Does undetectable troponin I at presentation using a contemporary sensitive assay rule out myocardial infarction? A cohort study

Anne-Maree Kelly, Sharon Klim

[1]Joseph Epstein Centre for Emergency Medicine at Western Health, Sunshine Hospital, St Albans, Victoria, Australia
[2]The University of Melbourne, Victoria, Australia

Correspondence to
Professor Anne-Maree Kelly, Joseph Epstein Centre for Emergency Medicine at Western Health (JECEMR), Sunshine Hospital, Furlong Road, St Albans 3021, Australia; anne-maree.kelly@wh.org.au

Received 22 October 2014
Revised 1 December 2014
Accepted 3 December 2014
Published Online First 31 December 2014

ABSTRACT

Aim Recent evidence suggests that an undetectable troponin level at emergency department (ED) presentation can rule out the presence of myocardial infarction (MI) in low-risk patients. The aim of this study was to investigate whether an undetectable troponin I (TnI) level at presentation using a contemporary troponin assay can accurately rule out MI at various front-door thrombolysis in myocardial infarction (fTIMI) score cut-offs.

Methods Planned substudy of a prospective observational cohort study of patients presenting to ED with chest pain without ECG evidence of ischaemia who underwent a 'rule out' acute coronary syndrome process. Clinical, investigational and outcome data were collected. A contemporary TnI assay (Siemens TnI Ultra) was used. Primary outcome of interest was diagnostic accuracy for MI of undetectable initial TnI at presentation at various fTIMI scores (sensitivity, specificity, positive predictive value and negative predictive value (NPV)).

Results 1076 patients were studied, of whom 156 had a final diagnosis of MI (14.5%). For patients with undetectable TnI and fTIMI scores 0, 0–1, 0–2 and 0–6, sensitivities were 98.7%, 98.1%, 97.4% and 97.4%, respectively, specificities were 22.6%, 41.7%, 53.8% and 69.9%, respectively, and NPV were 99%, 99.2%, 99.2% and 99.4%, respectively. If early presenters (<2 h of symptoms) were excluded, undetectable initial troponin had 100% sensitivity (95% CI 95.2% to 100%) and NPV (95% CI 98.8% to 100%).

Conclusions Using a contemporary TnI assay, undetectable initial TnI has high but not perfect sensitivity and NPV, unless early presenters are excluded.

Trial registration number ACTRN12612000990820.

Key messages

What is already known on this subject?
A small number of studies suggest that a single undetectable troponin level in patients with chest pain suspicious for acute coronary syndrome with non-ischaemic ECG may be sufficient to rule out myocardial infarction.

What this study adds?
Our study suggests that while negative predictive value of an 'at presentation' undetectable troponin is high, a small number of patients with myocardial infarction would be missed by this approach. Those missed presented with chest pain of <2 h from onset.

INTRODUCTION

Coronary artery disease is common, and failure to identify and treat it may result in preventable morbidity or mortality.[1] A major challenge facing emergency departments (EDs) worldwide is to determine which patients with chest pain have an acute coronary syndrome (ACS). A recent study,[2] using a high-sensitivity troponin T (TnT) assay, reported that an undetectable TnT at presentation had a sensitivity of 99.8% (95% CI 99.1% to 100%) and a negative predictive value (NPV) of 99.4% (95% CI 96.6% to 100%) for final diagnosis of myocardial infarction (MI). A validation study,[3] using a contemporary troponin I (TnI) assay, reported lower sensitivity (98.2%; 95% CI 92.9% to 99.7%) but similar NPV (99.1%; 95% CI 96.4% to 99.8%). The patients in that study that were missed all had high thrombolysis in myocardial infarction (TIMI) scores (5 and above). In that study, no patient with a TIMI score of 0–2 and an undetectable TnI at ED presentation had a type I MI identified, and it was suggested that this approach should be further investigated. This study aims to test the hypothesis that undetectable TnI at presentation in combination with a risk score ('front-door' TIMI (fTIMI) score[4]) can accurately exclude MI.

