3% (365/4979) of patients scored as 0 and 1, respectively. Table 1 summarises cohort demographics for patients with HEAR scores of 0, 1 and greater than 1. Patients with HEAR scores>2 were significantly older, had more comorbid diseases and suffered higher rates of MI and revascularisation than those with HEAR scores≤1 (p<0.001 for all measurements).

Table 2 Test characteristics of hear sores 0,≤1 and ≤1 with at least 2 negative cTn measurements for the detection of major adverse cardiac events at 30 days

Risk score	HEAR 0 (95% CI) n=3809	HEAR ≦1 (95% CI) n=3809	HEAR ≦1 + troponin (95% CI) n=3278
Sensitivity	99.5% (97.0% to 100.0%)	97.8% (94.5% to 99.4%)	99.4% (96.9% to 100.0%)
Specificity	2.2% (1.8% to 2.8%)	12.2% (11.2% to 13.3%)	9.2% (9.2% to 10.3%)
PPV	4.9% (4.2% to 5.6%)	5.3% (4.6% to 6.1%)	5.9% (5.1% to 6.9%)
NPV	98.8% (93.4% to 100.0%)	99.1% (97.7% to 99.8%)	99.7% (98.1% to 100.0%)
+LR	1.017 (1.005 to 1.029)	1.114 (1.087 to 1.142)	1.095 (1.078 to 1.112)
−LR	0.245 (0.034 to 1.748)	0.179 (0.068 to 0.473)	0.061 (0.009 to 0.430)

cTn, cardiac troponin; HEAR, History ECG Age Risk factor ; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Safety

MACE at 30 days occurred in 0.9% (4/447; 95% CI 0.2% to 2.3%) of patients with a HEAR score ≤1 with two deaths, two MIs and 0 revascularisations. Both deaths occurred due to complications from malignancies that were unrelated to acute coronary syndrome. In patients with a HEAR score of 0, the MACE rate was 1.2% (1/82; 95% CI 0.03% to 6.6%) while 0.8% (3/365; 95% CI 0.2% to 2.4%) of patients with a HEAR score of 1 had MACE. Table 2 summarises test characteristics of very low-risk patients (HEAR score ≤1) with or without troponin testing. HEAR score sensitivity and NPV for ruling out MACE were similar and excellent in very low-risk patients with or without troponin testing (sensitivity HEAR score ≤1 970.8%, 95% CI 94.5% to 99.4% vs HEAR score ≤1 plus troponin 99.4%–95% CI 96.9% to 100.0%). Moreover, specificity and the PPV for predicting MACE were poor in these low-risk patients, and the addition of troponin testing lowered the specificity (HEAR score ≤1 120.2%–95% CI 11.2% to 13.3% vs HEAR score ≤1 plus troponin 9.2%–95% CI 9.2% to 10.3%). A sensitivity analysis including only patients with complete follow-up did not substantively change results (see online supplementary appendix 1).

Table 3 describes the patient characteristics of positive and negative reclassifications for MACE events in very low-risk patients. No patients with a HEAR score of 0 had elevated troponin testing. Among the two patients a HEAR score of 1 and elevated troponin measurements, one was in the setting of cocaine use. Troponin testing in patients with HEAR scores<1 correctly reclassified two patients with MACE (two MIs), and was elevated among seven patients without MACE yielding an NRI of 0.9% (95%CI −0.7 to 2.4%). Based on the NRI, there was no significant improvement in risk classification when adding troponin to a HEAR score of ≤1 (p=0.26).

DISCUSSION

Herein, we objectively identify a population of patients with chest pain with the potential to be safely discharged from the ED without cTn testing. Among patients with a HEAR score ≤1, MACE at 30 days occurred in 0.9% with two deaths, two MIs and 0 revascularisations. Thus, the point estimate for MACE at 30 days among patients with a HEAR score ≤1 was under the 1% benchmark that is generally considered the threshold of acceptability. However, the boundaries of the 95% CI for MACE, which extend from 0.2% to 2.3%, suggest that additional validation is needed before adopting a strategy of excluding ACS based on a HEAR score ≤1without cTn testing[16]

Table 3 Summary of positive and negative reclassifications due to cTn testing along with non-reclassified mace events among very low-risk chest pain patients with hear score ≤1

