High-Sensitivity Troponin Highlights the Need for New Methods to Evaluate Diagnostic Tests

See Article by Adamson et al.

Jenny Doust, MBBS, PhD
Paul Glasziou, MBBS, PhD

To be clinically useful, diagnostic tests need high precision. The original troponin assays had poor precision: they had high variability, particularly at the level used to determine whether a myocardial infarction (MI) was present.[1] To address this problem, high-sensitivity troponin (hs Tn) assays were developed, the sensitivity referring not to the tests' diagnostic sensitivity, but the analytic sensitivity with lower limits of detection and greater precision, including at the upper reference limit used to determine the presence of MI. This makes hs Tn more useful for ruling out MI and acute coronary syndrome in patients presenting with acute chest pain, allowing a greater proportion of patients to be discharged home earlier and potentially reducing the sex bias in the diagnosis of MI. These assays have been in use in Europe and Australasia since about 2010 but have only recently been approved by the Food and Drug Administration for clinical use in the United States.[2]

The study by Adamson et al[3] in this issue of *Circulation: Cardiovascular Quality and Outcomes* demonstrates that hs Tn can also help determine which patients in a rapid access chest pain clinic are likely to have obstructive coronary artery disease. This is a well-conducted substudy of a larger trial although 50 of the 987 participants were excluded from the analysis: 44 did not have a troponin level and in 6 the coronary computed tomographic angiogram was not diagnostic, which may overestimate the diagnostic accuracy a little. Using the coronary computed tomographic angiogram as the reference standard, adding troponin to a validated risk score, the coronary artery disease Consortium risk model,[4] modestly improved the diagnostic accuracy (C-statistic increased by 0.012 from 0.788 to 0.800; P=0.004) and the calibration of the model. Because the risk model includes the results of the coronary calcium score and coronary computed tomographic angiogram is used as a reference standard, an incorporation bias is possibly present although the direction of the bias is difficult to predict. The new model improved the net reclassification index, primarily through correctly identifying patients without obstructive coronary artery disease as low risk. The analysis was performed using a noncommercial form of the assay, but a sensitivity analysis using a commercial hs Tn I assay showed similar results.

CURRENT DILEMMA

Despite its many advantages, the new test presents a dilemma. Although a higher proportion of patients presenting with acute chest pain have low enough levels that they can be discharged early, a higher proportion of patients will have an elevated troponin level during the observation period and will require further evaluation: ≈22%, a level considerably higher than the 9% to 14% quoted for the conventional forms of the assay.[5] This raises the question of whether hs Tn contributes to overdiagnosis and overinvestigation.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Jenny Doust, MBBS, PhD, Centre for Research in Evidence Based Practice, Level 2 Health Sciences and Medicine Bldg, Bond University, Gold Coast, 4226 Australia. E-mail jdoust@bond.edu.au

Key Words: Editorials ■ disease definitions ■ high sensitivity troponin ■ medical overuse

The 2012 Universal Definition of Myocardial Infarction[6] reaffirmed the 2007 definition,[7] differentiating type 1 MI (caused by acute coronary plaque disruption) from type 2 MI (caused by an imbalance between myocardial supply and demand of oxygen leading to necrosis) and both from myocardial injury. The 2012 definition broadened the types of conditions that could cause an imbalance between myocardial supply and demand of oxygen, including conditions such as respiratory failure. The impact that this widened definition and the higher proportion of people with raised hs Tn levels will have on the incidence of acute coronary syndrome, MI, and the various subtypes of these diseases, such as type 1 and type 2 MI is unclear. Estimates of the impact of hs Tn on MI vary from a small decline[8] to an increase of 47%[9] and depend greatly on the types of patients included and the assay used. Smaller estimates are seen in patients with acute chest pain presenting to emergency departments, and larger estimates when a wider spectrum of patients is included. An Australian hospital tested hs Tn levels for all blood samples submitted over a 24-hour period.[10] Other than patients in the emergency department and coronary care units, the largest proportion of patients with elevated hs Tn were in intensive care unit and medical units. On the medical inpatient wards, 19% of men and 41% of women had levels above the 99th centile with a hs Tn I assay, and 55% of men and 44% of women with a hs Tn T assay. The introduction of hs Tn is possibly one factor contributing to the divergence seen in the apparent incidence of non–ST-segment–elevation MI in Australia compared with the United States although it does seem to occur somewhat earlier than the introduction of hs Tn around 2010 (Figure).

