Troponin: more lessons to learn

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This editorial refers to ‘Risk stratification in patients with acute chest pain using three high-sensitivity cardiac troponin assays’1, by P. Haaf et al., on page 365

Cardiac troponin entered our diagnostic armamentarium 20 years ago and—unlike any other biomarker—is going through constant expansion in its application. Troponin started out as a marker of risk in ‘unstable angina’, then was used as gold standard for risk stratification and therapy guiding in acute coronary syndrome (ACS) patients, served further to redefine myocardial infarction, and has finally also become a risk factor in apparently healthy subjects.1–6

The recently introduced high-sensitivity cardiac troponin (hs-cTn) assays have not only expanded the potential of troponins, but have also resulted in a certain amount of confusion among unprepared users. After many years of scepticism, troponins were accepted as the gold standard for patients with chest pain by classifying them into troponin-positive and troponin-negative patients. The new generation of hs-cTn assays has improved the accuracy at the lower limit of detection and provided incremental diagnostic information especially in the early phase of myocardial infarction.7 Moreover, low levels of measurable troponins unrelated to ACS have been associated with an adverse long-term outcome. Several studies demonstrated that these low levels of cardiac troponin measurable only by hs-cTn assays are able to predict mortality in patients with ACS as well as in patients with presumed stable coronary artery disease.6,8 Furthermore, hs-cTn has the potential to play a role in care of patients undergoing non-cardiac surgery.9 The additional determination of hs-cTnT improves perioperative risk stratification despite established risk scores providing both diagnostic and prognostic information.

The daily clinical challenge in using the highly sensitive assays is to interpret the troponin concentrations, especially in patients with concomitant diseases influencing cardiac troponin concentrations independently from myocardial ischaemia (e.g., chronic kidney disease or stroke).10 The troponin test lost its ‘pregnancy test’ quality with a simple ‘positive—negative’ interpretation and thereby makes diagnosis finding more complex than before. This uncertainty probably has boosted the number of diagnoses of ACS and invasive diagnostic procedures in some locations. This is more than understandable, since different opinions exist on the change of hs-cTn levels compared with the baseline value before the diagnosis of acute myocardial infarction (AMI) can be made.11 What is a relevant change in concentrations compatible with acute myocardial necrosis and what is only biological variation for the specific biomarker and assay? Changes in serial measurements between 20% and 200% have been debated, and the discussion is ongoing.12 Furthermore, it has been proposed that absolute changes in cardiac troponin concentrations have a higher diagnostic accuracy for AMI compared with relative changes, and it might be helpful in distinguishing AMI from other causes of cardiac troponin elevation.13

Do we obtain any helpful directives from experts and guidelines for our daily practice? Foreseeing this dilemma, the 2011 European Society of Cardiology (ESC) Guidelines on non ST-elevation ACS provided a general algorithm on how to manage patients with hs-cTn values in the ‘grey zone’.14 This was and still is based on limited data. The ‘Study Group on Biomarkers in Cardiology’ suggested a rise of 50% from the baseline value at low concentrations. However, this group of experts could also not find a substitute for the missing data.5 The story is just too complex: different troponin assays with different epitope targets, different patient populations, different sampling protocols, different follow-up lengths, and much more. Therefore, any study that helps us to see better through the fog is welcome here.

Haaf et al have now presented the results of their study of three different hs-cTn assays (hs-cTnT, Roche Diagnostics; hs-cTnI, Beckman-Coulter; and hs-cTnI, Siemens) with respect to the outcome of patients with acute chest pain. The authors examined 1117 consecutive patients presenting with acute chest pain [341 patients with ACS (30.5%)] from the Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) study. Blood was collected directly on admission and serially thereafter at 1, 2, 3, and 6 h. Eighty-two patients (7.3%) died during the 2-year follow-up. The main finding of the study is that hs-cTnT predicts mortality during a 2-year follow-up more accurately than the hs-cTnI assays in patients with suspected AMI. Furthermore, this study suggests that a single measurement is sufficient and, therefore, challenges the paradigm that serial measurements of troponins are necessary for prognosis prediction in chest pain patients.

