Current Recommendations for Interpretation of the Highly Sensitive Troponin T Assay for Diagnostic, Therapeutic and Prognostic Purposes in Patients with a Non-ST-segment-elevation Acute Coronary Syndrome

Evangelos Giannitsis and Hugo A Katus

Medical Department III, Heidelberg University Hospital

Abstract

The presence of the cardiospecific cardiac troponins (cTns) I (cTnI) and T (cTnT) alongside signs or symptoms of myocardial infarction (MI) are indicative of an acute MI. As these proteins are not typically found in the sera of healthy individuals, any concentration of cTns exceeding the 99th percentile is interpreted as myocardial necrosis. Recently, new cTnI and cTnT with increased sensitivity and precision have been introduced to improve the detection and diagnosis of acute MI, the newest of which, the Elecsys® Troponin T highly sensitive assay, has demonstrated a particular advantage with high precision even in the 99th percentile. These enhanced properties are expected to increase the incidence of MI diagnoses, but currently it is not clear how to approach therapy in response to the detection of cTnT levels. The detection of elevated cTn levels alone is not sufficient for a diagnosis of acute MI, and requires an in-depth assessment of clinical presentation to determine the source and severity of myocardial damage.

Keywords

Cardiac troponin T, myocardial infarction, acute coronary syndrome, sensitivity, precision, assay

Disclosure: The authors have no conflicts of interest to declare.
Acknowledgements: Editing support was provided by Touch Medical Communications.
Received: 14 December 2009 **Accepted:** 11 January 2010
Correspondence: Evangelos Giannitsis, Medical Department III, Heidelberg University Hospital, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany.
E: evangelos_giannitsis@med.uni-heidelberg.de

Support: Supported by Roche Diagnostics. The views expressed are those of the authors and not necessarily those of Roche Diagnostics.

Highly Sensitive Troponin T Assay and Diagnosis of Acute Myocardial Infarction

According to the new definition of myocardial infarction (MI) issued by the European Society of Cardiology/American College of Cardiology (ESC/ACC) Committee for the Redefinition of Myocardial Infarction, acute MI has occurred when cardiac troponin (cTn) is present in the blood of a patient who also exhibits signs or symptoms of MI.[1] As cTn is not present or is at only very low concentrations in the serum of healthy individuals, a serum concentration above the 99th percentile in a healthy reference population has been accepted as abnormal and, therefore, indicative of myocardial necrosis. As earlier generations of the cTn I (cTnI) and T (cTnT) assays were unable to measure these low concentrations with a sufficient degree of precision, the convention followed was to employ those concentrations as a discriminator of MI, which could still be measured with an optimal level of analytical imprecision (coefficient of variation ≤10%).[2]

The sensitivity and precision of troponin assays have greatly improved since the new definition of MI was issued by the ESC/ACC in 2000, revolutionising the ability to detect and diagnose acute MI. Several ultrasensitive cTnI assays provided by various manufacturers are already available for clinical use. Until recently, cTnT assays were limited by their low sensitivity at the time of a patient's presentation and a lack of precision at the lower concentrations above the 99th percentile. The newest generation of cTnT assays has recently been launched on the market as the Elecsys® Troponin T highly sensitive (TnT-hs) assay (Roche Diagnostics), and has the potential to address both of these concerns. The refinement of this new generation of tests has been achieved by improving the signal in a number of ways: modification of ruthenium loading, reduction of background noise by modification of the buffer and increasing the specimen volume. These changes have improved the analytical sensitivity to nearly one-third of its previous value, from 0.010 to 0.003µg/l. The value for the 99th percentile was determined in several independent healthy reference populations and in a multicentre reference population. For the TnT-hs assay, the 99th percentile value, as obtained from the multicentre reference population, yielded a cut-off point of 14pg/ml, which is very close to the values ranging between 12 and 13.4ng/l (0.012–0.013µg/l) found in other reference studies.[3] Therefore, this new assay satisfies the requirements of the new MI definition in terms of precision, with a particular advantage owing to its higher precision in the 99th percentile. In this article, we will discuss the clinical importance of cTns and the relevant assays with enhanced precision and higher sensitivity in the diagnosis of acute MI.