Most studies of the impact of hs Tn have tended to focus on improved outcomes per case diagnosed, but if the additional cases diagnosed are low risk or overdiagnosed, this will artificially improve outcomes. Some comfort, however, comes from a study of the implementation of hs Tn in Scotland.[13] In the first phase of the study, both conventional and hs Tn levels were tested but only the conventional assay results were communicated to the treating clinicians. In this phase of the study, the additional diagnosed patients—with elevated hs Tn but not elevated conventional troponin—had a worse prognosis. In the implementation phase of the study, when clinicians were aware of the results of the hs Tn, patients received more investigations and treatments and the difference in prognosis disappeared.

In the study in this issue, 2.9% of patients had a hs Tn level greater than the 99th centile. The authors have posed the question whether these patients might have subclinical myocardial necrosis. However, it is not at all clear whether such changes should be diagnosed and what should be done for such patients. This question has also been raised by other authors.[14] Five percent of those aged 60 to 65 years have a troponin level >99th centile.[15] Should this be considered a normal part of aging or pathological?

Compounding this problem is the fact that there is no standard way of defining the reference interval for the assay. The 99th centile depends greatly on the age of the patients included in the reference interval

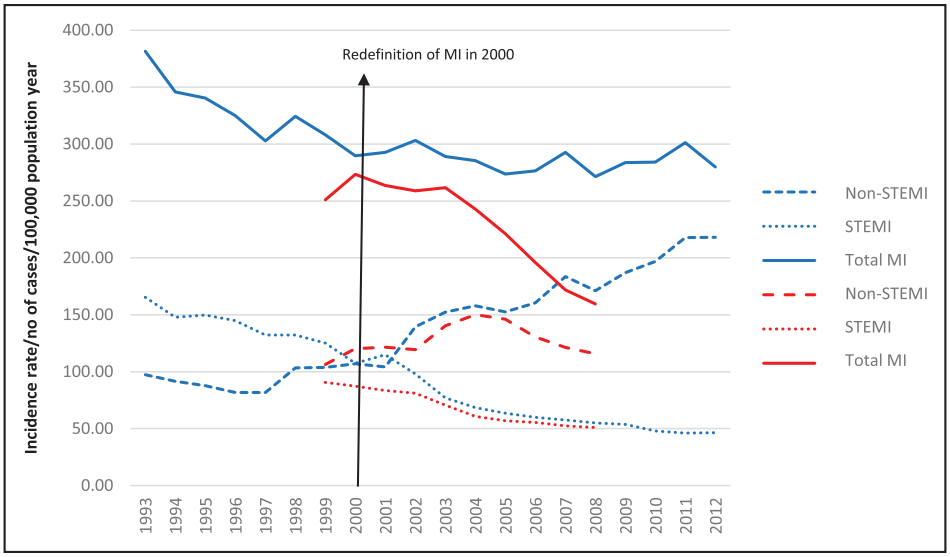

Figure. Age- and sex-standardized incidence of myocardial infarction in the United States (red, 1999–2008)[11] and Australia (blue, 1993–2012).[12]

Red lines: Kaiser Permanente Northern California myocardial infarction (MI) hospital admissions, standardized by age and sex to the population in 2008.[11] The total does not include patients with MI who were not hospitalized. The use of troponin testing rose between 2000 and 2004, but remained at stable levels after 2004. Blue lines: Western Australian MI hospital admissions and mortality register data, standardized by age and sex to the population in 2010.[12] The total data also includes fatal MIs that were not classified as ST-segment–elevation myocardial infarction (STEMI) or non-STEMI before death.

Table. Major Population Studies Looking at 99th Percentiles for hs-cTnI and hs-cTnT

Investigator	Specimen Type	Coning Strategy Definition of Normal	n	99th Percentile, ng/L			Age, y
				Overall	Male	Female	
Abbott ARCHITECT hs-cTnI							
Lipowski Abbott	All	BNP, HbA1c, eGFR	4593	26.2	34.2	15.6	21–75
	EDTA	BNP, HbA1c, eGFR	1531	27.8	35.1	16.7	
	Serum	BNP, HbA1c, eGFR	1529	22.3	28.3	14.7	
	Li Hep	BNP, HbA1c, eGFR	1531	26.9	34.5	14.3	
Blankenberg	Serum	No coning	4138	27.0	33.1	19.9	35–74
		NT-proBNP, eGFR	3799	21.5	25.9	13.9	
Aw	Serum	BNP, HbA1c, eGFR	1091	21.0	30.7	17.7	35–65
Apple	Li Hep	Blood donors and questionnaire	524	23.0	36.0	15.0	18–64
Venge	Li Hep	With outlier exclusion	417	25.0	24.2	15.2	57–73
Koerbin	Serum	BNP, eGFR	497	13.9	14.6	11.3	20–84
Roche hs-cTnT							
Giannitsis	Serum, plasma	Blood donors and apparently healthy subjects	616	13.5	14.5	10.0	20–71
Saenger	Serum, plasma	Questionnaire	533	14.2	15.5	8.9	20–71
Mingels	Serum	Cardiobiomarkers	479	16.0	18.0	8.0	26–71
Apple	Plasma	Blood donors and questionnaire	525	15.0	20.0	13.0	18–64

