Original Article

Low High-Sensitivity Troponin Thresholds Identify Low-Risk Patients With Chest Pain Unlikely to Benefit From Further Risk Stratification

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ABSTRACT

Background: Very low high-sensitivity cardiac troponin T (hs-cTnT) thresholds on presentation can rule out acute myocardial infarction (AMI), but the ability to identify patients at low risk of 30-day major adverse cardiac events (MACE) is less clear. This study examines the sensitivity of low concentrations of hs-cTnT on presentation to rule out 30-day MACE.

Methods: This prospective cohort study enrolled patients with chest pain presenting to the emergency department with nonischemic electrocardiograms who underwent AMI rule-out with an hs-cTnT assay. The primary outcome was 30-day MACE; secondary outcomes were individual MACE components. Because guidelines recommend using a

RÉSUMÉ

Contexte : Un seuil de troponine T cardiaque hypersensible (TnTc-hs) très bas au moment de la consultation permet d'écarter le diagnostic d'infarctus aigu du myocarde (IAM), mais l'utilité de ce paramètre pour reconnaître les patients exposés à un faible risque d'événement cardiaque indésirable majeur (ECIM) à 30 jours est moins bien établie. Les auteurs examinent la sensibilité de la présence d'une faible concentration de TnTc-hs à la consultation comme critère pour écarter la possibilité d'un ECIM à 30 jours.

Méthode : Ont été admis dans cette étude de cohorte prospective les patients qui se sont présentés à l'urgence en raison d'une douleur à la poitrine, dont l'électrocardiogramme n'a pas révélé d'ischémie et chez

Chest pain is one of the most common reasons for visiting emergency departments (EDs) worldwide, and exclusion of acute myocardial infarction (AMI) through measurement of serum troponin concentrations for many of these patients is essential. Because high-sensitivity cardiac troponin (hs-cTn) assays can reliably measure normal physiologic concentrations of troponin in most healthy individuals,[1] they have the potential to expedite the exclusion of AMI by dramatically shortening the testing period. Indeed, a single hs-cTn concentration below the limit of detection sampled on

presentation more than 3 hours after the onset of symptoms was endorsed as sufficient to rule out AMI by the European Society of Cardiology (ESC) 2015 Guidelines.[2] This is clearly attractive from an operations standpoint by facilitating rapid decision-making, improving ED throughput, and decreasing resource use.

Although there is a large body of research demonstrating the high sensitivity of very low hs-cTn thresholds on presentation to exclude index AMI for patients with chest pain presenting to the ED,[3-22] there is less research examining the exclusion of 30-day AMI and major adverse cardiac events (MACE).[22] Moreover, many of the multicenter hs-cTn studies to date have been conducted in Europe or Australasia, relying on samples processed by a single core laboratory (likely representing optimal assay performance), and their results may not be generalizable to everyday clinical practice. Further complicating the evaluation of patients with chest pain in the United States, the Food and Drug Administration (FDA) has restricted the lowest concentration US laboratories

single hs-cTnT strategy only for patients with more than 3 hours since symptom onset, a subgroup analysis was performed for this population. Outcomes were adjudicated on the basis of review of medical records and telephone follow-up.

Results: Of 1167 patients enrolled, 125 (10.7%) experienced 30-day MACE and 97 (8.3%) had AMI on the index visit. More than one-third of patients (35.6%) had presenting hs-cTnT concentrations below the limit of detection (5 ng/L), which was 94.4% (95% confidence interval [CI], 88.8-97.7) sensitive for 30-day MACE and 99.0% (95% CI, 94.5-100) sensitive for index AMI. Of 292 patients (25.0%) with hs-cTnT < 5 ng/L and at least 3 hours since symptom onset, only 3 experienced 30-day MACE (sensitivity 97.6%; 95% CI, 93.2-100) and none had AMI within 30 days (sensitivity 100%; 95% CI, 96.3-100).