Cardiac Troponins as Markers of Myocardial Ischaemia

Clinical context is crucial for the correct interpretation of cTn values. The clinical probability of the existence of an acute coronary

syndrome (ACS) is based on a wide variety of indicators, e.g. type of symptoms, number of risk factors, presence of diabetes, electrocardiogram (ECG) changes and, of course, cTnT.[4] The cTn isoforms cTnT and cTnI are expressed only in cardiac muscle, conferring absolute cardiospecificity. However, every kind of myocardial damage that is accompanied by a loss of cell membrane integrity causes a release of troponin, appearing in the blood after two to four hours and persisting for up to 10–21 days. As this is true of myocardial inflammation, toxic myocardial damage and other clinical entities, not every elevation of troponin can be equated with acute MI.[5] As such, it is of paramount importance that the entire clinical picture is taken into account when interpreting cTn values.

According to the new Universal Definition of Myocardial Infarction,[6] the criteria for acute MI require the demonstration of cTn levels above the 99th percentile together with a rise and later fall of the concentration, as well as at least one of the following criteria:

- symptoms of ischaemia;
- ECG changes indicative of new ischaemia (e.g. new ST-segment depression or a new complete left bundle branch block);
- development of pathological Q-waves in the ECG; and
- demonstration of a new area of infarction or disturbance of regional wall motility by imaging.

Additionally, MI can be assumed if a patient with symptoms or suspicious ECG changes dies suddenly before serum values can be obtained, or if normal serum values are obtained prior to the appearance of cardiac biomarkers. Furthermore, following percutaneous coronary intervention or aortocoronary bypass procedures, certain thresholds of cardiac biomarkers must be exceeded (three times the 99th percentile upper reference limit) before the diagnosis of post-interventional infarction can be made. Clinical symptomatology alone is frequently not sufficient to establish the diagnosis since ≤50% of all patients exhibit no typical signs of angina pectoris.

Acute MI typically leads to a sudden rise and subsequent fall of cTn concentrations. This pattern of a rise and/or fall of the cTn concentration can be used for retrospective confirmation of the diagnosis or early recognition of acute MI. A rise and/or fall of the troponin concentration of >20% is typically accepted as significant for differentiating between an acute event and a chronic clinical entity,[6] but recent biological variability data suggest that a significant change requires a much higher increment than 20%.[7]

Highly Sensitive Troponin T Assay – Implications for Prognosis

The prognostic importance of cTnT has been clearly substantiated by numerous studies and meta-analyses.[8] Most of the studies use the higher receiver operating characteristic (ROC)-optimised cut-off value of 0.1µg/l. However, several studies have also confirmed the benefits of using a discriminator concentration (0.03µg/l) for the identification of a higher short- and long-term cardiac risk. There is evidence that the cardiac risk can be predicted by a concentration <0.03µg/l; however, these measurements were made by tests of the second to fourth generation, which did not yet display adequate measurement precision.

The advantage of the new TnT-hs assay is its improved precision in the 99th percentile. With this new assay, improved estimation of risk could theoretically be expected because of the clear interpretation of test results it affords, with fewer false-negatives and false-positives. In fact, the results of the Treat Angina with aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy – Thrombolysis In Myocardial Infarction (TACTICS-TIMI 18) study, which was performed with a well-defined patient population with confirmed ACS, showed that low concentrations of cTnI barely above the 99th percentile (≥0.1ng/ml, cardiovascular [CV] 20%) were associated with a tripling of the risk of a subsequent MI or fatal outcome.[9] Similar observations were made in the Orbofiban in Patients with Unstable coronary Syndromes – TIMI 16 (OPUS-TIMI-16)[10] and Fragmin and Fast Revascularisation during InStability in Coronary artery disease II trial (FRISC II) studies[11] and in one registry study.[12] However, all of these measurements were made with a cTnI assay that displays a high rate of imprecision of >20% at the 99th percentile. Therefore, the introduction of a new sensitive and precise assay now offers the possibility for a critical review of the value of using very low discriminator concentrations for risk stratification in patients with an ACS.