METHODS

This was a planned substudy of a prospective cohort study that was conducted between 16 April 2012 and 3 February 2013 in ED of a community teaching hospital with an annual adult ED census of approximately 36 000.

Patients were screened for inclusion if they presented with chest pain. Exclusion criteria were chest pain due to trauma, aged <18 years, no chest pain within 24 h of the index ED visit, chest pain lasting <10 min, no ECG or no troponin assay performed within 24 h of index ED visit, a clear alternative diagnosis at initial medical officer assessment, ischaemic ECG changes at ED presentation, haemodynamic instability, advanced terminal disease, inability to communicate in English and declined/unavailable for follow-up.

TnI samples were taken at ED arrival and at least 3–4 h later or 6 h from symptom onset in accordance with current National Heart Foundation

To cite: Kelly A-M, Klim S. *Emerg Med J* 2015;**32**:760–763.

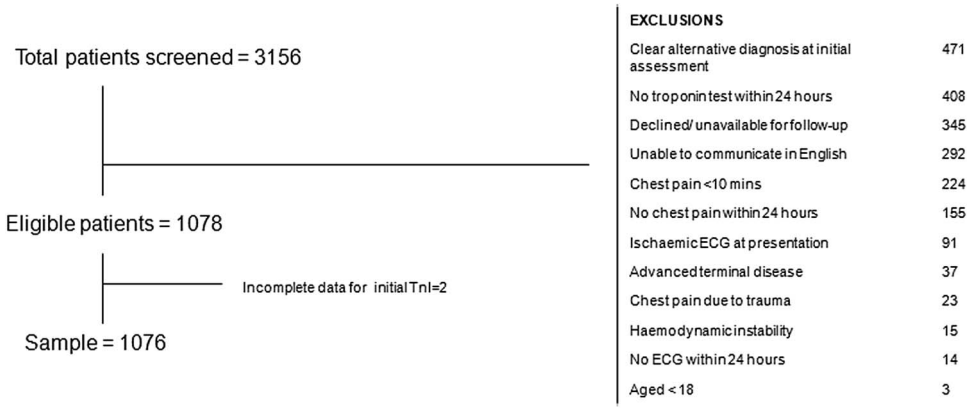

Figure 1 Sample derivation. TnI, troponin I.

(Australia) guidelines.[5] The troponin assay used by the laboratory was TnI Ultra by Siemens Diagnostics performed on an Advia Centaur analyser. The test has a reported range of 0.006–50 μg/L. Coefficient of variation is 10% at TnI 0.03 μg/L, 5.3% at 0.08 μg/L and 4.1% at 0.18 μg/L. The 99th centile is 0.04 μg/L (95% CI 0.03 to 0.05 μg/L) (manufacturer's information). Undetectable troponin was defined as <0.006 μg/L.

Data collected included demographics, cardiac risk factors, biomarker assay results, ED disposition, final diagnosis, data to calculate the Global Registry of Acute Coronary Events (GRACE) risk and freedom from events scores and TIMI and fTIMI scores. Front-door TIMI score is calculated using the same parameters as the TIMI score but without the biomarker data.[4] It takes into consideration that treating clinicians do not usually have biomarker data at initial clinical assessment. We also collected 7-day and 30-day outcome for major adverse cardiac events (MACE) by medical record review and telephone follow-up. We defined MACE as death, new MI, cardiac arrest or significant arrhythmia within 30 days of index visit.

Final diagnosis was assigned by a physician unaware of the study. An independent cardiologist adjudicated on final diagnosis for the subgroups where patients with troponin elevations on any assay exceeded the 99th centile and were coded as non-ACS and for patients without troponin elevations who were coded as ACS.

The primary outcome of interest was the final diagnosis of MI in patients with an undetectable TnI on their presentation TnI assay, analysed by front-door TIMI score. Unplanned post hoc secondary analyses were conducted for the same endpoint but excluding patients presenting within the first hour and the first two hours, respectively, of symptoms.