Conclusions: Among patients with nonischemic electrocardiograms and > 3 hours since symptom onset, low hs-cTnT thresholds on presentation confer a very low risk of 30-day MACE. In the absence of a high-risk clinical presentation, further risk stratification is likely to be low yield.

qui le diagnostic d'IAM a été écarté au moyen d'un dosage de la TnTc-hs. Le critère d'évaluation principal était la survenue d'un ECIM à 30 jours; les critères d'évaluation secondaires étaient les composantes individuelles de l'ECIM. Comme les lignes directrices recommandent le recours à un simple dosage de la TnTc-hs seulement pour les patients présentant des symptômes depuis plus de 3 heures, une analyse a été réalisée dans ce sous-groupe de la population à l'étude. Les critères d'évaluation ont été confirmés par un examen des dossiers médicaux et par un suivi téléphonique.

Résultats : Des 1167 patients retenus, 125 (10,7 %) ont présenté un ECIM à 30 jours et 97 (8,3 %) avaient reçu un diagnostic d'IAM à la visite de référence. Au moment de la consultation, plus du tiers des patients (35,6 %) présentaient une concentration de TnTc-hs sous le seuil de détection (5 ng/l), ce qui représente une sensibilité de 94,4 % (intervalle de confiance [IC] à 95 % : de 88,8 à 97,7) dans le cas de l'ECIM à 30 jours et de 99,0 % (IC à 95 % : de 94,5 à 100) dans le cas de l'IAM de référence. Des 292 patients (25,0 %) présentant un taux de TnTc-hs < 5 ng/l et des symptômes apparus depuis au moins 3 heures, seulement 3 ont subi un ECIM à 30 jours (sensibilité de 97,6 %; IC à 95 % : de 93,2 à 100) et aucun n'a subi d'IAM dans les 30 jours (sensibilité de 100 %; IC à 95 % : de 96,3 à 100).

Conclusions : Chez les patients dont l'électrocardiogramme ne révèle pas d'ischémie et qui présentent des symptômes depuis au moins 3 heures, un seuil de TnTc-hs faible au moment de la consultation est associé à un très faible risque d'ECIM à 30 jours. En l'absence d'un tableau clinique associé à un risque élevé, il est peu probable qu'une stratification du risque plus poussée soit utile.

can report (limit of quantitation [LoQ]) for the hs-cTnT assay to 6 ng/L, which is higher than the validated cutoff of < 5 ng/L recommended by the ESC 2015 Guidelines,[2] and may be less sensitive for AMI and MACE. This may limit the clinical utility of the assay, because an international survey of emergency physicians and cardiologists reported that a majority of respondents would only accept a miss rate for 30-day MACE of 0.5%,[23] even though this may be difficult to practically achieve and is well below the previously described test threshold of 2% at which the risks of additional testing may exceed the potential benefits.[24]

Our main objective was to quantify the sensitivity of low thresholds of hs-cTnT on ED presentation to exclude 30-day MACE in a Canadian population under real-world testing conditions, considering 3 previously described diagnostic thresholds: limit of blank (< 3 ng/L), (limit of detection, < 5 ng/L) and FDA-approved LoQ) (< 6 ng/L). Our second objective was to attempt to define a very low-risk population unlikely to benefit from routine early objective testing. Our hypothesis is that very low thresholds of hs-cTnT on ED presentation are highly sensitive for 30-day MACE and can identify a very low-risk population for whom further risk stratification is of low yield.

Materials and Methods

Setting

This prospective cohort study was conducted at a large urban level 1 trauma and regional percutaneous coronary intervention center in Calgary, Alberta, Canada, from August 2014 to September 2016. The ED has an annual patient volume of approximately 80,000 visits, including approximately 2500 annual visits for chest pain, and is staffed exclusively by board-certified emergency physicians.