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These results of APACE remain in contrast to recent findings from a GUSTO IV cohort of 1335 patients with ACS (Table 1). In samples collected 48 h after the study commenced, the prognostic capacity of four different sensitive cardiac troponin assays (hs-cTnT; Roche Diagnostics, cTnI and hs-cTnI; Abbott Diagnostics, and Acc-cTnI; Beckman-Coulter) were compared. In total, 119 patients (8.9%) died during the 1-year follow-up. Looking at their receiver operating characteristic curve (ROC) analyses, there were only negligible differences between the assays.

Contrasting results have also been reported in patients (n = 3,623) with stable coronary artery disease and preserved systolic left ventricular function from the PEACE trial (Table 1). During a median follow-up period of 5.2 years, there were 203 (5.6%) cardiovascular deaths or first hospitalization for heart failure. Concentrations of hs-cTnI (Abbott Diagnostics) at or above the limit of detection of the assay were measured in 3567 patients (98.5%), but concentrations of hs-cTnI at or above the gender-specific 99th percentile were found in only 105 patients (2.9%). This study revealed that there was a strong and graded association between increasing quartiles of hs-cTnI concentrations and the risk for cardiovascular death or heart failure. hs-cTnI provided incremental prognostic information over conventional risk markers and other established cardiovascular biomarkers, including hs-cTnT. In contrast to the APACE results, only hs-cTnI, but not hs-cTnT, was significantly associated with the risk for AMI.

Is there a real difference between cardiac troponin T and cardiac troponin I in predicting long-term prognosis?

The question arises of whether there is a true clinically relevant difference between cTnT and cTnI. Given the biochemical and analytical differences, the two troponins display rather similar serum profiles during AMI. While minor biological differences between cTnT and cTnI are apparently not relevant for diagnosis and clinical management in the acute setting of ACS, the different features could potentially play a role for long-term risk stratification of patients with and without ACS and is disclosed by the use of high sensitivity assays.

This is a provocative theory, but appears premature in our opinion. Above all, the results of the current study appear too inconsistent to allow such conclusions. In the present study, hs-cTnT (Roche Diagnostics) outperformed hs-cTnI (Siemens and Beckman-Coulter) in terms of mortality prediction in unstable patients with suspected ACS, whereas GUSTO IV could not reveal relevant differences between hs-cTnT (Roche Diagnostics) and hs-cTnI (Abbott Diagnostics). In further contrast, hs-cTnT (Abbott Diagnostics) outperformed hs-cTnT (Roche Diagnostics) in terms of very long-term prediction of cardiovascular death and heart failure in stable patients. It appears unlikely that cTnT and cTnI perform differently in stable and unstable patients. Unfortunately, we do not know how hs-cTnI from Abbott Diagnostics performs in the APACE cohort. Furthermore, the number of patients and endpoints provided by the APACE registry are rather low, especially by dividing the patients with the endpoint into those with (n = 40) and without AMI (n = 42). Therefore, the result could be a chance finding.

Accordingly, the concept of differentiating between cTnT and cTnI is attractive, but it is far too early to favour one high sensitivity assay over the other. The findings need confirmation by other prospective studies with appropriate hs-cTnT assays, adequate sample size, and comparable sampling protocols.

Implications for clinical practice

There is no doubt that high-sensitivity assays are the analytical method of choice in terms of risk stratification in patients with ACS. What is new? A single measurement of hs-cTn seems to be adequate for long-term risk stratification in patients without AMI.
However, the question of which troponin might be preferable for long-term risk stratification remains unanswered. The new finding that we may have to differentiate between the role of troponins for acute and long-term risk stratification could be a paradigm change. Accordingly, in the same population, troponins fulfill the role of a marker of acute risk as well as serving as a risk factor in the long term. As a marker of acute risk, the dynamic change is still crucial, predominantly to establish the correct diagnosis. A single measurement of hs-cTn seems to be sufficient for risk estimation in patients without ACS. For the use as a long-term risk marker, hs-cTn is competing with high-sensitivity measured C-reactive protein (hsCRP) and brain natriuretic peptide (BNP).

Troponin measured as a long-term risk factor will only find acceptance in clinical practice if this result leads to therapeutic consequences, i.e. the improvement of prognosis by pharmacological management. In patients with elevated hsCRP, this has been nicely demonstrated for statins. There is not such a well-established concept for patients with elevated BNP levels. Potential candidates for a targeted treatment appear difficult to identify, as long as we are still debating the pathophysiological reasons for low levels of troponin. However, it appears worthwhile to explore statins or aldosterone antagonists in this setting.

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