Management of patients with chest pain presenting to the emergency department: in need for the implementation of the 1 h rapid rule-out algorithm using high-sensitivity troponin I assays in clinical practice

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Submitted Dec 04, 2015. Accepted for publication Dec 09, 2015.
doi: 10.3978/j.issn.2305-5839.2015.12.31
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.12.31

Introduction

Each year, about 6 million people with acute chest pain present to the emergency department (ED) in the US for diagnostic evaluation. Comparable data are reported from Europe: during the last 20-year period, the number of hospital admissions due to chest pain has tripled in the United Kingdom. In current guidelines, the presence or absence of acute myocardial infarction (MI) is diagnosed by prudent balancing elements of patient history, 12-lead electrocardiogram (ECG) recordings, and dynamic changes of cardiac troponin (cTn) levels above recommended cutoff levels within a 3 h observational period (1). Of note, the majority of these patients does not have MI, but need time consuming evaluation. Due to diagnostic uncertainty and the lack to rule out MI rapidly, some of those patients are being hospitalized. To reduce the length of stay in the ED and the hospital, new diagnostic pathways are welcome to accelerate the diagnostic evaluation of affected patients with chest pain in the ED (2). Thus, the report of the High-STEACS trial (High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study) recently published in *The Lancet* is welcome and of major importance (3).

High-sensitivity troponin I assay may rule out mi in large number of chest pain patients

In the observational "High-STEACS study", consecutive patients with suspected acute coronary syndrome (ACS) presented to the EDs of four hospitals in Scotland and the United States. Patients were excluded if they had been admitted previously during the study period, were pregnant, or did not live in participating centers. The study was conducted by Anoop S.V. Shah, MD, *et al*., University of Edinburgh, Scotland, between June 2013 and January 2014. Using a sample of 4,870 patients, they derived a threshold at which they could rule out MI even at the time of presentation to the ED. This diagnostic pathway of patient presenting with chest pain was validated in two validation cohorts. The inclusion and exclusion criteria for the validation cohort were the same as for the derivation cohort.

Plasma cardiac troponin I (cTnI) levels were measured at presentation using a commercially available sensitive assay (ARCHITECT$_{STAT}$; Abbott Laboratories). Clinical decision making was done using currently recommended time dependent changes of cTnI levels. In parallel, blood samples were drawn and cTnI levels were measured using a high-sensitivity assay (ARCHITECT$_{STAT}$ high-sensitive troponin I assay; Abbott Laboratories) for the study. The results of high-sensitivity cTnI (hs-cTnI) measurements were blinded and not available to the decision making physician.

In the first part of the study, investigators studied 4,870 patients, 19% of whom had a cardiac event within 30 days. Overall, 16% of patients had an index MI, defined as a type

1 MI arising during the first clinical episode, and 1% and 2% of patients returned to the hospital with MI and died of cardiac causes, respectively, within 30 days. Troponin concentrations using the high-sensitivity assay were below 5 ng/L in 61% of derivation cohort patients who did not have MI at presentation. Hs-cTnI levels below 5 ng/L had a high negative predictive value of 99.6% for the composite of index MI or type 1 MI or cardiac death at 30 days (primary endpoint), exceeding the goal of at least 99.5% that was prespecified by the trial's steering committee. At 1 year of follow-up, patients with troponin levels below 5 ng/L had a lower risk of MI or cardiac death compared with patients with higher levels (0.6% *vs.* 3.3%; adjusted HR =0.41; 95% CI, 0.21-0.80).

In the second phase of the study, the proposed rapid rule-out algorithm was validated in two validation cohorts using the 5 ng/L cutoff level. About 56% of patients had levels below this threshold. The negative predictive value to rule-out MI using first blood drawings was 99.4%. The 5 ng/L threshold's negative predictive value was consistent across subgroups defined by age, sex, risk factors, prior cardiovascular disease, the Global Registry of Acute Coronary Events (GRACE) score, and presence of myocardial ischemia on presenting ECG. Across the derivation and validation cohorts, 12 patients (0.4%) with troponin concentrations less than 5 ng/L at presentation met the primary endpoint at 30 days—10 had an index MI, including 5 who had clear evidence of myocardial ischemia at presentation. The other 2 were in cardiac arrest when they arrived and later died. Thus, 1 in 200 patients still had an index or 30-day event and others had evidence of myocardial ischemia.

