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EDITORIAL COMMENT

# Time for a New Strategy for High-Sensitivity Troponin in the Emergency Department*

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Over the course of >2 decades, investigations have established cardiac troponin (cTn) as the core marker for diagnosing myocardial infarction (MI) (1,2). Successive generations of more sensitive assays have enabled the reliable detection of myocardial injury at increasingly lower concentrations. The arrival of high-sensitivity cTn (hs-cTn) in the clinical setting has provided great benefit, particularly for its negative predictive value in terms of more rapidly and confidently excluding acute myocardial injury. Coupled with dynamic changes over time, clinicians have greater ability to identify acute conditions earlier (3-6). The use of hs-cTn, however, has also posed significant challenges for clinicians because elevated concentrations are frequently detected in diverse clinical settings and have a variety of causes, including supply-demand mismatch, structural heart disease, inflammation, and others. As a result, increasing numbers of patients are found to have stable, low-level elevations or measurable values between the limit of detection and the upper reference limit. How to interpret these findings has been a challenge for clinicians, and it is in this setting that the analysis by Roos et al. (7) in this issue of the *Journal* provides important information.

Beyond its diagnostic utility, cTn has repeatedly been shown to be a potent prognostic marker, particularly of cardiovascular death and heart failure. Even low-level elevations in the setting of acute coronary syndrome (ACS) are associated with important increases in future cardiovascular risk (8,9). Several studies have extended the prognostic importance of hs-cTn to levels below traditional cutpoints used for the diagnosis of MI and to stable populations, including those that are apparently healthy (10-14). The broader clinical utility for hs-cTn as a prognostic marker, however, has not been routinely adopted in practice as clinicians struggle to understand how to respond in terms of additional testing and changes in treatment. In addition, the dramatically increasing frequency of stable, low-level cTn elevations detected with high-sensitivity assays in patients without ACS may lead clinicians to disregard results and be falsely reassured.

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It is within this context that the paper by Roos et al. (7) evaluating the prognostic importance of hs-cTn in >22,000 patients presenting to a hospital in Sweden with chest pain but without an acute illness is an important reminder to clinicians that cTn is not only a diagnostic marker. Although all patients were clinically evaluated, found to have no acute illness, and sent home presumably with reassurance, more than one-third had measurable levels greater than the 5 ng/l limit of detection. This group had a clear and graded increased risk of mortality ranging from 2- to 10-fold. Patients with an hs-cTn concentration between 10 and 14 ng/l (below the 99th percentile cutpoint) had an order of magnitude increase in the annual rate of mortality relative to patients with hs-cTn concentrations <5 ng/l (0.5% vs. 5.1%). Additionally, in the 7.9% of the population with elevated values above the 14 ng/l 99th percentile cutpoint, annual rates of mortality ranged from 12% to 22%.

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This pattern was consistent in sensitivity analyses that restricted the population to exclude dynamic changes (2 sensitivity analyses for all-cause mortality were performed, 1 where only patients with a delta-troponin [delta-Tn] concentration of 0 to 2 ng/l were included, and a second where only patients with a change in delta-Tn of <20% were included). Rates of cardiovascular death, heart failure, and ischemic outcomes all showed similar patterns. Therefore, the lack of an identified acute illness did not equate to a "low-risk" intermediate- to long-term prognosis. The extension of prognostic ability to levels traditionally considered "negative" below the 99th percentile as seen in prior studies underscores the evolution of cTn as a powerful continuous marker of subclinical illness rather than solely as a dichotomous test for ACS.

The key question for clinicians, however, is how to respond to this information. Although cTn was a potent marker of cardiovascular death and heart failure, it was relatively modest at predicting ischemic heart disease. In addition, it was a potent marker of noncardiovascular death. The detailed causes of death show that cancer caused a significant proportion of deaths, particularly in those patients with measurable values below the 99th percentile. Therefore, is the elevated hs-cTn telling us about subclinical coronary disease, subclinical structural heart disease, or myocardial inflammation, or is it a broad marker of sicker patients? In spite of adjustment for baseline differences, the association between hs-cTn and noncardiovascular mortality must make us recognize the potential for unresolved confounding.