Patients

Patients were eligible if they were aged 25 years or older, presented to the ED with Canadian Emergency Department Information System standardized chief symptoms[25] of "chest pain — cardiac features" or "cardiac type pain," and required troponin testing to rule out AMI at the discretion of the attending emergency physician. Patients were excluded from the study if, according to the attending emergency physician, they had ST-elevation myocardial infarction, clear acute ischemic changes, or new arrhythmia on the initial electrocardiogram (ECG) (not including sinus tachycardia, premature atrial contractions, premature ventricular contractions, paced rhythm, or rate-controlled atrial fibrillation/atrial flutter); were diagnosed with an acute coronary syndrome (ACS) in the 30 days before the index visit; were hemodynamically unstable; had advanced renal failure requiring peritoneal or hemodialysis; or were unable to provide consent secondary to language barriers or cognitive issues.

Troponin assay

Hs-cTnT (Roche Elecsys High-sensitivity, 5th generation, troponin T assay performed on the Cobas e601 instrument as per the manufacturer's specifications; Roche, Basel, Switzerland) results were obtained for all patients on presentation as part of clinical care. Four lots of reagent were used during the study period, and manufacturer-recommended maintenance schedules were followed on the instruments.
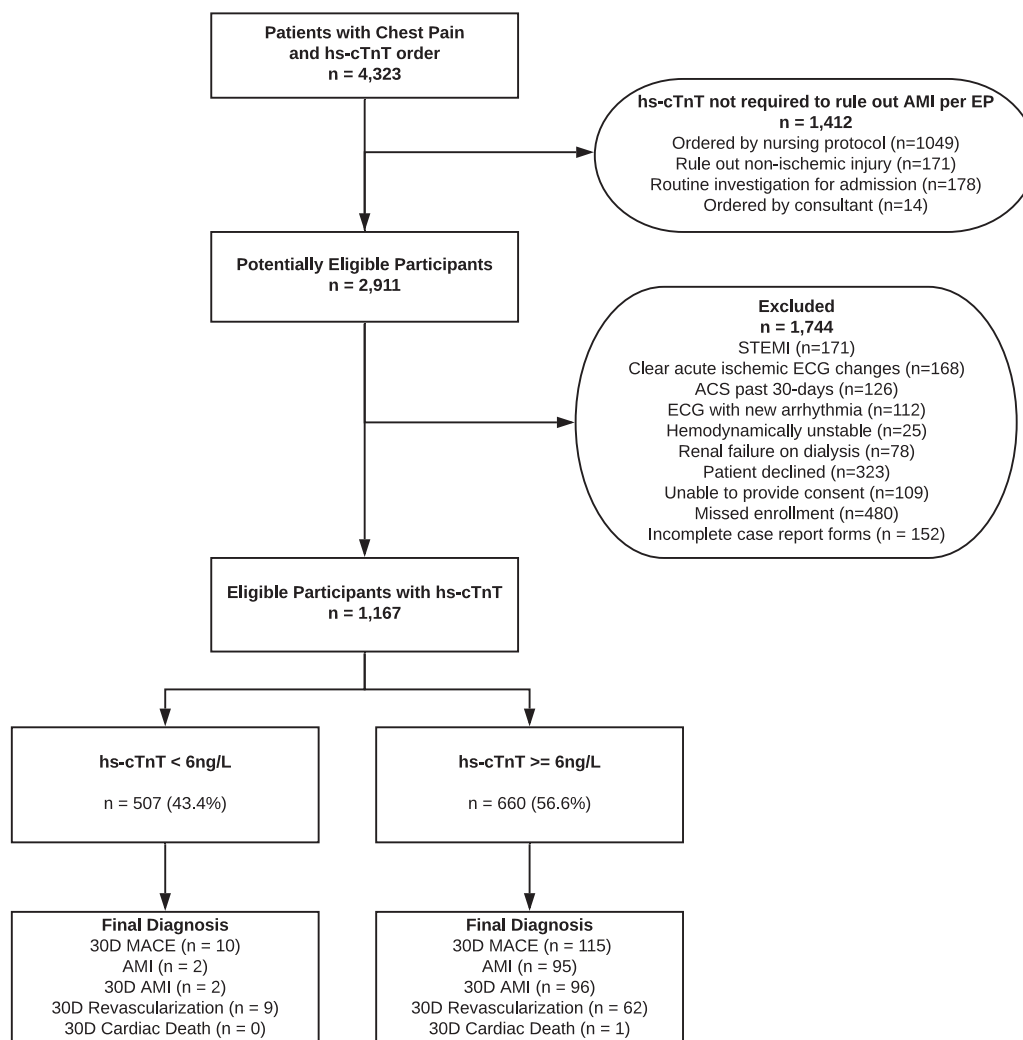
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Figure 1. Standards for Reporting of Diagnostic Accuracy Studies (STARD) diagram. ACS, acute coronary syndrome; AMI, acute myocardial infarction; ECG, electrocardiogram; EP, emergency physician; hs-cTnT, high-sensitivity cardiac troponin T; MACE, major adverse cardiac events; STEMI, ST-elevation myocardial infarction.