BNP indicates B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1C, glycated haemoglobin (A1c); hs-cTn, high-sensitivity cardiac troponin; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Source: Koerbin et al.[14]

study, which factors are used to determine the healthy cohort of patients included in the study and to exclude unhealthy participants and the methods used for excluding outliers (Table). The variation observed in the 99th centile in the United States (19 ng/L) and in Europe (14 ng/L) for the same hs Tn T assay[5] could be because of a true difference in the prevalence of pathology between the 2 regions or could be because of differences in the study designs determining the upper reference level.

WAY FORWARD

hs Tn illustrates how new diagnostic tests are often introduced into healthcare without a full understanding of their impact on clinical practice and outcomes. New diagnostic tests that alter the spectrum of positive diagnoses often cannot be assessed with traditional diagnostic accuracy studies and ultimately will require methods for determining which ways are best to categorize patients according to clinical factors: their impact on the prognosis of patients and response to treatment.[16] Prognostic studies require prospective cohorts accounting for all known prognostic factors, blinding of outcomes, and accounting for potential treatment effects. Determining how diagnostic tests affect response to treatment generally requires randomized controlled trials, but these are complicated by the need for study protocols to determine a priori the spectrum of patients that will be tested and a tight relationship between the test result and management decisions.[17] Trials of diagnostic tests also require large numbers as only participants with discordant results between the old and new test contribute to the differences in outcomes. Real-world implementation studies, such as the one conducted in Scotland, can be a useful compromise. We also need to find greater agreement on how to determine reference intervals.

Finally, we need better ways to determine when new tests are widening the definition of disease and whether this is of benefit or harm to patients. One of the first steps is the recently published checklist for groups considering a modification of a disease definition[18] (http://www.g-i-n.net/working-groups/overdiagnosis). Guideline committees and others need to consider how their changes to disease definitions will affect the prevalence of a disorder, the best available evidence on the potential harms and benefits of diagnosing disease in those newly labeled with the disorder, and whether these changes ultimately do more good than harm.

FOOTNOTES

Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org.

AFFILIATION

From the Centre for Research in Evidence Based Practice, Bond University, Gold Coast, Australia.

ACKNOWLEDGMENTS

We thank Katy Bell for her helpful comments on drafts and Sean Randall for providing data used in the Figure.

SOURCES OF FUNDING

We have received funding from the Australian National Health and Medical Research Council (NHMRC Fellowship No. 1080042, Centres of Research Excellence grant No. 1104136: Creating sustainable healthcare: ensuring new diagnostics avoid harms, improve outcomes and direct resources wisely, and Program grant No. 1113532: Using healthcare wisely: reducing inappropriate use of tests and treatments). The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

DISCLOSURE

None.

