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 threshold 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 Australia, 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 could 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.

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.

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
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, 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% 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.

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 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 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.
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 Alberta Provincial Project for Outcome Assessment in Coronary Heart 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. 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. 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...
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. 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 755 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 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 997 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.

### 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%)   |

### 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.
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 647 (5.4%) | 30-d MACE 157 790 0 127 99.8 (98.0, 100) 100 (99.0, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| Index AMI 97 777 0 127 98.0 (98.0, 99.1) 99.0 (98.1, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| 30-d AMI 98 962 1 126 99.1 (98.1, 100) 99.1 (98.0, 99.1) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| 30-d revascularization 69 903 0 126 99.0 (98.0, 99.1) 99.0 (98.0, 99.0) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| 30-d cardiac death 1 975 0 126 98.9 (98.1, 99.6) 99.6 (99.0, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| <5 ng/L 906 (7.2%) | 30-d MACE 138 721 0 126 99.9 (99.0, 100) 100 (99.0, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| Index AMI 96 750 1 126 98.9 (98.0, 99.1) 99.0 (98.0, 99.0) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| 30-d AMI 97 656 0 126 99.0 (98.0, 99.1) 99.0 (98.0, 99.0) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| 30-d revascularization 68 687 4 126 99.5 (98.7, 99.8) 99.0 (98.1, 99.1) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| 30-d cardiac death 1 975 0 126 98.9 (98.1, 99.6) 99.6 (99.0, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| <6 ng/L 507 (41.4%) | 30-d MACE 97 292 0 126 99.9 (99.0, 100) 100 (99.0, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| Index AMI 96 292 0 126 99.9 (99.0, 100) 100 (99.0, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| 30-d AMI 97 289 0 126 99.9 (99.0, 100) 100 (99.0, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| 30-d revascularization 67 289 5 126 99.9 (99.0, 100) 100 (99.0, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| 30-d cardiac death 0 292 0 126 99.9 (99.0, 100) 100 (99.0, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |

FN, false-negative; TP, true-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.

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 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) | 0 (0-N) | 0 (0-NA) |
| Index AMI 97 879 0 191 100 (96.3, 100) 100 (98.1, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| 30-d AMI 98 878 0 191 100 (96.3, 100) 100 (98.1, 100) 0 (0-NA) | 0 (0-N) | 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) | 0 (0-NA) | 0 (0-NA) |
| 30-d cardiac death 1 975 0 191 98.1 (98.1, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |
| <5 ng/L 507 (43.4%) | 30-d MACE 115 545 10 497 92.0 (85.8, 96.1) 98.0 (94.9, 99.1) 0.17 (0.09, 0.31) | 0 (0-N) | 0 (0-NA) |
| Index AMI 95 565 2 505 97.9 (92.8, 99.9) 99.6 (98.6, 100) 0.04 (0.01, 0.17) | 0 (0-N) | 0 (0-NA) |
| 30-d AMI 96 564 2 505 98.0 (92.8, 99.8) 99.6 (98.6, 100) 0.04 (0.01, 0.17) | 0 (0-N) | 0 (0-NA) |
| 30-d revascularization 62 598 9 498 87.3 (77.6, 93.2%) 98.2 (96.7, 99.9) 0.28 (0.15, 0.52) | 0 (0-N) | 0 (0-NA) |
| 30-d cardiac death 1 659 0 507 100 (98.1, 100) 100 (99.0, 100) 0 (0-NA) | 0 (0-N) | 0 (0-NA) |

AMIconfidence 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.32 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 nonspecific 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 nonspecific 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.

Acknowledgements

The authors acknowledge the assistance of our research team, including Heidi Boyda, Katrina Koger, and Tiffany Junghans, in the completion of this study.

Funding Sources

This research was funded by an investigator-initiated, unrestricted research grant from Roche Diagnostics Canada. None of the study investigators received any direct or indirect compensation for the conduct of this study.

Disclosures

The authors have no conflicts of interest to disclose.
References

1. Apple FS. A new season for cardiac troponin assays: it’s time to keep a scorecard. Clin Chem 2009;55:1303-6.

2. Roffi M, Patrono C, Collet J-P, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315.

3. Body R, Carley S, McDowell G, et al. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. J Am Coll Cardiol 2011;58:1332-9.

4. Aldous SJ, Flookowski CM, Crozier IG, et al. Comparison of high sensitivity and contemporary troponin assays for the early detection of acute myocardial infarction in the emergency department. Ann Clin Biochem 2011;48( pt 3):241-8.

5. Aldous SJ, Richards M, Cullen L, Troughton R, Than M. Diagnostic and prognostic utility of early measurement with high-sensitivity troponin T assay in patients presenting with chest pain. CMAJ 2012;184:E260-8.

6. Than M, Cullen L, Aldous S, et al. 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. J Am Coll Cardiol 2012;59:2091-8.

7. Rubini Giménez M, Hoeller R, Reichlin T, et al. Rapid rule out of acute myocardial infarction using undetectable levels of high-sensitivity cardiac troponin. Int J Cardiol 2013;168:3896-901.