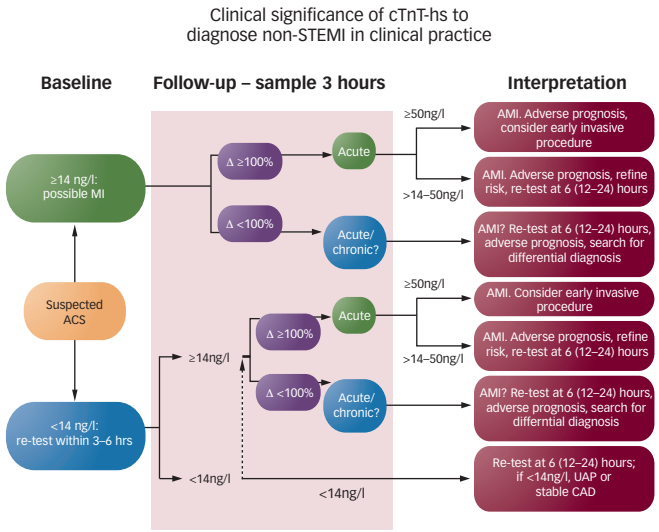
With the ability to now precisely measure cTn levels at, and even below, the current 99th percentile, the incidence of MI diagnoses is expected to increase, with these patients at substantial post-infarction risk.[13] Studies have shown that these previously undetectable cTn levels have also been associated with worse outcomes in patients with ACS,[13] particularly if the minute cTn elevations continue post-event.[14] These poorer prognoses are also the case among patients with heart failure,[15] stable angina pectoris[16] and even elderly cohorts who appear healthy.[17,18] Concentrations of cTn below the 99th percentile have also been associated with cardiovascular high-risk features, greater atherosclerotic plaque burden in the carotid arteries and impaired cardiac performance.[19] The new TnT-hs assay not only meets the criteria for defining MI as outlined by international guidelines in terms of precision requirements, but has also demonstrated the best level of assay designation with 95% measurable normal values below the 99th percentile.[20] A recent comparative evaluation between four highly sensitive cTn assays has found TnT-hs to have the highest sensitivity and negative predictive values.[21]

Highly Sensitive Troponin T Assay – Implications for Patient Management

Unlike their predecessors, the newer-generation cTn assays are better able to detect cTn levels at the time of a patient's presentation.[21] This allows for a more rapid diagnosis of acute MI, which could otherwise only be determined following prolonged monitoring over a period of six to 12 hours and serial blood sampling. Importantly, the clinical benefits associated with the potential to achieve revascularisation, be treated in the coronary care unit and receive the appropriate treatment for acute MI at an earlier time-point may ultimately improve overall management of patients with acute MI.[6,22,23]

Earlier studies established a correlation between cTns and a higher risk of thrombotic coronary events. Accordingly, treatment with low-molecular-weight heparin or glycoprotein IIb/IIIa inhibitors was seen to be beneficial only for patients with elevated cTnT.[24–26] In most of the studies, a cTnT cut-off value of 0.1µg/l was used. It was shown in later studies that a lower cTnT concentration >0.03µg/l is suitable for identifying the subgroup of patients who will benefit

Figure 1: Proposed Algorithm for the Highly Sensitive Troponin T Assay in Clinical Practice



ACS = acute coronary syndrome; AMI = acute myocardial infarction; CAD = coronary artery disease; cTnT-hs = highly sensitive cardiac troponin T assay; MI = myocardial infarction; STEMI = ST-elevation myocardial infarction; UAP = unstable angina pectoris.

from intensive pharmacotherapy or early invasive treatment.[9,27,28] Accordingly, the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2) study showed a corresponding reduction of cardiac events in patients with non-ST-elevation MI (non-STEMI; defined as cTnT >0.03µg/l) as a result of treatment with aspirin, 600mg of clopidogrel and a single dose of abciximab.[28] Moreover, the TACTICS-TIMI-18 study showed that cTnT concentrations just above the 99th percentile identified patients who will benefit from early coronary intervention with the protection of a glycoprotein IIb/IIIa inhibitor.[9] This method makes it possible to lower the mortality rate and rate of subsequent MI to half of the previous value in troponin-positive patients. However, because the measurement of cTnT or cTnI in the 99th percentile was made with very high imprecision (CV ≥20%) in the TACTICS-TIMI-18 study, it must be assumed that a larger number of study participants were erroneously identified as high-risk patients.

