Editorial

TIMI score and a single baseline troponin for safe discharge of chest pain patients

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Chest pain is a common complaint among patients at the emergency department (ED) and accounts for about 5–10% of all ED visits (1). The list of differential diagnoses is long, but it is normally the perceived likelihood of acute coronary syndrome (ACS), i.e., acute myocardial infarction (AMI) or unstable angina (UA) that drives management. The fear of missing cases of ACS leads to lengthy ED assessments and high admission rates for serial troponin samples and non-invasive testing or coronary angiography (2,3). In the end however, less than 25% of all admitted chest pain patients prove to have ACS (2,4). There is thereby room for significant improvement in our assessment of chest pain patients. The now commonly used high-sensitivity cardiac troponins (hs-cTn), have an improved analytical and diagnostic sensitivity compared to previous generations of cTn, and enable faster rule-out of AMI (5). The use of a presentation hs-cTn below the limit of detection (LoD) of the assay in patients without signs of acute ischemia on their ECG has a very high negative predictive value (NPV) for AMI (6,7). This approach is therefore recommended (class 1) by the European Society of Cardiology guidelines (8).

The 2016 update of the National Institute for Health and Care Excellence (NICE) Chest Pain of Recent Onset guidelines however state that this approach should only be used in patients identified as low risk by a validated tool, such as the TIMI score (9). Although the TIMI score was originally developed as a tool for patients with confirmed ACS (10), a low score has also been shown to identify ED chest patients with a low pre-test probability of ACS (2).

Carlton *et al.* have now evaluated the performance of the NICE approach using both the Roche Elecsys hs-cTnT (LoD 5 ng/L) and Abbott ARCHITECT hs-cTnI (LoD 2 ng/L) in a pooled sample of six prospective observational studies (11). Carlton *et al.* analyzed the diagnostic accuracy of combining a low TIMI score with a hs-cTn < LoD in patients without signs of acute ischemia on their ECG for ruling out 30-day major adverse cardiac events (MACE), a composite outcome which includes AMI, death due to cardiac ischemia, unplanned revascularization and serious arrhythmias. They found that combinations with a TIMI score of 0 or ≤1 both had a NPV of ≥99.5% for both hs-cTnT and hs-cTnI. Since the sensitivity was <99% for the combinations with a TIMI score ≤1, the authors conclude that a TIMI score threshold of 0 should be used to identify low risk patients.

However, one could argue that most ED physicians would accept a NPV >99% (12) and that a combination with a TIMI score ≤1 would achieve this goal and also identify a larger proportion of patients for rule-out (about 30% versus about 20% with a TIMI score of 0). Interestingly, a TIMI score ≤1 combined with a higher hs-cTnT cut-off of 6 to 7 ng/L also performed well, which is in line with recent reports that a cut-off of <6 ng/L instead of <5 ng/L (LoD) is sufficient for rule-out (5). This is important, especially in the US where the FDA has only approved reporting of hs-cTnT results down to 6 ng/L.

Are the results valid?

The included cohorts are from several well performed prospective observational studies with sound methodology. The baseline characteristics and the overall MACE

prevalence (10% in hs-cTnT cohort, 12% in hs-cTnI cohort) were similar to those in other studies on ED chest pain patients (13,14), and the data were from centers in Australia, New Zealand and the UK, which increases generalizability. However, some limitations merit further attention. Firstly, there was a considerable number of patients excluded due to missing data (n=2,157 for hs-cTnT and n=784 for hs-cTnI). Secondly, the cohorts were all observational (like most studies in this field) meaning patients were not actually managed according to the tested strategy. However, the results confirm the findings in a previous publication (15) where a TIMI score of ≤1 in patients with a non-ischemic ECG and a hs-cTnT <5 ng/L also conferred a high NPV. It is reasonable also from a Bayesian perspective to expect this approach to perform well. Hs-cTnI < LoD or <5 ng/L, and hs-cTnT <5 ng/L combined with a non-ischemic ECG alone have all had a high NPV in unselected chest pain patients (7,16,17). In patients with an even lower pre-test probability, e.g., a low TIMI score, the strategy should therefore identify patients with an even lower likelihood of disease.

