CJEM *Debate Series*

CJEM Debate Series: #TropandGo – Negative high sensitivity troponin testing is safe as a final test for most emergency department patients with chest pain

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INTRODUCTION

Paul Atkinson (@eccucourse)

This series of editorials provides *CJEM* readers with an opportunity to hear differing perspectives on topics pertinent to the practice of emergency medicine. The debaters have been allocated opposing arguments on topics where there is some controversy or perhaps scientific equipoise.

We continue with the topic of the safe yet rapid disposition of emergency department (ED) patients with chest pain, a considerable source of debate and discussion among researchers and clinicians. We have recently seen a transformative change in the way that emergency physicians assess chest pain patients, with the advent of rapid cardiac marker testing, with increasing sensitivity. These tests have evolved alongside a growing number of clinical risk scores. So, have we reached a point where the readily available tests and scores in the ED provide "definitive" testing for most patients with chest pain, allowing final safe discharge? Or is there still a role and need for further "objective" testing and follow up with cardiology consultation? Does "Trop and go" provide a safe approach to those who have other negative tests in the ED, or might we be missing critical cardiac disease in this patient cohort?

Andrew McRae and James Andruchow from the University of Calgary propose that most patients can safely be discharged from the ED screening without further objective testing based upon low concentrations of high sensitivity cardiac troponin alongside normal electrocardiogram and clinical assessment findings, with Frank Scheuermeyer and Jim Christenson from the University of British Columbia responding that many patients have greater nuance and that further testing may be required in certain patients to avoid undesirable outcomes.

Readers can follow the debate on Twitter and vote for either perspective, by going to @CJEMonline or by searching #CJEMdebate.

FOR:

Andrew D. McRae (@Andrew_McRae_EM) and James E. Andruchow

"Most ED chest pain patients with non-ischemic ECGs and low-risk high-sensitivity troponin results do not require additional objective cardiac testing."

Chest pain is one of the most common reasons for visiting EDs across the developed world. Most patients have non-ischemic electrocardiogram (ECG) findings and normal cardiac troponin concentrations and, in Canadian EDs, are subsequently discharged home *without* additional investigations. The risk of short-term major

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adverse cardiac events (MACE) among patients with low-risk ECG and normal *conventional* troponin concentrations has been quoted as 2%–5%,[1] with the risk of missed myocardial infarction (MI) being only 0.2%.[2] Validated high-sensitivity troponin diagnostic algorithms have an even lower risk of missed acute coronary syndrome (ACS) than earlier-generation troponin assays.[3] In spite of the exceedingly low risk of adverse events in these patients, and even after clinical risk stratification with a tool such as the HEART score, 40%–70% of patients with chest pain may undergo additional objective testing such as exercise stress testing, myocardial perfusion imaging, or coronary CT angiography (CCTA) after an MI has been ruled out.[3] This leads to substantial unnecessary resource utilization, false-positive additional testing, and iatrogenic harms for low-risk patients.

Proponents of early objective testing (particularly CCTA) recommend objective testing for nearly all patients who have had MI ruled out in the ED. Arguments in favor of objective testing often quote the very high negative predictive value (NPV) of CCTA for MACE and clinically significant coronary disease, and compliance with American Heart Association recommendations to screen for coronary disease after ruling out MI.[4]

We disagree with this advice for several reasons. Firstly, guidelines recommending objective testing of low-risk patients were developed long before the availability of high-sensitivity cardiac troponin (hs-cTn) and do not reflect the improved diagnostic performance of these assays. Patients who have had MI ruled out with hs-cTn have a substantially lower risk of MACE than those patients evaluated using conventional troponin assays, and therefore early objective testing for patients should have a much more limited role in the high-sensitivity troponin era. Secondly, there is ample evidence that a liberal testing strategy does more harm than good. Positive stress test findings in low-risk patients are most frequently false-positives, and recent evidence suggests that CCTA use in low-risk patients increases rates of angiography and revascularization (and their attendant complications) without improving patient-centred outcomes such as downstream MI risk.[5] Thirdly, the high NPV of an objective testing strategy is largely a function of the inherent low-risk of the population being tested, rather than the performance of the test itself. Finally, the available objective testing modalities, including exercise stress testing, myocardial perfusion imaging, and CCTA, have worse predictive performance for MACE risk than hs-cTn testing. Using a diagnostic test with worse test characteristics to further evaluate patients with low-risk hs-cTn findings simply makes no sense.

Surveys of Canadian emergency physicians suggest that the acceptable risk of missed ACS is 1%–2%.[6] For patients with an ACS risk of less than 2%, the harms associated with objective testing likely outweigh the benefits.[7] We believe that patients with a 2% or lower risk of 30-day MACE are unlikely to benefit from additional testing. ED chest pain patients who have low-risk ECG and hs-cTn results generally have a short-term MACE risk below that threshold.