The advent of new, more potent medications for inhibition of platelet aggregation and for anticoagulation introduces an increased risk of haemorrhage. For this reason, it is unclear whether – and at what concentrations – patients with demonstrated cTnT benefit from early invasive treatment and concomitant therapy with potent drugs. By contrast, data from the International Citicoline Trial on Acute Stroke (ICTUS) study show that the benefits of early intervention are not clearly established for patients with cTnT >0.03µg/l, as in this group of patients the advantages of the intervention have to be weighed against the disadvantage of a higher rate of peri-interventional infarction.[29] At a concentration of TnT-hs exceeding 53pg/ml (corresponding to a concentration >0.03µg/l measured by a fourth-generation TnT assay), early coronary interventions are supported. By comparison, patients with lower concentrations between 14 and 53pg/ml would require subsequent observation to help to differentiate the presence of acute MI from myocardial injury of non-ischaemic origin with an unfavourable prognosis. In such cases, the diagnosis and the patient's risk should be critically evaluated. As the recommendations contained in the current treatment guidelines for patients with an ACS allow a period of ≤72 hours between the onset of symptoms and early coronary intervention, the diagnosis can be confirmed by additional diagnostic imaging studies – and/or a specific treatment can be instituted, depending on the differential diagnosis – during this period. Of course, this presumes that a higher-risk situation has been ruled out in the particular case. The question of whether the outcome can be improved by coronary intervention or more aggressive concomitant therapy in patients with cTn concentrations within this observation time period must be further explored in prospective, randomised, therapeutic interventional studies.

Beyond the 99th Percentile

The development of highly sensitive cTn assays now allows the measurement of cTn concentrations in the range of pg/ml rather than ng/ml. This ability to identify cTn at previously undetectable levels has introduced greater potential to identify and diagnose ACS in patients. Notably, an elevation of cTn levels alone is not sufficient for a diagnosis of acute MI. As such, we include an algorithm that is proposed to reflect the clinical significance of the TnT-hs assay (see *Figure 1*). Currently, the TnT-hs assay is the only assay with demonstrated sensitivity in detecting cTnT levels below 0.01µg/ml, and with such high sensitivity it has great promise for early diagnosis, as well as exclusion, of acute MI.

On presentation of a patient with suspected ACS, the TnT-hs assay can be applied immediately, with subsequent testing at follow-up to determine the severity of a patient's condition. Although this algorithm has not yet been validated, we believe that use of the TnT-hs assay in such a manner may have the best potential impact in clinical practice.

Summary and Conclusions

The improved precision of the new TnT-hs assay allows the requirements of MI, as defined by the ESC/ACC, to be satisfied. According to this assay, patients with serum cTnT concentrations ≥14pg/ml presenting with laboratory findings that are supported by an ischaemic context are deemed to have had an acute MI. Furthermore, where previous studies had shown cTn concentrations to indicate a higher rate of death and MI at the lower detection limits, even when these concentrations were measured with a very high coefficient of variation (>20%), the TnT-hs assay allows for precise measurements in the 99th percentile. In these terms, there are strong implications for precise risk assessment, although this is an area that needs to be further examined in clinical studies to completely explore all of the benefits associated with the assay.

Moreover, higher cTnT concentrations ranging between 0.03 and 0.1µg/l, as measured by the fourth-generation TnT test (corresponding to 0.05–0.1µg/l with the new TnT-hs assay), have been shown to be suitable for identifying patients who can benefit from treatment with low-molecular-weight heparin, glycoprotein IIb/IIIa inhibitors or early invasive strategies. It is currently not clear what therapeutic advantages are associated with coronary intervention or aggressive drug therapy in patients with a troponin concentration >0.03µg/l; as such, it is recommended that patients with cTnT-hs levels between 14 and 50pg/ml be monitored under an observation period, with treatment tailored to the individual. ■