Positive reclassifications	Patient characteristics
Type 2 MI	A 47-year-old man with HEAR score 1; frequent cocaine abuse and chronic elevation in cTn on multiple visits; no intervention
Type 2 MI	A 56-year-old woman with HEAR score 1; acute chest tightness and peak cTn of 7.950 ng/mL; widely patent coronary arteries and cardiac catheterization consistent with Takotsubo cardiomyopathy
Negative reclassifications	**Patient characteristics**
Pericarditis	A 42-year-old woman with HEAR score 1; recurrent, pleuritic chest pain and peak cTn of 0.417 ng/mL; mild, non-obstructive disease on cardiac catheterisation
Pericarditis	A 38-year-old woman with HEAR score 1; sharp, pleuritic chest pain and single cTn elevation of 0.127 ng/mL; negative CTA of the chest and cardiac MRI
Undifferentiated chest pain	A 34-year-old man with HEAR score 1 and acute chest pain; initial cTn elevated to 0.050 ng/mL and normal subsequent values; no intervention
Non-Ischaemic ventricular tachycardia	A 45-year-old man with HEAR score 1; polysubstance abuse and unstable monomorphic ventricular tachycardia; cTn elevation peaked at 0.418 ng/mL after multiple attempts at cardioversion; widely patent coronary arteries on cardiac catheterisation
Undifferentiated chest pain	A 58-year-old woman with HEAR score 1; recurrent chest pain and palpitations; single cTn elevation to 0.067 ng/mL thought to be laboratory error; no intervention.
Undifferentiated chest pain	A 29-year-old man with HEAR score 1, non-exertional, acute chest pain and isolated cTn elevation to 0.042 ng/mL thought to be laboratory error; negative stress echocardiogram
Breast cancer	A 48-year-old woman with HEAR score 1, metastatic breast cancer, pleuritic chest pain, and malignant pleural effusions; peak cTn 0.084 mg/nL; pain attributed to effusions and treated with tube thoracostomy
Non-reclassified MACE events	
Death from lymphoma	A 43-year-old man with HEAR score 0, shortness of breath, chest pain, hypoxia and diffuse lymphadenopathy from lymphoma; death within 24 hours of admission from complications related to malignancy
Death from lung cancer*	A 50-year-old man with stage IV neuroendocrine lung cancer, atrial fibrillation with a rapid ventricular response, and chest pain; single normal troponin was performed; discharged to hospice within 30 days

*Indicates a patient not included in net reclassification analysis due to in adequate troponin data.
cTn, cardiac troponin; HEAR, History ECG Age Risk factor; MACE, major adverse cardiac event; MI, myocardial infarction.

Closer examination of the deaths in the 30-day follow-up period finds that the patients succumbed to complications from metastatic cancer that were unrelated to ACS. Although one patient had a single troponin measurement performed in the ED, both patients had multiple indications for admission at the time of ED presentation aside from chest pain such as significant tachycardia, arrhythmia or hypoxia. Thus, there were no unexpected cardiac deaths attributable to ACS in this low-risk cohort making our calculations of the sensitivity and NPV for MACE very conservative estimations of what most clinicians will encounter in practice. Moreover, careful evaluation of patients with positive cTn values (table 3) suggests that the vast majority of these patients had acute or chronic myocardial injury without type 1 or 2 MI from conditions such as pericarditis or malignancy, and a few were attributed to laboratory error by the clinical team. In these cases, the addition of cTn testing produced a low NRI, lowered specificity for MACE, increased non-therapeutic testing and possibly resulted in admission that was not value added to the visit.

Prior studies used accelerated diagnostic pathways to facilitate early discharge for low-risk patients, but these studies incorporated at least one measurement of cTn to safely exclude MACE.[16–19] However, increased use of cTn testing in low-risk populations with atypical symptoms or lacking ischaemic ECG findings is associated with downstream unnecessary resource use.[4 6] Patients presenting with atypical symptoms such as shortness of breath or fatigue are identified as potential populations where cTn testing may be value lost as these are associated with inappropriate cTn use and less likely to benefit from angiography or secondary prevention than patients with chest pain.[4] On the other hand, ours is the first study to identify a sizeable cohort of chest pain patients who are at very low-risk for ACS and unlikely to benefit from any cTn testing as the addition of troponin testing lowered specificity with no real improvement in the PPV or NPV. If further validated, this could represent a significant improvement in ED value (laboratory costs, length of stay, etc) when applied to the 7–9 million annual chest pain visits that occur each year in the USA. In our study, positive reclassifications for MACE, based on the use of cTn, occurred in the setting of type 2 MI due to cocaine use or Takotsubo (stress-induced) cardiomyopathy. While the latter is rare, the incidence of MI in patients with chest pain after cocaine use is between 0.7% and 6.0%.[20] Current recommendations support the use of accelerated diagnostic pathway in these patients since they generally have favourable outcomes at 1 year.[21 22] However, all of these pathways recommend some form of cTn testing, and it is reasonable to expect that patients with type 2 MIs due to cocaine use benefit from medical therapies such as benzodiazepines and aspirin.[23] Thus, we support the approach of measuring cTn even in very low-risk patients who abuse cocaine or other stimulants.