A large meta-analysis of recent literature has shown that the combination of a non-ischemic ECG and an undetectable hs-cTn concentration at ED arrival is over 98% sensitive for 30-day MACE.[8] Put another way, of all patents with MACE, less than 2% of patients with be missed using a single undetectable troponin strategy. These patients (approximately one-third of all ED chest pain patients) simply do not need additional objective testing. Similarly, a 1-hour serial testing algorithm with high-sensitivity troponin has a sensitivity for 30-day MACE of over 98% and was applicable to 43% of patients.[9] Based on these estimates, it appears to be both feasible and safe to use an ECG and biomarker-only strategy to identify patients who need not be referred for additional cardiac testing after an ED evaluation for chest pain.

So how should ED physicians investigate suspected ACS in the high-sensitivity troponin era?

We suggest a stepwise approach to evaluating the patient with suspected ACS, based on the sequential performance of diagnostic tests that are relevant to time-sensitive clinical and disposition decisions. The first step is ECG examination to recognize patients with ST-elevation or other signs of myocardial ischemia that, in the presence of concordant symptoms, identifies patients requiring immediate treatment. For patients with non-ischemic ECGs, the next step is troponin testing to assess for myocardial injury. In the hs-cTn era, this entails the use of a validated diagnostic algorithm. These algorithms can reliably rule-in or rule-out MI for more than two-thirds of patients in as little as 1 to 2 hours. Patients with myocardial injury ruled out that using a validated hs-cTn algorithm

can generally be discharged without the need for additional investigations.[10] The remaining minority of patients who have non-diagnostic ECG and hs-cTn findings should undergo additional troponin testing to rule out MI, followed by clinical risk stratification using a validated risk prediction tool to guide disposition decisions.[10]

While it has become increasingly commonplace to use clinical risk prediction tools such as the HEART score to guide decision-making around which patients refer to for additional testing after MI has been ruled out, it is important to note that these tools were developed in the *conventional troponin era* to identify patients with ACS on the index visit, not to predict risk of MACE in patients with normal ECG and troponin results. The derivation studies included undifferentiated chest pain patients with high-risk ECG and troponin findings. The outcome of interest in these studies – typically 30-day or 6-week MACE – includes MI diagnosed on the index visits. Clinical risk scores cannot provide additional prognostic value to patients with normal ECGs and low-risk hs-cTn results. These patients have a much lower pretest probability than the patients in which the various risk scores were developed. Perhaps counterintuitively, if a clinical risk score is applied to a patient with normal ECG and hs-cTn findings, it may actually overestimate short-term MACE risk and commit patients to unnecessary and potentially harmful additional testing.

We are not advocating that clinicians forgo clinical judgment in favor of a biomarker-only strategy for every patient. Rapid diagnostic algorithms using hs-cTn at best allow us to exclude the need for additional testing in about two-thirds of patients (which is still better than referring 40%–70% of patients for objective testing). Patients with abnormal ECGs, those whose hs-cTn concentrations do not meet the rule-in or rule-out cutoffs of validated rule-out algorithm, or those with a high-risk clinical presentation such as classic crescendo angina clearly merit clinical risk stratification and/or additional testing.

Notwithstanding the patient with a high-risk clinical presentation, the combination of low-risk ECG and hs-cTn findings can reliably identify a patient population at low risk of short-term MACE who do not need additional testing. Clinical risk scores such as HEART ought only to be applied to patients with non-diagnostic hs-cTn and ECG findings, and objective testing should be reserved for those select few patients who cannot be classified as low risk after ECG, hs-cTn testing, and/or clinical risk stratification.

AGAINST:

Frank Scheuermeyer and Jim Christenson

"A negative troponin does not rule out serious coronary disease."

Acute chest pain is responsible for over 8 million visits to American EDs annually. Historically, 2%–5% of patients with chest pain who had an ACS within 30 days were discharged from the ED with an incorrect minimizing diagnosis and no follow-up,[1] and emergency physician tolerance for "missed MI" has been estimated at 2%.[6] To reduce the chance of such missed events, the American Heart Association/American College of Cardiology guidelines have long endorsed prolonged observation, serial cardiac investigations, likely admission, and probable follow-up investigations such as echocardiography, exercise stress testing, nuclear medicine scanning, or CCTA.[11] These tests are often performed in a population with a low pretest probability of disease, and false positives may outweigh true positives.

However, the aforementioned studies were conducted 2 decades ago and new techniques have ensured that the "miss" rate of MI (acute) is now less than 1%;[12] moreover, it seems likely that acute myocardial infarction (AMI) can be ruled in[13] or ruled out[8,9] with a single high-sensitivity troponin test (hs-cTn). Given that, in North American settings, less than 10% of ED chest pain patients are diagnosed with ACS within 30 days, and that EDs are increasingly crowded, it may be tempting to accept a 1% "miss" rate and quickly discharge chest pain patients who have a non-ischemic initial ECG and a negative hs-cTn.

Additionally, while a single ECG and negative hs-cTn may rule out AMI, some patients may benefit from additional observation – for example, to capture additional pain episodes – or sequential ECGs or biomarkers. Patients with more subtle ACS presentations, such as unstable angina, may often only be diagnosed with a careful history and physical examination, or minor yet dynamic ECG changes, and these elements in will be lost in some patients if the chest pain evaluation is condensed to a seemingly normal ECG and single negative hs-cTn.