1. Alpert JS, Thygesen K, Antman E, et al., Myocardial infarction redefined – a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction, *J Am Coll Cardiol*, 2000;36:959–69.
2. Apple FS, Wu AH, Jaffe AS, European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: how to use existing assays clinically and for clinical trials, *Am Heart J*, 2002;144: 981–6.
3. Beyrau R, Braun S, Cooray R, et al., Multicentre evaluation of a high sensitive Elecsys troponin T assay, *Clin Chem Lab Med*, 2009;47:S128.
4. Braunwald E, Antman EM, Beasley JW, et al., ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina), *J Am Coll Cardiol*, 2000;36: 970–1062.
5. Hamm CW, Giannitsis E, Katus HA, Cardiac troponin elevations in patients without acute coronary syndrome, *Circulation*, 2002;106:2871–2.
6. Thygesen K, Alpert JS, White HD, Universal definition of myocardial infarction, *J Am Coll Cardiol*, 2007;50:2173–95.
7. Wu AH, Lu QA, Todd J, et al., Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice, *Clin Chem*, 2009;55:52–8.
8. Heidenreich PA, Alloggiamento T, Melsop K, et al., The prognostic value of troponin in patients with non-ST elevation acute coronary syndromes: a meta-analysis, *J Am Coll Cardiol*, 2001;38:478–85.
9. Morrow DA, Cannon CP, Rifai N, et al., Ability of minor elevations of troponins I and T to predict benefit from an early invasive strategy in patients with unstable angina and non-ST elevation myocardial infarction: results from a randomized trial, *JAMA*, 2001;286:2405–12.
10. Morrow DA, Rifai N, Sabatine MS, et al., Evaluation of the AccuTnI cardiac troponin I assay for risk assessment in acute coronary syndromes, *Clin Chem*, 2003;49:1396–8.
11. Venge P, Lagerqvist B, Diderholm E, et al., Clinical performance of three cardiac troponin assays in patients with unstable coronary artery disease (a FRISC II substudy), *Am J Cardiol*, 2002;89:1035–41.
12. Kontos MC, Shah R, Fritz LM, et al., Implication of different cardiac troponin I levels for clinical outcomes and prognosis of acute chest pain patients, *J Am Coll Cardiol*, 2004;43:958–65.
13. Kavsak PA, Newman AM, Lustig V, et al., Long-term health outcomes associated with detectable troponin I concentrations, *Clin Chem*, 2007;53:220–27.
14. Eggers KM, Lagerqvist B, Venge P, et al., Persistent cardiac troponin I elevation in stabilized patients after an episode of acute coronary syndrome predicts long-term mortality, *Circulation*, 2007;116:1907–14.
15. Latini R, Masson S, Anand IS, et al., Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure, *Circulation*, 2007;116:1242–9.
16. Schulz O, Paul-Walter C, Lehmann M, et al., Usefulness of detectable levels of troponin, below the 99th percentile of the normal range, as a clue to the presence of underlying coronary artery disease, *Am J Cardiol*, 2007;100:764–9.
17. Daniels LB, Laughlin GA, Clopton P, et al., Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study, *J Am Coll Cardiol*, 2008;52:450–59.
18. Zethelius B, Johnston N, Venge P, Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: a community-based cohort study, *Circulation*, 2006; 113:1071–8.
19. Eggers KM, Lind L, Ahlstrom H, et al., Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects, *Eur Heart J*, 2008;29:2252–8.
20. Apple FS, A new season for cardiac troponin assays: it's time to keep a scorecard, *Clin Chem*, 2009;55:1303–6.
21. Reichlin T, Hochholzer W, Bassetti S, et al., Early diagnosis of myocardial infarction with sensitive cardiac troponin assays, *N Engl J Med*, 2009;361:858–67.
22. Bassand JP, Hamm CW, Ardissino D, et al., Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes, *Eur Heart J*, 2007;28:1598–1660.
23. Anderson JL, Adams CD, Antman EM, et al., ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine, *Circulation*, 2007; 116:e148–304.
24. Lindahl B, Venge P, Wallentin L, Troponin T identifies patients with unstable coronary artery disease who benefit from long-term antithrombotic protection. Fragmin in Unstable Coronary Artery Disease (FRISC) Study Group, *J Am Coll Cardiol*, 1997;29:43–8.
25. Morrow DA, Antman EM, Tanasijevic M, et al., Cardiac troponin I for stratification of early outcomes and the efficacy of enoxaparin in unstable angina: a TIMI-11B substudy, *J Am Coll Cardiol*, 2000;36:1812–17.
26. Newby LK, Ohman EM, Christenson RH, et al., Benefit of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes and troponin t-positive status: the paragon-B troponin T substudy, *Circulation*, 2001;103: 2891–6.
27. Diderholm E, Andren B, Frostfeldt G, et al., The prognostic and therapeutic implications of increased troponin T levels and ST depression in unstable coronary artery disease: the FRISC II invasive troponin T electrocardiogram substudy, *Am Heart J*, 2002;143:760–67.
28. Kastrati A, Mehilli J, Neumann FJ, et al., Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 randomized trial, *JAMA*, 2006;295:1531–8.
29. de Winter RJ, Windhausen F, Cornel JH, et al., Early invasive versus selectively invasive management for acute coronary syndromes, *N Engl J Med*, 2005;353: 1095–1104.