8. Meune C, Balmelli C, Vogler E, et al. Consideration of high-sensitivity troponin values below the 99th percentile at presentation: does it improve diagnostic accuracy? Int J Cardiol 2013;168:3752-7.

9. Hammerer-Lercher A, Ploner T, Neururer S, et al. High-sensitivity cardiac troponin T compared with standard troponin T testing on emergency department admission: how much does it add in everyday clinical practice? J Am Heart Assoc 2013;2:e000204.

10. Bandstein N, Ljung R, Johansson M, Holzmann MJ. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. J Am Coll Cardiol 2014;63:2569-78.

11. Body R, Burrows G, Carley S, et al. High-sensitivity cardiac troponin t concentrations below the limit of detection to exclude acute myocardial infarction: a prospective evaluation. Clin Chem 2015;61:983-9.

12. Shah ASV, Anand A, Sandoval Y, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet Lond Engl 2015;386:2481-8.

13. Thelin J, Melander O, Öhlin B. Early rule-out of acute coronary syndrome using undetectable levels of high sensitivity troponin T. Eur Heart J Acute Cardiovasc Care 2015;4:403-9.

14. Carlton E, Greenslade J, Cullen L, et al. Evaluation of high-sensitivity cardiac troponin I levels in patients with suspected acute coronary syndrome. JAMA Cardiol 2016;1:405-12.

15. Parsonage WA, Mueller C, Greenslade JH, et al. Validation of NICE diagnostic guidance for rule out of myocardial infarction using high-sensitivity troponin tests. Heart Br Card Soc 2016;102:1279-86.

16. Body R, Mueller C, Giannitsis E, et al. The use of very low concentrations of high-sensitivity troponin T to rule out acute myocardial infarction using a single blood test. Acad Emerg Med Off J Soc Acad Emerg Med 2016;23:1004-13.

17. Chenevié-Gobeaux C, Meune C, Lefèvre G, et al. A single value of high-sensitive troponin T below the limit of detection is not enough for ruling out non ST elevation myocardial infarction in the emergency department. Clin Biochem 2016;49:1113-7.

18. Vafaie M, Slagman A, Möckel M, et al. Prognostic value of undetectable hs troponin T in suspected acute coronary syndrome. Am J Med 2016;129:274-82.e2.

19. Sandoval Y, Smith SW, Love SA, et al. Single high-sensitivity cardiac troponin I to rule out acute myocardial infarction. Am J Med March 2017;130:1076-1078.e1.

20. McRae AD, Innes G, Graham M, et al. Undetectable concentrations of an FDA-approved high-sensitivity cardiac Troponin T assay to rule out acute myocardial infarction at emergency department arrival. Acad Emerg Med 2017;24:1267-77.

21. Zhelev Z, Hyde C, Youngman E, et al. Diagnostic accuracy of single baseline measurement of Elecsys Troponin T high-sensitive assay for diagnosis of acute myocardial infarction in emergency department: systematic review and meta-analysis. BMJ 2015;350:h15.

22. Pickering JW, Than MP, Cullen L, et al. Rapid rule-out of acute myocardial infarction with a single high-sensitivity cardiac troponin T measurement below the limit of detection: a collaborative meta-analysis. Ann Intern Med 2017;166:715-24.

23. Than M, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. Int J Cardiol 2013;166:752-4.

24. Kline JA, Johnson CL, Pollack CV, et al. Pretest probability assessment derived from attribute matching. BMC Med Inform Decis Mak 2005;5:26.

25. Graffstein E, Bullard MJ, Warren D, Unger B; CTAS National Working Group. Revision of the Canadian Emergency Department Information System (CEDIS) Presenting Complaint List version 1.1. CJEM 2008;10:151-73.

26. Ghalia WA, Knudston ML. Overview of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease. On behalf of the APPROACH investigators. Can J Cardiol 2000;16:1225-30.

27. Thyesen K, Alpert JS, Jaffé AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581-98.

28. Hicks KA, Tcheng JE, Bodurka J, et al. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). Circulation 2015;132:302-61.

29. Andruchové J, Kvasak P, McRae AD. Contemporary emergency department management of patients with chest pain: a concise review and guide for the high-sensitivity troponin era. Can J Cardiol 2018;34:98-108.

30. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e139-228.
31. Natsui S, Sun BC, Shen E, et al. Evaluation of outpatient cardiac stress testing after emergency department encounters for suspected acute coronary syndrome. Ann Emerg Med 2019;74:216-23.

32. Khare RK, Powell ES, Venkatesh AK, Courtney DM. Diagnostic uncertainty and costs associated with current emergency department evaluation of low risk chest pain. Crit Pathw Cardiol 2008;7:191-6.

33. Twerenbold R, Jaeger C, Rubini Gimenez M, et al. Impact of high-sensitivity cardiac troponin on use of coronary angiography, cardiac stress testing, and time to discharge in suspected acute myocardial infarction. Eur Heart J 2016;37:3324-32.

**Supplementary Material**

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