Other questions remain. The differentiation between a "type 2" MI caused by supply-demand mismatch and a stable cTn elevation depends on the clinician's evaluation of the context. Because this population was presenting with chest pain, some patients with cTn elevations >14 ng/l may have had type 2 MI, particularly if concentrations had plateaued before presentation. The consistency in sensitivity analyses excluding large deltas is reassuring in this regard. The absence of information about left ventricular hypertrophy or systolic dysfunction is another major limitation. Additionally, the prognostic ability of cTn in this setting accounting for other biomarkers such as of brain-natriuretic peptide and D-dimer would be of great interest. As a retrospective cohort analysis, the investigators were limited to those tests that the treating clinician believed were necessary, and therefore it is possible that diagnoses were missed. Indeed, 5 patients with elevated cTn concentrations died of aortic dissection, and given the number of patients with cancer, it is possible that pulmonary emboli could have caused chest pain and elevated hs-cTn concentrations.

These limitations, however, do not diminish the observation that hs-cTn is a potent prognostic marker. The data presented by Roos et al. (7) should remind clinicians not to be falsely reassured when ACS is "ruled out" by a lack of dynamic changes or a hs-cTn level that is measurable but below the 99th percentile threshold. Even in the presence of apparent clinical stability and no apparent acute condition, these patients remain at heightened intermediate- to long-term risk. We must begin to interpret hs-cTn in this context as an indicator of important subclinical disease that warrants additional evaluation.

How to proceed with an outpatient recently discharged after exclusion of acute illness but who has a stable elevation in cTn or a measurable level below the 99th percentile requires careful patient evaluation and thoughtful clinical consideration. Although there is no defined diagnostic algorithm in this setting, evaluation for underlying structural heart disease with echocardiography may be reasonable. In patients with cTn elevations, particularly patients with risk factors for coronary disease, testing for ischemia coupled with an assessment of left ventricular function may be warranted. In patients with abnormal echocardiography findings or concerning indicators for inflammatory or infiltrative disease, cardiac magnetic resonance imaging may reveal underlying pathology. The goal of testing would be to identify the "subclinical" disease indicated by the hs-cTn so that intensive management could be initiated and hopefully improve outcomes.

The study by Roos et al. (7) is therefore an important addition to the broad range of work that has consistently shown the prognostic importance of hs-cTn. It is time to extend our use of hs-cTn in the acute setting beyond just "ruling out" acute illness. For patients whose test results reveal no acute pathology, we must transition to considering hs-cTn as a potent continuous marker of subclinical pathology. In patients with measurable levels below the 99th percentile or stable low-level elevations, we should not be reassured, and careful evaluation for subclinical disease is warranted.

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## REFERENCES

**1.** Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.

**2.** Roffi M, Patrono C, Collet JP, 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.** Morrow DA, Bonaca MP. Real-world application of "delta" troponin: diagnostic and prognostic implications. J Am Coll Cardiol 2013;62:1239–41.

**4.** Morrow DA. Evidence-based algorithms using high-sensitivity cardiac troponin in the emergency department. JAMA Cardiol 2016;1:379–81.

**5.** Morrow DA. Clinician's guide to early rule-out strategies with high-sensitivity cardiac troponin. Circulation 2017;135:1612–6.

**6.** Twerenbold R, Boeddinghaus J, Nestelberger T, et al. Clinical use of high-sensitivity cardiac troponin in patients with suspected myocardial infarction. J Am Coll Cardiol 2017;70:996–1012.

**7.** Roos A, Bandstein N, Lundbäck M, Hammarsten O, Ljung R, Holzmann MJ. Stable high-sensitivity cardiac troponin T levels and outcomes in patients with chest pain. J Am Coll Cardiol 2017;70:2226–36.

**8.** Bohula May EA, Bonaca MP, Jarolim P, et al. Prognostic performance of a high-sensitivity cardiac troponin I assay in patients with non-ST-elevation acute coronary syndrome. Clin Chem 2014;60:158–64.

**9.** Bonaca MP, O'Malley RG, Murphy SA, et al. Prognostic performance of a high-sensitivity assay for cardiac troponin I after non-ST elevation acute coronary syndrome: analysis from MERLIN-TIMI 36. Eur Heart J Acute Cardiovasc Care 2015;4:431–40.

**10.** de Lemos JA, Drazner MH, Omland T, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010;304:2503–12.

**11.** deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304:2494–502.

**12.** Omland T, Pfeffer MA, Solomon SD, et al. Prognostic value of cardiac troponin I measured with a highly sensitive assay in patients with stable coronary artery disease. J Am Coll Cardiol 2013;61:1240–9.

**13.** Everett BM, Brooks MM, Bhatt DL. Troponin in stable ischemic heart disease and diabetes. N Engl J Med 2015;373:1978–9.

**14.** Eisen A, Bonaca MP, Jarolim P, et al. High-sensitivity troponin I in stable patients with atherosclerotic disease in the TRA 2°P-TIMI 50 trial. Clin Chem 2017;63:307–15.

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