Analysis was by descriptive statistics and clinical performance analysis (sensitivity, specificity, positive predictive value (PPV) and NPV).

RESULTS

In total, 1076 patients were studied. Sample derivation is shown in figure 1. Patient characteristics are shown in table 1. In total, 156 patients had a final diagnosis of MI (14.5%, 95% CI 12.5% to 16.7%). Also, 647 patients (60.1%) had undetectable TnI at ED presentation.

The sensitivity, specificity PPVs and NPVs of undetectable initial TnI for ruling out MI in the various fTIMI score groups are shown in table 2. Clinical features of patients with an undetectable TnI initially who went on to have a type I MI diagnosed are shown in table 3. The absolute risk for MI in patients with initially undetectable TnI was 0.58% (95% CI 0.23% to 1.5%). There were no deaths or subsequent MI (not detected at index visit) within 30 days (0%; 95% CI 0% to 0.56%).

Excluding patients presenting within the first hour of symptoms, two MI would have been missed in 992 patients yielding a sensitivity of 98.6% (95% CI 94.5% to 99.8%) and an NPV of 99.7% (95% CI 98.6% to 99.9%). Excluding patients presenting within 2 h of symptom onset would have missed no MI in 681 patients yielding a sensitivity of 100% (95% CI 95.2% to 100%) and an NPV of 100% (95% CI 98.8% to 100%). This

Table 1 Sample characteristics

Variable	Overall (N=1076)
Gender (N, male, %)	614 (57.1%)
Age (years, median, IQR)	59 (48–70)
Ambulance arrival (N, %)	851 (79.1%)
Risk factors	
Hypertension (N, %)	621 (57.7%)
Diabetes (N, %)	267 (24.8%)
Current smoker (N, %)	255 (23.7%)
Known renal impairment (N, %)	87 (8.1%)
Family history of CAD (N, %)	359 (33.4%)
Hypercholesterolaemia (N, %)	598 (55.6%)
Known CAD (N, %)	251 (23.3%)
Delay from chest pain onset to ED presentation (h)	
<1 (N, %)	86 (8%)
1–2 (N, %)	309 (28.7%)
2–4 (N, %)	258 (24%)
4–6 (N, %)	203 (18.9%)
>6 (N, %)	220 (20.4%)
Risk scores	
Front-door TIMI score (median, IQR)	2 (1–3)
GRACE risk score (median, IQR)	95 (76–118)
GRACE freedom from events score (median, IQR)	305 (274–324)
Disposition (home, N, %)	742 (69%)
Discharge diagnosis	
MI (N, %)	156 (14.5%)
Non-MI ACS (N, %)	64 (5.9%)
Non-ACS cardiac (N, %)	61 (5.7%)
Chest pain of uncertain cause (N, %)	784 (72.8%)
Non-cardiac (N, %)	11 (1%)

ACS, acute coronary syndrome; CAD, coronary artery disease; ED, emergency department; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction.

Table 2 Clinical performance of undetectable initial TnI in combination with various front-door TIMI score group cut-offs

fTIMI score	Number undetectable TnI	Number of missed MI	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	PPV (%, 95% CI)	NPV (%, 95% CI)
0	210	2	98.7% (95% to 99.8%)	22.6% (20% to 25.5%)	17.8% (15.3% to 20.5%)	99% (96.2% to 99.8%)
0–1	387	3	98.1% (94% to 99.5%)	41.7% (38.5% to 45%)	22.2% (19.2% to 25.5%)	99.2% (97.6% to 99.8%)
0–2	499	4	97.4% (93.2% to 99.2%)	53.8% (50.5% to 57.1%)	26.3% (22.8% to 30.2%)	99.2% (97.8% to 99.7%)
0–6	647	4	97.4% (93.2% to 99.2%)	69.9% (66.8% to 72.8%)	35.4% (30.1% to 40.2%)	99.4% (98.3% to 99.8%)

fTIMI, front-door thrombolysis in myocardial infarction; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value; TnI, troponin I.

approach would have allowed 37.1% of patients (399/1076; 95% CI 34.2% to 40%) to be discharged after clinical assessment and a single TnI assay.