Caveats

The authors performed subgroup analyses which suggested that the NPV was >99% even in patients presenting less than 3 h from symptom onset. We would however caution against using single troponin rule-out strategies in early presenters as the NPV in other studies has consistently been lower among early presenters. In a study by Shah *et al.* the NPV was only 97.6% among patients with hs-cTnI sampling ≤2 h from symptom onset versus 99.8% in the remaining patients (16). Similarly, Body *et al.* reported that the hs-cTnT <5 ng/L strategy had a NPV of only 98.7% among very early presenters (<2 h), compared to 100% among other patients (≥2 h) (18), and Rubini Gimenez *et al.* found the NPV to be 96.4% (<3 h) versus 99.5% (≥3 h) (19). With current knowledge, we would therefore recommend additional hs-cTn testing after 2–3 h in patients with a 0 h hs-cTnT sampled ≤2 h from symptom onset due to the potential risk of false negative tests. It is also important to remember that the results of Carlton *et al.* are only valid for the hs-cTn assays evaluated, i.e., Roche Elecsys hs-cTnT and Abbott ARCHITECT hs-cTnI.

General remarks

Before implementing single hs-cTn < LoD rule-out strategies, the following need to be considered:

(I) The purpose of these strategies is to identify low risk patients, and the remaining patients are not necessarily high-risk. They simply cannot be ruled out with a single hs-cTn, and need further testing with e.g., an additional hs-cTn at 1 h (8,20). The approach is similar to that in patients with suspected venous thrombo-embolism (VTE); a low pre-test probability (Wells score in patients with possible VTE, and TIMI score and ECG in patients with possible ACS) make the likelihood so low that a single blood sample (D-dimer or hs-cTn) can safely rule out disease;

(II) In patients with a 0 h hs-cTnT ≤2 h from symptom onset, we recommend additional hs-cTn testing after 2–3 h as stated above;

(III) Patients are low risk if they have an hs-cTn < LoD, an ECG without signs of acute ischemia, and do not have a high-risk history. If a patient for example has a history described as a clear crescendo angina we would not recommend discharge, as the probability for ACS in these patients will be too high, even with a normal ECG and a hs-cTn < LoD. We thus support the NICE guidelines, and believe that hs-cTn should always be interpreted in the proper clinical context, like any test. We also find it unreasonable to believe that ED physicians will manage chest pain patients based solely on an hs-cTn and an ECG, without considering the patient history. However, we do not believe that the TIMI score must be used for risk stratification, as e.g., the clinical Gestalt has been shown to perform at least as well (6). The optimal approach for risk stratification, whether it is an unstructured clinical assessment (Gestalt) or a formal risk score such as TIMI, EDACS, or HEART, remains to be determined;

(IV) Even though a combination of hs-cTn < LoD and a non-ischemic ECG has a high NPV for AMI, these patients may still have UA (although uncommon) (6);

(V) The local ACS prevalence must be kept in mind, as the NPV of rule-out strategies will be lower in EDs with a higher prevalence than in the study settings, possibly making the strategies unsafe;

(VI) All studies evaluating the LoD strategies have been observational. How these strategies perform in routine care is unknown. If they are implemented, a clinical audit should be performed to ensure

patient safety;

(VII) The results of hs-cTn studies are assay dependent, and can only be applied to the hs-cTn assays studied.

In conclusion, there is abundant evidence that a hs-cTn < LoD together with a non-ischemic ECG identifies patients at low risk, and this approach is recommended to be combined with clinical risk stratification. The well-performed study by Carlton *et al.* (11) confirms this view and shows that when a low TIMI score is used in this combination, it identifies patients with a very low risk of 30-day MACE.

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Footnote

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