The conclusion of the investigators was that patients with hs-cTnI concentrations of <5 ng/L at presentation had a very low risk of MI within a follow-up of 30 days. Thus, about 60% of patients presenting to the ED with suspected ACS display minimal risk of a cardiac event, if cardiac hs-cTnI levels were below 5 ng/L as measured by a high-sensitivity assay. These low-risk patients would be eligible for immediate discharge rather than hospitalization.

The challenge of clinical application

These findings are very important and highly promising as suggested by the accompanying comment of Cullen *et al.* (4). Of note, fewer than 42% (1,608 of 3,799) patients had serial troponin testing. This low number of patients with serial troponin testing could have led to missed events. In patients presenting very early, the second cTn level should be obtained at 3 h, due to the time dependency of troponin release. Therefore, the 54-min median time from hospital arrival to initial blood sampling could have beneficially influenced the negative predictive value in this study.

Secondly, patients presenting very early within 1 h from chest pain onset represent only a small proportion (5%) of all patients in the study. Because the use of a single troponin test did not meet the predefined negative predictive value of 99.5% in early presenters, the test may not be as sensitive in patients who present very early to the ED. The negative predictive value was slightly lower for patients tested for troponin within 2 h of chest pain onset compared with after longer intervals (97.6% *vs.* 99.8%) confirming the need for cautious diagnostic reasoning in early presenters.

Thirdly, the results of the high-sensitivity assay were not used for clinical decision making. Although the investigators determined the number of patients who could be safely discharged, whether clinicians can effectively implement this threshold in clinical practice and whether this will substantially improve rates of discharge is unknown. Especially, the diagnosis of ACS among older patients is a major challenge. Atypical complaints and inconclusive findings of ECG are reported in an older patient cohort (5-7). Therefore, this threshold should not be implemented in isolation and without regard to appropriate clinical assessment. The best diagnostic assessments so far are clinical prediction tools [e.g., Thrombolysis in Myocardial Infarction (TIMI) and HEART score] that incorporate elements of the history and physical examination along with the initial ECG and cTn results (8).

Last but not least, no data about later investigations and treatments exist from this study analysis. Implementation of this threshold is expected to reduce healthcare costs but these benefits might be lost if recurrent presentations or additional outpatient consultations increase.

Conclusions

Clinical evaluation of chest pain patients includes elements of patient history, 12-lead ECG recordings and dynamic changes of cTn measurements usually needing a 3 h follow-up evaluation. This study suggests a new diagnostic strategy using a single measurement using a specific hs-cTnI assay to rule-out MI even after sampling blood only during presentation. If hs-cTnI levels are below the suggested cutoff point, a MI can be excluded in about two-thirds of the patients with an acceptable false-negative rate. Those

patients could be safely discharged from the ED and display an excellent prognosis during short-term follow-up. Use of this approach is likely to have major benefits for both patients and healthcare providers. There is further need for clinical studies validating this new diagnostic approach before the one hour rapid rule-out algorithm may be implemented in clinical practice.

Acknowledgements

None.

Footnote

Provenance: This is a Guest Commentary commissioned by the Section Editor Zhide Hu, MD (Department of Laboratory Medicine, General Hospital of Ji'nan Military Region, Ji'nan, Shandong Province, China).
Conflicts of Interest: P Bahrmann and CC Sieber do not have to declare any potential conflicts of interest. T Bertsch performs reagent evaluation studies for Roche Diagnostics GmbH, Mannheim, Germany. M Christ received grant and speakers honoraria from Roche Diagnostics GmbH, Mannheim, Germany.

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Cite this article as: Bahrmann P, Bertsch T, Sieber CC, Christ M. Management of patients with chest pain presenting to the emergency department: in need for the implementation of the 1 h rapid rule-out algorithm using high-sensitivity troponin I assays in clinical practice. Ann Transl Med 2016;4(1):18. doi: 10.3978/j.issn.2305-5839.2015.12.31

