Admission troponin measurement for the diagnosis of myocardial infarction - the search for one and done continues.

Professor Paul Collinson. Departments of Clinical Blood Sciences and Cardiology, St George’s University Hospitals NHS Foundation Trust and St George’s University of London, Cranmer Terrace London SW17 0QT, UK

Running title Admission troponin and risk scores

Words 1326 words

Figures 0

Tables 0

Keywords

Cardiac troponin

Cardiac troponin I

Cardiac Troponin T

Risk Scoring

Chest Pain

Acute Coronary Syndromes

Correspondence to: Professor Paul Collinson. Department of Clinical Blood Sciences, St George’s University Hospitals NHS Foundation Trust, Cranmer Terrace, London SW17 0QT, UK.

Tel 0208 725 5934 Fax 0208 725 5838

Email: paul.collinson@stgeorges.nhs.uk

Abstract

Rapid diagnosis or exclusion of acute myocardial infarction based on a single admission troponin measurement is a highly attractive option and has been endorsed by the European Society of Cardiology. It is accepted that risk factor scoring is required in addition to troponin measurement. The paper reviewed in this editorial suggests that the current scoring system included in the guidelines, the Global Registry of Acute Coronary Events score may not be appropriate and also highlights differences between findings from clinical study populations and audit of routine clinical practice.

The ideal test for confirmation or exclusion of acute myocardial infarction (AMI) would be a single test on admission that was 100% sensitive and 100% specific. It would also fully explain the cause of the patients symptoms. Although the Star Trek tricordor has these abilities, this technology is not currently available. Diagnostic strategies in AMI have evolved from the electrocardiogram (ECG) to ECG plus daily cardiac enzyme measurements. Subsequently came serial measurements of creatine kinase and its MB isoenzyme over 4 to 8 hours from admission. Now we are in the cardiac troponin (cTn) era. But we want the diagnosis now.

The original use of cTn was a single measurement 10-12 hours from admission to provide a dichotomous diagnosis of AMI or not. Subsequent improvements in measurement technology for cTn plus the redefinition of AMI with cTn as the defining test, has had unintended consequence(1). It has been clearly demonstrated that cTn elevations occur in myocardial infarction but also in acute and chronic myocardial injury. Indeed acute and chronic myocardial injury now accounts for more cases of cTn elevation in patients presenting to the Emergency Department (ED) than AMI(2). The development of high sensitivity cTn assays has brought this to its logical conclusion. It must be remembered that high sensitivity assays are not measuring a different form of cTn. By definition, they measure with an analytical imprecision (the ability to measure repeated values reliably) of <10% at the 99th percentile of a reference population and will detect cTn in >50% of healthy normals. In practice this means troponin can be measured down to very low levels in most patients and that those measurements are repeatable at very low levels. Analytical imprecision is often 5% or less at low cTn values.

The ability to measure low levels reliably and repeatedly (with low imprecision) has produced an evolution in the diagnostic strategies in patients presenting with chest pain?acute coronary syndromes (ACS). Initially diagnosis was based on a rising troponin which then exceeded the 99th percentile (the upper limit of normal). The advent of hs troponin assays reduced the time frame required for diagnosis. Initially, measurement was performed on admission then 6 and 12 hours from admission. This evolved to measurement on admission and 6 hours from admission, then to measurement of admission and 3 hours from admission. This strategy is based on the ability of high sensitivity assays to detect change earlier. Use of admission and 3 hour measurement was endorsed by the European Society of Cardiology (ESC) in guidelines(3) and by health technology assessment(4). More recently, rapid diagnostic algorithms have been developed which utilise the ability to measure low levels of troponin accurately plus the ability to measure repeated values reliably (with low imprecision). These algorithms have two components. The first is an admission measurement to define a very low troponin value which will be predictive (hence prognostic) of the risk of a cardiac event, AMI or death, over the index admission and a subsequent follow up period, typically 30 days. The initial measurement is therefore not diagnostic but based on the probability that the initial measurement will predict the probability that a subsequent measurement, taken 10-12 hours later, would exceed the diagnostic threshold (the 99th percentile).The second component utilises two measurements taken a short time interval apart (typically 1 to 2 hours). Evidence of a rising cTn indicates active myocardial necrosis, presumed due to AMI, is occurring. Failure of the two values to change significantly indicates that either there is no active myocardial necrosis or the troponin value reflects a chronic elevation.