DISCUSSION

Our findings suggest that, using a contemporary TnI assay, a small number of patients with initially undetectable TnI will have a final diagnosis of MI. NPV was of the order of 99% with CIs going down to 96.2%. This finding is similar to that of Body *et al*,[2] who reported that an undetectable high-sensitivity TnT at ED presentation had a sensitivity of 99.8% (95% CI 99.1% to 100.0%) and an NPV of 99.4% (95% CI 96.6% to 100.0%) for diagnosis of MI. The results are also very similar to the previous validation study.[3] Diagnostic performance is improved if early presenters (<2 h of symptoms) are excluded.

Recently, a further study exploring undetectable troponin and outcome has been published. Bandstein *et al*[6] studied a cohort of patients presenting with chest pain and having at least one high-sensitivity troponin T assay (hsTnT). They report, in the cohort with undetectable hsTnT and a non-ischaemic ECG, an absolute risk of MI of 0.17% and only an NPV for MI of 99.8% (95% CI 99.7% to 99.8%). Of note, 2% of patients admitted to hospital had a final diagnosis of MI. While these results are promising, that study has some significant methodological flaws, particularly a low serial biomarker testing rate and an administrative data set follow-up process. These issues are well described by Cullen *et al*.[7] Without testing this approach in a prospective rule out ACS cohort with structured follow-up, it cannot be considered suitable for implementation.

The four studies so far reported have very similar NPV but somewhat different sensitivities. The difference may, in part, be due to differences in the inclusion criteria as well as differences in the assays used.

If an undetectable TnI at ED presentation in patients with >2 h of symptoms was adopted as a criterion for ruling out MI, approximately 37% of patients would potentially be eligible for early discharge without further observation or serial biomarker testing. This would represent significant cost and efficiency savings for hospitals. In our post hoc analysis, this approach had 100% sensitivity and specificity, but as this was a post hoc analysis it requires validation. This proportion of patients suitable for an accelerated process is similar to that reported by the Advantageous Predictors of Acute Coronary Syndromes Evaluation study,[8] which by using TIMI ≤1, non-ischaemic ECG and high-sensitivity troponin assay <99th centile at 0 and 2 h classified approximately 40% of patients as low risk and suitable for early discharge with an NPV in excess of 99%. It is higher than the proportion of patients defined as suitable for early discharge by the ADAPT[9] and ASPECT[10] studies (using TIMI=0, non-ischaemic ECG and troponin assay <99th centile at 0 and 2 h) with reported 9.8% and 20% of patients suitable for accelerated assessment with an NPV 99.7% (95% CI 98.6% to 100%) and 99.1% (95% CI 97.3% to 99.8%), respectively.

There are no studies specifically investigating 'missed' MI rate in the era of high-sensitivity troponin assays; however, a Canadian group using a 'standard' TnT assay (Roche Elecsys) and a 6 h observation and biomarker protocol reported a missed MI rate of 0% (95% CI 0% to 2.4%).[11]

An interesting finding was that the use of the TIMI score for risk stratification did not result in much additional risk discrimination above undetectable troponin. Indeed, the sensitivity and NPV for MI are very similar and specificity increases as TIMI score stratification classification is reduced (table 2). The TIMI

Table 3 Characteristics of patients with MI

Patient	A	B	C	D
Age	53	50	43	58
Gender	Male	Male	Male	Male
Mode of arrival	Ambulance	Ambulance	Self transport	Ambulance
Known CAD	Yes	Yes	No	No
Delay from pain onset to ED presentation	<1 h	1–2 h	<1 h	1–2 h
Front-door TIMI score	1	1	0	2
GRACE risk score	110	65	76	77
Peak ED TnI	0.37	0.1	0.14	0.05
ED disposition	Admit	Admit	Admit	Admit
Angiogram result	50–75% stenosis	>70% stenosis	No significant stenosis	>70% stenosis
Revascularisation within 30 days	Yes	Yes	No	Yes
MACE* at 30 days	No	No	No	No