This assay has a limit of blank of 3 ng/L, a limit of detection of 5 ng/L, an FDA-approved LoQ of 6 ng/L, and a 99th percentile of 14 ng/L in a healthy population.

Study procedures

Trained research assistants approached patients between 8:00 AM and 8 PM 7 days per week to obtain written informed consent and collect demographic data. Attending ED physicians used standardized case report forms to collate detailed clinical information regarding patient presentation, medical history, and gestalt risk assessment of ACS (low, moderate, high risk). All patients consented for 30-day telephone follow-up and detailed review of medical records. Emergency physicians were not blinded to hs-cTnT results because they were collected as part of routine clinical care. No changes to patient care were made as part of this study. This study was approved by the University of Calgary Conjoint Health Research Ethics Board.

All patients underwent detailed review of medical records incorporating the 30-day period after the index visit. Outcome events were also ascertained using hospital administrative databases, Alberta provincial vital statistics, and the **A**lberta **P**rovincial **Pr**oject for **O**utcome **A**ssessment in **C**oronary **H**eart Disease (APPROACH) registry. APPROACH is a registry that prospectively collects data on all patients admitted with a cardiac diagnosis or who have a revascularization procedure in the province of Alberta.[26] Attempts were made to contact all patients by telephone at 30 days to confirm outcomes.

Outcomes

The primary outcome was 30-day MACE, including AMI, revascularization, or cardiac death. Secondary outcomes included individual MACE components. AMI was adjudicated on the basis of an increase or decrease of hs-cTnT above the 99th percentile in the appropriate clinical context, in accordance with the Third Universal Definition of Myocardial Infarction.[27] AMI was further characterized as type 1 (spontaneous clinical syndrome related to decreased myocardial blood flow from acute intraluminal thrombus) or type 2 (spontaneous clinical syndrome where a condition other than

Table 1. Patient demographics

Characteristic	N (%)
N	1167
Median age (IQR)	60 (50-70)
Male	674 (57.8%)
Arrival by ambulance	359 (30.8%)
CAD history	331 (28.4%)
Vascular disease history	64 (5.5%)
Hypertension	539 (46.2%)
Hyperlipidemia	478 (41.0%)
Diabetes	181 (15.5%)
Obesity	238 (20.4%)
Family history of CAD	225 (19.3%)
Smoker	159 (13.6%)
Chest pain onset < 3 h	327 (28.0%)
High-risk presentation per ED physician	136 (11.7%)

CAD, coronary artery disease; ED, emergency department; IQR, interquartile range.

coronary artery disease contributes to an imbalance between myocardial oxygen supply and demand). Thirty-day AMI included all AMI events in the 30-day period after enrolment, including AMI on the index visit. Revascularization included any successful or attempted coronary reperfusion, including thrombolysis, percutaneous coronary intervention, or coronary artery bypass graft. Cardiac death was adjudicated in accordance with the American College of Cardiology/American Heart Association 2014 Definitions for Cardiovascular Endpoints.[28] All outcomes were independently adjudicated by 2 physicians (board-certified cardiologist and board-certified emergency physician) after the review of all available clinical documentation, ECGs, hs-cTnT results, cardiac imaging, and procedures. Disagreements were resolved by consensus.