While these chest pain patients do not appear to have an MI or die within 30 days, it is challenging to endorse that all patients without abnormalities during a single episode of objective testing can be discharged directly to primary care follow-up of variable timing and quality. Unfortunately, the goal of scoring systems such as

HEART[14] is to provide an estimate of the risk of ACS or MACE, and, although this estimate may be accurate on a population level, when personalized care is considered, there are likely many patients who are at zero risk and some who are at elevated risk. For example, both a 35-year-old smoker and a 64-year-old with severe chronic kidney disease could have similarly low HEART scores, yet one would expect the latter to have a far higher MACE risk. Although such scores are popular, they do not necessarily provide emergency physicians with evidence-based advice for post-discharge care for the individual patient.

Indiscriminate discharge of chest pain patients with apparently low-risk stories and negative investigations may not be wholly safe. In 1,116 consecutive chest pain patients at a single Canadian site, 17% of patients were admitted, whereas 23% were discharged with outpatient provocative cardiac testing. Of the 120 patients (10.8%) with ACS, one-fifth was diagnosed only when they had a high-risk outpatient test.[15] While it is important to realize that this protocol did not employ hs-cTn, it is apparent that patients may derive benefit from additional testing; unfortunately, there is currently no widely accepted cohort of patients who may safely forego testing.

Two prospective analyses may furnish physicians with further evidence. The no objective testing rule, which have been developed in 2,396 Australian and New Zealand chest pain patients with a 5.3% ACS rate, demonstrated that 31% of patients could safely be discharged home with no further testing, although this requires validation.[16] The Vancouver chest pain rule enrolled 1,669 patients at a single urban site with a combined 17.0% 30-day ACS rate, and developed and validated an algorithm that enabled safe early discharge of 21% of patients without additional cardiac-specific testing.[17] While there is a positive association between positive testing, coronary artery disease, and ACS/MACE, patients who did not have a 30-day ACS outcome may still have benefitted from testing. Conversely, those who had a 30-day ACS outcome may not have benefitted from further testing if treatments were not altered or offered. However, in the absence of any other evidence, these studies assist physicians by confirming that within a heterogeneous pool of chest pain patients, they can be reasonably confident that selective outpatient testing is acceptable.

In addition, there is a cohort of patients with potential ACS who do not present with classic chest pain symptoms (they may complain of nausea, weakness, shortness of breath, or back or abdominal pain), and such patients have been little investigated by studies that generally limit entry criteria to acute chest pain. As such, even though emergency physicians may manage these patients as "rule out ACS" or chest pain equivalents, there is little evidence on which to base this practice. In particular, female patients, the elderly, and diabetic patients may present with alternative complaints, and may therefore be systematically underrepresented in current research. In these patients, although additional provocative testing may not necessarily diagnose an ACS, discharge after a single troponin may not be warranted.

Finally, most research has focused on the outcomes of ACS and MACE. However, this may not even cover all relevant cardiovascular outcomes. Even the most rigorous studies have not ascertained the potentially important 30-day outcome of new acute heart failure,[18] which most patients and physicians would likely consider relevant. It is important to note that physicians developed these traditional outcomes[19] and therefore reflect the concerns of physicians and the healthcare system, including costs. However, these outcomes do not reflect the patient's quality of life, including physical, emotional, and social states. A 60-year-old female with multiple cardiac risk factors, including a strong family history, may not be reassured by a 1-hour stay and a negative troponin, although it may be the medically "correct" approach. Conversely, an 88-year-old male referred from an extended care facility and with advanced dementia, with a chronically poor ejection fraction after remote bypass surgery, might medically benefit from additional testing resulting in another ACS diagnosis; however, this may not change overall management or ultimate outcome. Greater involvement of patients in decision-making has led to better outcomes including satisfaction,[20] and we encourage physicians to discuss goals and expectations with patients and caregivers before embarking on any particular diagnostic strategy.

We propose the following strategy to best assist clinicians in expediting safe, rapid discharge for chest pain patients from the ED while matching patient need to appropriate resources, including follow-up investigations:

Unstable patients, or those with an ischemic ECG, clear history of accelerating angina, or positive hs-cTn will warrant urgent referral. Those at clinically very low risk (younger with no cardiac risk factors) will benefit from rapid discharge and minimal specialty follow-up

after a single normal ECG and negative hs-cTn. However, the cohort of patients who do not fit into either category, including those with atypical or changing pain, an uncertain history including communication barriers, baseline ECG abnormalities, or mild hs-cTn elevations, may benefit from additional testing. In this group, patient goals and expectations, along with anticipated risks and benefits of testing, should be carefully clarified in an individualized manner.

Future research should define both cohorts of patients, as well as the timing and type of these investigations.

Keywords: Emergency medicine, coronary artery disease, acute coronary syndromes, myocardial infarction

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