There is widespread acceptance that cTn measurement alone cannot be used as the sole criterion to confirm or exclude myocardial infarction and that additional data is required. Clinical judgement alone is a relatively poor decision strategy(5) although clinical assessment of the patient remains essential. Combination of troponin measurement with the presence of a normal ECG has been shown to be an effective strategy. In a meta-analysis of studies there was variable sensitivity for rule out for the combination of a very low cardiac Troponin T plus normal ECG although the pooled analysis supported such an approach(6). A widespread strategy has been to use a risk scoring system. A variety of scoring systems have been proposed. The current guidelines of the European Society Cardiology (ESC) include a recommendation for use of the Global Registry of Acute Coronary Events score (GRACE) score(3).

The current study by Marcusohn and colleagues has some very interesting findings to add to the debate on what constitutes an optimal strategy for single test rule out(7). They have performed a large retrospective cohort study of patients investigated for suspected ACS but managed by conventional rather than a rapid rule out algorithm. All patients had troponin measurement performed using a high sensitivity cardiac troponin I (cTnI) assay, the Abbott architect assay. A minimum of two samples were taken. The initial blood sample was taken six hours or more from admission. 60 day follow-up for major adverse cardiac events was available and the GRACE score could be calculated on all of them. They have selected those patients in whom the presentation cTnI was <5 ng/L and calculated the GRACE score for this group of patients.

This cohort therefore provides an excellent opportunity to evaluate the value of the GRACE score and a validation of a single troponin for rule out on admission. 9236/13800 (66.9%) of the patients evaluated had cTnI <5 ng/L with full data available on 7705/9236 (83.4%). Overall, the 60 day event rate was 2.3% but there were significant differences when the patients were split according to GRACE score. Patients with a score <109 had significantly lower risk of adverse events. One of the most powerful predictors was age. Age less than 53 years alone had a negative predictive value of 99.1%. They found that a lower threshold for GRACE score of 73 was required to achieve a negative predictive value of 99%.

This study raises two questions. First, whether it is appropriate to use a scoring system not developed in a low risk chest pain population for risk stratification for rule out. It would support the view that specific scoring systems developed for rule out in the Emergency Department are more appropriate. The corollary is that the recommendations in the current ESC guidelines need to be revisited. The findings by by Marcusohn and colleagues are consistent with others who have directly compared the GRACE score with other scoring systems(8, 9). Hence, although the GRACE score may be appropriate once a diagnosis of acute coronary syndrome has been made, it should be reserved for the ACS population and not used as part of a rule out strategy.

The second question is the event rate observed in this study. Overall the 60 day event rate was 2.3%. In a previous study which first suggested a diagnostic discriminant of <5 ng/L the 30 day event rate (for death or AMI) was 0% and only 0.6% at one year(10). Similar low event rates have been reported elsewhere(11). Does this therefore represent the difference between audit of routine clinical practice compared with research orientated studies, where a Hawthorne effect may occur? Or, does it represent a difference in population studied or subsequent treatment during follow-up. Is interesting to note that a recent reported clinical trial comparing rapid diagnosis using cTn compared with conventional diagnostic strategies (although the conventional diagnosis arm used a decision limit of twice the upper reference limit for troponin) reported a 1% event rate at 30 days(12).

Rapid diagnosis based on admission troponin plus clinical scoring is an attractive option and from is performed to date seems likely to be safe. However, the correct clinical scoring system needs to be selected, based on an appropriate population, and critically evaluated. This scoring system should then be incorporated into the decision-making algorithm. Most importantly, the time for observational studies of rapid diagnostic strategies is passed and well-designed prospective randomised controlled trials need to be performed.

Acknowledgements None

Funding None

Conflicts of interest None

References

 1. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2018.