Finally, our findings are specific to the HEART Pathway and should not be generalised to other accelerated diagnostic pathways or risk scores including the original HEART score. The HEART Pathway uses a modified HEART score, which has key structural differences from the HEART score (see online supplementary appendix 2). For example, the HEART score uses clinician gestalt to classify the suspiciousness of the history, while the HEART Pathway replaces the subjective components of the HEART score with objective binary questions and applies an algorithm to quantify each HEAR score element.[9 10 24 25] The HEART Pathway also prompts clinicians for specific ECG abnormalities such as non-specific T-wave abnormalities, bundle branch blocks and paced rhythms to calculate an ECG score rather than relying on the clinician to recognises these abnormalities as significant.

Furthermore, the HEART score is often manually calculated which may lower reproducibility and reliability compared with a pathway integrated into the EHR. We have previously demonstrated that the HEART Pathway is superior to estimations of risk based on gestalt and feel that the objective nature of the HEART Pathway is a key safety feature.[26]

Limitations

The study's pre–postinterrupted time series design has limitations compared with randomised design. For example, provider maturation effects may adversely impact the validity of our results. Moreover, reliance on an EHR to identify events may be less accurate than traditional methods of performing follow-up. There were also some inequities in patient accrual into the post-implementation and preimplementation phases that may have created some selection bias due to availability of the HEART Pathway tool for non-chest pain presentations at later time points. Although our three sites were diverse in size and location, our results may not be generalisable to other parts of the US or different healthcare systems. For example, European studies have noted higher rates of MACE and MI than seen in our study population which may lower the NPV of our findings when applied to these populations.[27 28] We also performed our analysis on a smaller subset of a larger cohort which can amplify the effects of verification and selection biases. Larger prospective studies are needed to validate our findings prior to concluding that all patients with a HEAR score ≤ 1 can be safely discharged without troponin testing. It is also possible that safety events related to the index visit occurred beyond the 30-day follow-up period. Finally, our population of interest was selected to be low risk by excluding patients having an STEMI on initial ECG, previously diagnosed obstructive CAD or acute ischaemia on ECG. Thus, our findings are not generalisable to the larger population of ED patients having chest pain.

CONCLUSIONS

Patients with objectively calculated HEAR scores of 0 and 1 using the HEART Pathway are at very low-risk for MACE and unlikely to benefit from cTn testing. If performed, cTn testing is unlikely to predict adverse events from ACS and may contribute to non-therapeutic downstream testing. Patients with acute chest pain who abuse cocaine or other stimulants but are otherwise low risk may benefit from cTn testing. Multisite prospective validation is needed to determine if foregoing troponin testing in these patients will safely improve value.

Contributors SAM oversaw the study design, provided key edits to this manuscript and is responsible for the overall content as guarantor. LS and ACS performed the primary data analysis and manuscript writing as well as assisting with the study design. NPA, DMH, BH, CDM, and BJW assisted with study design and manuscript editing. KML assisted with data analysis.

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Competing interests SAM receives research funding from Roche Diagnostics, Abbott Point of Care, Ortho Clinical Diagnostics, Creavo Medical Technologies, PCORI, AHRQ and NHLBI (1 R01 HL11826301). He is a consultant for Roche Diagnostics and Amgen. SAM is the chief medical officer for Impathiq. JPS receives research funding from Roche Diagnostics and Abbott Point of Care. LS receives research funding from Forest Devices and the NHLBI (1 R01 HL144624-01). CDM receives research funding from Abbott, Siemens, NHLBI 118263, Creavo Medical Technologies.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study was approved by our Institutional Review Board (IRB00025114).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplementary information. All original data are maintained by Wake Forest University Health Sciences and is available on request from the corresponding author.

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