*Death, new MI, cardiac arrest or significant arrhythmia within 30 days of index visit.
CAD, coronary artery disease; ED, emergency department; GRACE, Global Registry of Acute Coronary Events; MACE, major adverse cardiac events; TIMI, thrombolysis in myocardial infarction; TnI, troponin I.

score was developed to predict adverse outcome in patients with diagnosed ACS[12] and in an era before sensitive troponin assays. Validation in ED chest pain cohorts has been limited to showing and association with adverse outcome.[13] Its utility for risk stratification for ACS in ED chest pain patients above that provided by sensitive troponin assays is worthy of further investigation.

An as yet unanswered question is the tolerance of clinicians, the community and the medicolegal system for missed MI. In this study, if an undetectable presentation TnI had been used for decision making, four MI would have been missed (NPV 99.4% (98.4% to 99.8%)); however, approximately 60% of patients would have been eligible for early discharge. There is evidence of significant between-patient variation in risk tolerance for adverse events after ED chest pain assessment,[14] of variation between physicians in risk tolerance[15] and of mismatch between patient and physician risk tolerance.[16] As 100% diagnostic accuracy is impossible and missed MI is among the most common malpractice claims in emergency medicine,[17] building consensus about an acceptable level of risk would assist in developing effective and appropriate chest pain assessment pathways.

Similarly, biochemists have raised concerns about assay precision at the limit of detection, particularly the impact of minor analytic issues that might cause detected concentrations to cross cut-off values.[18] Whether this is a significant clinical issue is yet to be determined. Emergency physicians may well see these issues as clinically insignificant. For them, the troponin assay is part of a multimodal assessment, and for low-risk patients, minor imprecision at the limit of detection may not be clinically relevant.

Failure to diagnose MI has serious implications for patients and health services. For patients, the risk-adjusted mortality rate for those who are discharged with unrecognised MI is almost twice that of admitted patients.[19] For health system, missed MI is the leading cause for malpractice claims.[17 20] Thus any potential cost savings from early discharge of selected patients need to be weighed against the costs of missed MI. It is also important to remember that troponin levels reflect myocardial necrosis. Some patients with unstable angina without MI would not be detected by a strategy driven by biomarker results alone. Careful clinical evaluation is important for the identification of 'at-risk' patients who have not (yet) suffered an MI. This study does not imply that a detectable TnI at ED presentation rules in MI. Higher-sensitivity troponin assays have less specificity than their predecessors.[21]

There are some limitations to this study that should be considered when interpreting the results. While patients were identified prospectively, some data were collected from the medical record with the inherent weaknesses associated. It was conducted at a single site, so may not be generalisable to other settings. Determination of risk factors, past history and time of symptom onset was by patient self-report. No attempt was made to confirm the information provided, reflecting the 'real-world' ED setting.

CONCLUSION

Using a contemporary TnI assay, undetectable initial TnI has high but not perfect sensitivity and NPV, unless early presenters are excluded.

Acknowledgements We would like to thank Dr Nadim Shah and Dr Kean Soon for assistance with adjudication of diagnosis, Dr Alan McNeil for help obtaining absolute troponin values and our team of data collectors.

Contributors AMK had the concept for the study, SK managed data collection and both authors designed the study, analysed and interpreted the data and approved the manuscript.

Funding This project was supported by departmental funds only. There was no external funding support.

Competing interests AMK was a coauthor of the National Heart Foundation (Australia) guidelines for the management of acute coronary syndromes and their addenda from 2005 to 2013.

Patient consent Obtained.