 2. Shah ASV, Sandoval Y, Noaman A, Sexter A, Vaswani A, Smith SW, Gibbins M, Griffiths M, Chapman AR, Strachan FE, Anand A, Denvir MA, Adamson PD, D'Souza MS, Gray AJ, McAllister DA, Newby DE, Apple FS, Mills NL. Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: prospective cohort study. *BMJ* 2017;**359**:j4788.

 3. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol C, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis ZJ. 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**(3):267-315.

 4. Diagnostic Guidance 15 [DG15] Diagnostics Assesment Committee National Institute for Helrth and Care Excellence. Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays). NICE. **https://**[**www.nice.org.uk/guidance/DG15**](http://www.nice.org.uk/guidance/DG15).

 5. Oliver G, Reynard C, Morris N, Body R. Can Emergency Physician Gestalt "Rule In" or "Rule Out" Acute Coronary Syndrome: Validation in a Multicenter Prospective Diagnostic Cohort Study. *Acad Emerg Med* 2020;**27**(1):24-30.

 6. Pickering JW, Than MP, Cullen L, Aldous S, Ter AE, Body R, Carlton EW, Collinson P, Dupuy AM, Ekelund U, Eggers KM, Florkowski CM, Freund Y, George P, Goodacre S, Greenslade JH, Jaffe AS, Lord SJ, Mokhtari A, Mueller C, Munro A, Mustapha S, Parsonage W, Peacock WF, Pemberton C, Richards AM, Sanchis J, Staub LP, Troughton R, Twerenbold R, Wildi K, Young J. Rapid Rule-out of Acute Myocardial Infarction With a Single High-Sensitivity Cardiac Troponin T Measurement Below the Limit of Detection: A Collaborative Meta-analysis. *Ann Intern Med* 2017;**166**(10):715-724.

 7. Marcusohn E, Epstein D, Roguin A, Zukermann R. Rapid rule out for suspected myocardial infarction - Is the algorithm appropriate for all? *Eur Heart J Qual Care Clin Outcomes* 2020.

 8. Poldervaart JM, Langedijk M, Backus BE, Dekker IMC, Six AJ, Doevendans PA, Hoes AW, Reitsma JB. Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department. *Int J Cardiol* 2017;**227**:656-661.

 9. Sanchis J, Valero E, Garcia BS, Barba E, Pernias V, Minana G, Braso J, Fernandez-Cisnal A, Gonzalez J, Noceda J, Carratala A, Chorro FJ, Nunez J, Pickering JW. Undetectable high-sensitivity troponin in combination with clinical assessment for risk stratification of patients with chest pain and normal troponin at hospital arrival. *Eur Heart J Acute Cardiovasc Care* 2020;2048872620907539.

 10. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, Chapman AR, Langdon T, Sandeman D, Vaswani A, Strachan FE, Ferry A, Stirzaker AG, Reid A, Gray AJ, Collinson PO, McAllister DA, Apple FS, Newby DE, Mills NL. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. *Lancet* 2015.

 11. Neumann JT, Sorensen NA, Ojeda F, Schwemer T, Lehmacher J, Gonner S, Jarsetz N, Keller T, Schaefer S, Renne T, Landmesser U, Clemmensen P, Makarova N, Schnabel RB, Zeller T, Karakas M, Pickering JW, Than M, Parsonage W, Greenslade J, Cullen L, Westermann D, Blankenberg S. Immediate Rule-Out of Acute Myocardial Infarction Using Electrocardiogram and Baseline High-Sensitivity Troponin I. *Clin Chem* 2017;**63**(1):394-402.

 12. Chew DP, Lambrakis K, Blyth A, Seshadri A, Edmonds MJR, Briffa T, Cullen LA, Quinn S, Karnon J, Chuang A, Nelson AJ, Wright D, Horsfall M, Morton E, French JK, Papendick C. A Randomized Trial of a 1-Hour Troponin T Protocol in Suspected Acute Coronary Syndromes: The Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T Study (RAPID-TnT). *Circulation* 2019;**140**(19):1543-1556.