REFERENCES

1. Sandoval Y, Smith SW, Apple FS. Present and future of cardiac troponin in clinical practice: a paradigm shift to high-sensitivity assays. *Am J Med*. 2016;129:354–365. doi: 10.1016/j.amjmed.2015.12.005.
2. Korley FK. The wait for high-sensitivity troponin is over-proceed cautiously [published online ahead of print December 13, 2017]. *JAMA Cardiol*. doi: 10.1001/jamacardio.2017.4626.
3. Adamson PD, Hunter A, Madsen DM, Shah ASV, McAllister DA, Pawade TA, Williams MC, Berry C, Boon NA, Flather M, Forbes J, McLean S, Roditi G, Timmis AD, van Beek EJR, Dweck MR, Mickley H, Mills NL, Newby DE. High-sensitivity cardiac troponin I and the diagnosis of coronary artery disease in patients with suspected angina pectoris. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004227. doi: 10.1161/CIRCOUTCOMES.117.004227.
4. Nieman K, Galema TW, Mollet NR, de Feyter PJ, Krestin GP, Alkadhi H, Leschka S, Desbiolles L, Meijs MF, Cramer MJ, Knuuti J, Kajander S, Bogaert J, Goetschalckx K, Cademartiri F, Maffei E, Martini C, Seitun S, Aldrovandi A, Wildermuth S, Stinn B, Fornaro J, Feuchtner G, De Zordo T, Auer T, Plank F, Friedrich G, Pugliese F, Petersen SE, Davies LC, Schoepf UJ, Rowe GW, van Mieghem CA, van Driessche L, Sinitsyn V, Gopalan D, Nikolaou K, Bamberg F, Cury RC, Battle J, Maurovich-Horvat P, Bartykowszki A, Merkely B, Becker D, Hadamitzky M, Hausleiter J, Dewey M, Zimmermann E, Laule M. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. *BMJ*. 2012;344:e3485. doi: 10.1136/bmj.e3485.
5. Peacock WF, Baumann BM, Bruton D, Davis TE, Handy B, Jones CW, Hollander JE, Limkakeng AT, Mehrotra A, Than M, Ziegler A, Dinkel C. Efficacy of high-sensitivity troponin T in identifying very-low-risk patients with possible acute coronary syndrome [published online ahead of print December 3, 2017]. *JAMA Cardiol*. doi: 10.1001/jamacardio.2017.4625.
6. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Glob Heart*. 2012;7:275–295. doi: 10.1016/j.gheart.2012.08.001.
7. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50:2173–2195. doi: 10.1016/j.jacc.2007.09.011.
8. Sandoval Y, Smith SW, Schulz KM, Murakami MM, Love SA, Nicholson J, Apple FS. Diagnosis of type 1 and type 2 myocardial infarction using a high-sensitivity cardiac troponin I assay with sex-specific 99th percentiles based on the third universal definition of myocardial infarction classification system. *Clin Chem*. 2015;61:657–663. doi: 10.1373/clinchem.2014.236638.
9. Reichlin T, Twerenbold R, Reiter M, Steuer S, Bassetti S, Balmelli C, Winkler K, Kurz S, Stelzig C, Freese M, Drexler B, Haaf P, Zellweger C, Osswald S, Mueller C. Introduction of high-sensitivity troponin assays: impact on myocardial infarction incidence and prognosis. *Am J Med*. 2012;125:1205.e1–1213.e1. doi: 10.1016/j.amjmed.2012.07.015.
10. Potter JM, Simpson AJ, Kerrigan J, Southcott E, Salib MM, Koerbin G, Hickman PE. Cross-sectional study of high-sensitivity cardiac troponins T and I in a hospital and community outpatient setting. *Clin Biochem*. 2017;50:105–109. doi: 10.1016/j.clinbiochem.2016.10.011.
11. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155–2165. doi: 10.1056/NEJMoa0908610.
12. Randall SM, Zilkens R, Duke JM, Boyd JH. Western Australia population trends in the incidence of acute myocardial infarction between 1993 and 2012. *Int J Cardiol*. 2016;222:678–682. doi: 10.1016/j.ijcard.2016.08.066.
13. Mills NL, Churchhouse AM, Lee KK, Anand A, Gamble D, Shah AS, Paterson E, MacLeod M, Graham C, Walker S, Denvir MA, Fox KA, Newby DE. Implementation of a sensitive troponin I assay and risk of recurrent myocardial infarction and death in patients with suspected acute coronary syndrome. *JAMA*. 2011;305:1210–1216. doi: 10.1001/jama.2011.338.
14. Koerbin G, Abhayaratna WP, Potter JM, Apple FS, Jaffe AS, Ravalico TH, Hickman PE. Effect of population selection on 99th percentile values for a high sensitivity cardiac troponin I and T assays. *Clin Biochem*. 2013;46:1636–1643. doi: 10.1016/j.clinbiochem.2013.08.004.
15. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, Hashim I, Berry JD, Das SR, Morrow DA, McGuire DK. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. *JAMA*. 2010;304:2503–2512. doi: 10.1001/jama.2010.1768.
16. Glasziou P, Irwig L, Deeks JJ. When should a new test become the current reference standard? *Ann Intern Med*. 2008;149:816–822.
17. Bossuyt PM, Reitsma JB, Linnet K, Moons KG. Beyond diagnostic accuracy: the clinical utility of diagnostic tests. *Clin Chem*. 2012;58:1636–1643. doi: 10.1373/clinchem.2012.182576.
18. Doust J, Vandvik PO, Qaseem A, Mustafa RA, Horvath AR, Frances A, Al-Ansary L, Bossuyt P, Ward RL, Kopp I, Gollogly L, Schunemann H, Glasziou P; Guidelines International Network (G-I-N) Preventing Overdiagnosis Working Group. Guidance for modifying the definition of diseases: a checklist. *JAMA Intern Med*. 2017;177:1020–1025. doi: 10.1001/jamainternmed.2017.1302.

Circulation
Cardiovascular Quality and Outcomes

High-Sensitivity Troponin Highlights the Need for New Methods to Evaluate Diagnostic Tests

Jenny Doust and Paul Glasziou

Circ Cardiovasc Qual Outcomes. 2018;11:
doi: 10.1161/CIRCOUTCOMES.117.004468
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-7705. Online ISSN: 1941-7713