Ethics approval Western Health Low Risk Ethics Panel. The study was approved by the institutional ethics panel and was registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12612000990820).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 AIHW. *Cardiovascular disease: Australian facts 2011. Cardiovascular disease series no. 35. Cat. no. CVD 53*. Canberra: AIHW, 2011.
2 Body R, Carley S, McDowell G, *et al*. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol* 2011;58:1332–9.
3 Kelly AM. Undetectable troponin I at presentation using a contemporary troponin assay does not rule out myocardial infarction. *Hong Kong J Emerg Med* 2014;21:31–6.
4 Conway-Morris A, Caeser D, Gray S, *et al*. TIMI risk score accurately risk stratifies patients with undifferentiated chest pain presenting to an emergency department. *Heart* 2006;92:1333–4.
5 Chew D, Aroney C, Aylward P, *et al*. 2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of Acute Coronary Syndromes (ACS) 2006. *Heart Lung Circ* 2011;20:487–502.
6 Bandstein N, Ljung R, Jahansson M, *et al*. Undetectable high-sensitivity cardiac troponin T level in the emergency department and risk of myocardial infarction. *J Am Coll Cardiol* 2014;63:2569–78.
7 Cullen L, Than M, Peacock WF. Undetectable hs-cTnT in the Emergency Department and Risk of Myocardial Infarction. *J Am Coll Cardiol* 2014;64:632–3.
8 Cullen L, Muller T, Parsonage WA, *et al*. Validation of high sensitivity troponin I in a 2-h diagnostic strategy to assess 30 day outcomes in emergency department patients with possible acute coronary syndrome. *J Am Coll Cardiol* 2013;62:1242–9.
9 Than M, Cullen L, Aldous S, *et al*. 2-hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol* 2012;59:2091–8.
10 Than M, Cullen L, Reid CM, *et al*. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. *Lancet* 2011;377:1077–84.
11 Scheuermeyer FX, Innes G, Grafstein E, *et al*. Safety and efficiency of a chest pain diagnostic algorithm with selective outpatient stress testing for emergency department patients with potential ischemic chest pain. *Ann Emerg Med* 2012;59:256–64.
12 Antman EM, Cohen M, Bernink PJ, *et al*. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835–42.
13 Hess EP, Agarwal D, Chandra S, *et al*. Diagnostic accuracy of the TIMI risk score in patients with chest pain in the emergency department: a meta-analysis. *CMAJ* 2010;182:1039–44.
14 Brown TB, Cofield SS, Iver A, *et al*. Assessment of risk tolerance for adverse events in emergency department chest pain patients: a pilot study. *J Emerg Med* 2010;39:247–52.
15 Than M, Herbert M, Flaws D, *et al*. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department? *Int J Cardiol* 2013;166:752–4.
16 Davis MA, Keerbs A, Hoffmann JR, *et al*. Admission decisions in emergency department chest pain patients at low risk for myocardial infarction: patient versus physician preferences. *Ann Emerg Med* 1996;28:606–11.
17 Brown TW, McCarthy ML, Kelen GD, *et al*. An epidemiologic study of closed emergency malpractice claims in a national database of physician malpractice insurers. *Acad Emerg Med* 2010;17:553–60.
18 Apple FS. High-sensitivity cardiac troponin assays: What analytical and clinical issues need to be addressed before introduction into clinical practice? *Clin Chem* 2010;56:86–91.
19 Pope JH, Aufderheide TP, Ruthazer R, *et al*. Missed diagnoses of acute cardiac ischaemia in the Emergency Department. *N Engl J Med* 2000;342:1163–70.
20 Karcz A, Korn R, Burke MC, *et al*. Malpractice claims against emergency physicians in Massachusetts: 1975–1993. *Am J Emerg Med* 1996;14:341–5.
21 Gualandro DM, Puelacher C, Mueller C. High-sensitivity cardiac troponin in acute conditions. *Curr Opin Crit Care* 2014;20:472–7.

Does undetectable troponin I at presentation using a contemporary sensitive assay rule out myocardial infarction? A cohort study

Anne-Maree Kelly and Sharon Klim

Emerg Med J 2015 32: 760-763 originally published online December 31, 2014
doi: 10.1136/emermed-2014-204442