Analysis

Descriptive statistics were performed for the cohort. Sensitivity, negative-predictive values, and negative likelihood ratios with 95% confidence intervals were calculated for the various hs-cTnT cutoffs. Because ESC 2015 guidelines recommend that a single hs-cTn rule-out strategy should be considered only for patients evaluated 3 or more hours after the onset of symptoms (because of the risk of false-negative results for very early presenters), a prespecified subgroup analysis was performed for this population. A sensitivity analysis was performed to estimate the effect of excluding patients with ischemic ECG findings on outcome prevalence. Statistical analyses were performed using R Version 3.2.3 (www.r-project.org). To obtain a 95% confidence interval of ±1.0% for the outcome of 30-day MACE (estimated prevalence 2%), a sample size of 753 patients was calculated. Interobserver agreement for the primary outcome of 30-day MACE was calculated using Cohen's kappa.

Results

A total of 1167 patients were enrolled in the study (Fig. 1). Enrolment exceeded the calculated minimum sample size because patients were also being recruited for a concurrent study performing serial hs-cTnT measurements, which required a larger sample size. Demographic characteristics of participants are listed in Table 1. Telephone follow-up was completed for 968 patients (82.9%), but 30-day outcomes

Table 2. Thirty-day patient outcomes

Outcome	N (%)
All patients	1167 (100%)
Admitted on index visit	230 (19.7%)
30-d ED revisit	121 (10.4%)
30-d hospital admission	35 (3.0%)
30-d MACE	125 (10.7%)
MACE on index visit	116 (9.9%)
MACE after index visit but within 30 d	9 (0.8%)
30-d AMI	98 (8.4%)
AMI during index presentation	97 (8.3%)
Type 1	74 (6.3%)
Type 2	23 (2.0%)
AMI after index visit but within 30 d	1 (0.1%)
30-d revascularization	71 (6.1%)
Revascularization on index visit	64 (5.5%)
PCI	49 (4.2%)
CABG	15 (1.3%)
Revascularization after index visit but within 30 d	7 (0.6%)
PCI	5 (0.4%)
CABG	2 (0.2%)
30-d cardiac death	1 (0.1%)
Cardiac death on index visit	0 (0.0%)
Cardiac death after index visit but within 30 d	1 (0.1%)
Discharged patients only	937 (80.3%)
Cardiology consult in the ED before discharge	62 (6.6%)
30-d cardiologist follow-up	253 (27.0%)
30-d family physician follow-up	416 (44.3%)
30-d ED revisit	94 (10.0%)

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; ED, emergency department; MACE, major adverse cardiac events; PCI, percutaneous coronary intervention.

and follow-up status were confidently obtained for all patients because of comprehensive medical record and database linkages. Cohen's kappa for the diagnosis of 30-day MACE between the 2 physician adjudicators was 0.88.

In the cohort, 125 patients (10.7%) experienced 30-day MACE, with 111 events (9.5%) occurring during the index visit and 14 events (1.2%) occurring during 30-day follow-up (Table 2). Ninety-seven patients (8.3%) were diagnosed with AMI on the index visit, of whom 74 (6.3%) had type 1 AMI and 23 (2.0%) had type 2 AMI. One additional patient was diagnosed with AMI during 30-day follow-up (30-day AMI 8.4%). Sensitivity analysis reveals that if all patients with acute ischemic ECG changes (n = 168) were included in this study and ultimately diagnosed with AMI, the prevalence of index AMI in this population could have been as high as 20%. Four patients (0.3%) died within 30 days of the index visit, but only 1 death (0.1%) was adjudicated as cardiac death. Although 937 patients (80.3%) were discharged from the ED during the index visit, 62 (6.6%) underwent cardiology assessment in the ED before discharge, and within the 30-day follow-up period, 253 patients (27.0%) saw a cardiologist, 416 patients (44.3%) had follow-up with a family physician, and 94 patients (10.0%) had a repeat ED visit (Table 2).

Test characteristics of the various hs-cTnT thresholds for MACE and its components are listed in Table 3. All thresholds were highly sensitive for AMI, 30-day AMI, and cardiac death, but had somewhat lower sensitivity for 30-day MACE, which was driven largely by 30-day revascularization events. Specificity for 30-day MACE was less than 50% for all cutoffs. All 10 patients with hs-cTnT < 6 ng/L and 30-day MACE are listed in Supplementary Table S1.

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Table 3. Test characteristics of very low hs-cTnT thresholds on presentation

hs-cTnT threshold	Eligible N (%)	Outcome	TP	FP	FN	TN	Sensitivity (95% CI)	NPV (95% CI)	LR− (95% CI)
< 3 ng/L	191 (16.4%)	30-d MACE	123	853	2	189	98.4 (94.3, 99.8)	99.0 (96.3, 99.9)	0.09 (0.02, 0.35)
		Index AMI	97	879	0	191	100 (96.3,100)	100 (98.1, 100)	0 (0, NA)
		30-d AMI	98	878	0	191	100 (96.3,100)	100 (98.1, 100)	0 (0, NA)
		30-d revascularization	69	907	2	189	97.2 (90.3-99.2)	99.0 (96.3, 99.9)	0.16 (0.04, 0.63)
		30-d cardiac death	1	975	0	191	100 (20.7, 100)	100 (98.1, 100)	0 (0, NA)
<5 ng/L	416 (35.6%)	30 d MACE	118	633	7	409	94.4 (88.8, 97.7)	98.3 (96.6, 99.3)	0.14 (0.07, 0.29)
		Index AMI	96	655	1	415	99.0 (94.5, 100)	99.8 (98.7, 100)	0 (0, NA)
		30 d AMI	97	654	1	415	99.0 (94.5, 100)	99.8 (98.7, 100)	0 (0, NA)
		30 d revascularization	64	687	7	409	90.1 (81.5, 95.3)	98.3 (96.6, 99.3)	0.26 (0.13, 0.52)
		30-d cardiac death	1	750	0	416	100 (20.7, 100)	100 (99.1, 100)	0 (0, NA)
<6 ng/L	507 (43.4%)	30-d MACE	115	545	10	497	92.0 (85.8, 96.1)	98.0 (96.4, 99.1)	0.17 (0.09, 0.31)
		Index AMI	95	565	2	505	97.9 (92.8, 99.8)	99.6 (98.6, 100)	0.04 (0.01, 0.17)
		30-d AMI	96	564	2	505	98.0 (92.8, 99.8)	99.6 (98.6, 100)	0.04 (0.01, 0.17)
		30-d revascularization	62	598	9	498	87.3 (77.6, 93.2%)	98.2 (96.7, 99.1)	0.28 (0.15, 0.52)
		30-d cardiac death	1	659	0	507	100 (20.7, 100)	100 (99.3, 100)	0 (0, NA)

FN, false-negative; FP, false-positive; hs-cTnT, high-sensitivity cardiac troponin T; LR−, negative likelihood ratio; MACE, major adverse cardiac events; NPV, negative predictive value; TN, true negative; TP, true-positive.

Among patients with chest pain onset at least 3 hours before presentation, the sensitivity of the various hs-cTnT thresholds for 30-day MACE improved considerably (ranging, 96.0%-100%), with a significant proportion of patients (11%-30%) still remaining eligible for these more restrictive criteria (Table 4).

Discussion

This prospective study confirms the high sensitivity of very low hs-cTnT thresholds at ED presentation for 30-day MACE in patients with nonischemic ECGs, irrespective of symptom timing, even when the assay is performed under real-world laboratory conditions and in a Canadian population. These findings are concordant with existing systematic reviews of European and Australasian studies,[21,22] and are similar to results obtained by McRae et al.[20] from a large administrative dataset of patients with chest pain presenting to Canadian EDs that suggests very low concentrations of hs-cTn effectively rule out on AMI on the index visit.

Restricting the single hs-cTn rule-out strategy to patients presenting at least 3 hours after the onset of symptoms as advised by ESC 2015 guidelines[2] significantly improves the sensitivity of this strategy for both AMI and 30-day MACE. This finding is intuitive because very early presenters with cardiac ischemia may present before sufficient myocardial injury has occurred to generate measurable serum hs-cTn concentrations. Among patients with nonischemic ECGs and 3 hours or more since symptom onset, the hs-cTnT thresholds of < 3, < 5, and < 6 ng/L at presentation had negative predictive values for 30-day MACE of 100%, 99.0%, and 98.6%, respectively. These values all correspond to a missed 30-day MACE rate of less than 2.0%, which is the previously described test threshold for ACS at which the risks of additional testing may exceed the potential benefits.[24] Moreover, the 10 patients with very low hs-cTnT concentrations who experienced 30-day MACE were clinically identified as high risk by physician gestalt on the index visit and admitted to hospital for further evaluation. Thus, although biomarkers alone were highly sensitive for 30-day MACE events, clinical judgment in combination with biomarker results achieved perfect sensitivity. These findings support early discharge for patients with a non—high-risk

Table 4. Test characteristics of very low hs-cTnT thresholds on presentation among patients with at least 3 hours since symptom onset

hs-cTnT threshold	Eligible N (%)	Outcome	TP	FP	FN	TN	Sensitivity (95% CI)	NPV (95% CI)	LR− (95% CI)
< 3 ng/L	126 (10.8%)	30-d MACE	125	916	0	126	100 (97.1-100)	100 (97.1-100)	0 (0-NA)
		Index AMI	97	944	0	126	100 (96.3-100)	100 (97.1-100)	0 (0-NA)
		30-d AMI	98	943	0	126	100 (96.3-100)	100 (97.1-100)	0 (0-NA)
		30-d revascularization	71	970	0	126	100 (95.0-100)	100 (97.1-100)	0 (0-NA)
		30-d cardiac death	1	1040	0	126	100 (20.7-100)	100 (97.1-100)	0 (0-NA)
< 5 ng/L	292 (25.0%)	30-d MACE	122	753	3	289	97.6 (93.2-100)	99.0 (97.0-99.8)	0.09 (0.03-0.27)
		Index AMI	97	778	0	292	100 (96.3-100)	100 (98.7-100)	0 (0-NA)
		30-d AMI	98	777	0	292	100 (96.3-100)	100 (98.7-100)	0 (0-NA)
		30-d revascularization	68	807	3	289	95.8 (88.3-98.6)	99.0 (97.0-99.8)	0.16 (0.05-0.49)
		30-d cardiac death	1	874	0	292	100 (20.7-100)	100 (98.7-100)	0 (0-NA)
< 6 ng/L	354 (30.3%)	30-d MACE	120	693	5	349	96.0 (90.9-98.7)	98.6 (96.7-100)	0.12 (0.05-0.28)
		Index AMI	97	716	0	354	100 (96.3-100)	100 (99.0-100)	0 (0-NA)
		30-d AMI	98	715	0	354	100 (96.3-100)	100 (99.0-100)	0 (0-NA)
		30-d revascularization	66	747	5	349	93.0 (84.6-97.0)	98.6 (96.7-99.4)	0.22 (0.10-0.52)
		30-d cardiac death	1	813	0	354	100 (20.7-100)	100 (99.0-100)	0 (0-NA)

AMI, acute myocardial infarction; CI, confidence interval; FN, false-negative; FP, false-positive; hs-cTnT, high-sensitivity cardiac troponin T; LR−, negative likelihood ratio; MACE, major adverse cardiac events; NA, not available; NPV, negative predictive value; TN, true negative; TP, true-positive.

clinical presentation meeting low hs-cTnT thresholds on presentation, as recommended in a recently published chest pain pathway using hs-cTn.[29] Finally, although the specificity of these same criteria for 30-day MACE is admittedly low, this fact does not impact their utility given their intended unidirectional use (ie, rule-out only). All other patients who do not meet these stringent criteria are recommended to proceed with serial hs-cTn sampling at fixed time intervals (usually 1 or 2 hours) to rule out acute myocardial injury.

Given the exceedingly low risk of 30-day MACE for patients with nonischemic ECGs and very low concentrations of hs-cTnT on presentation 3 hours after symptom onset (and the perfect sensitivity of these parameters combined with clinical judgment), the utility and cost-effectiveness of *routine* urgent objective testing are doubtful for this population. In contrast, American College of Cardiology/American Heart Association guidelines recommend that, after having AMI ruled out, patients with chest pain should undergo urgent objective testing with treadmill ECG, stress myocardial perfusion imaging, stress echocardiography, or coronary CT angiography to screen for coronary artery disease.[30] However, early outpatient stress testing has not been shown to have an impact in reducing MACE,[31] and positive objective test results in low-risk patients are more likely to be false-positives than true-positives,[32] leading to costly and potentially harmful interventions. It thus seems prudent that guidelines are updated to incorporate the hs-cTn literature and reflect the even lower benefit, and potential real harms of *routine* objective testing for this population. These data suggest that early objective testing for patients meeting low hs-cTn thresholds on presentation is best reserved for only those patients with high-risk clinical presentations, as determined by physician gestalt or an objective risk stratification tool. Using such a strategy would decongest ED observation units, cardiology inpatient units, and outpatient clinics by removing very low-risk patients least likely to benefit from further risk stratification, leading to more timely assessment of higher risk patients, resource savings, and more efficient healthcare delivery. Although this hypothesis should be prospectively tested, the implementation of hs-cTn assays has already been shown to reduce stress testing and time to discharge,[33] suggesting such a strategy is feasible.

Limitations

This study was performed in a single Canadian ED, enrolling patients with a chief symptom of "chest pain" from 8:00 AM to 8 PM on a daily basis based on research assistant availability. However, we have no reason to suspect that given the large sample collected the patients included are likely to systematically differ from the general ED population with chest pain. Patients with potential alternate presentations of cardiac ischemia (eg, dyspnea, weakness, back pain, nausea, and abdominal pain) were not included, and it is possible that this systematically underrepresents women, patients with diabetes, elderly patients, and other subgroups who are less likely to report chest pain. However, requiring a chief symptom of chest pain as one of the primary enrolment criterion is commonplace in the myocardial infarction diagnostic literature and may prevent dilution of disease prevalence in the cohort when presentations unlikely to be cardiac are included. Still, the prevalence of index AMI (8.3%) and 30-day AMI (8.4%) in this cohort is lower than in many prior studies, which ranged between 7% and 20%,[22] likely because of the exclusion of patients with recent ACS, clear acute ischemic ECG changes, and ST-elevation myocardial infarction. Because these patients clearly represent a high-risk subgroup, standard of practice dictates that these patients undergo serial hs-cTn sampling rather than disposition after a single hs-cTn result, and even in the presence of normal serial hs-cTn concentrations, most are likely to be admitted for further evaluation. Thus, the exclusion of these high-risk patients from this study is unlikely to change our conclusions. Finally, because all patients did not have urgent follow-up with a cardiologist or receive early objective testing, it is possible that patients with symptomatic coronary disease may have only been diagnosed or revascularized outside the 30-day follow-up window reported in the study, leading to an underestimate of near-term MACE. However, given that a majority of discharged patients were assessed by a cardiologist or family physician, or had a repeat ED visit in the 30-day follow-up period, we believe the number of patients with undiagnosed symptomatic coronary disease after 30-day follow-up is low.

Conclusions

Among patients presenting to the ED with chest pain of suspected cardiac origin and a nonischemic ECG, the sensitivity of low hs-cTnT thresholds for 30-day MACE is high. Sensitivity can be optimized by following ESC guidelines recommending a single hs-cTn strategy only for patients presenting 3 hours after symptom onset, while still identifying a large proportion of patients as low risk. Because the incidence of 30-day MACE is so low in this population, the utility of routine early objective testing is doubtful in the absence of a high-risk clinical presentation. Guideline authors should consider the improved test characteristics of hs-cTn assays in identifying patients at low risk of 30-day MACE and may want to reconsider routine early objective testing recommendations for those patients meeting very low hs-cTn thresholds and with low-risk clinical presentations.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca and at https://doi.org/10.1016/j.cjco.2019.08.002.