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Recommendations for the Use of Troponin
Assays for Rapid Diagnosis of Acute Coronary
Syndrome in the Emergency Department

Supporting Informed Decisions

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the “source documentation”) available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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TABLE OF CONTENTS

1	BACKGROUND	1
2	SUMMARY OF THE EVIDENCE	3
	2.1 Clinical Evidence	3
	2.2 Economic Evidence.....	4
3	SUMMARY OF RECOMMENDATIONS	5
4	REFERENCES	7
	APPENDIX 1: EXPERT PANEL AND CONTRIBUTORS	8
	APPENDIX 2: KEY POINTS FROM HTERP DELIBERATIONS	9
	APPENDIX 3: ABBREVIATIONS	10

1 BACKGROUND

Acute Coronary Syndrome (ACS) represents a spectrum of clinical presentations of myocardial ischemia ranging from ST-segment elevation myocardial infarction (STEMI) to non-STEMI (NSTEMI) and unstable angina (UA).¹⁻³ In Canada, there are roughly 60,000 hospital admissions for ACS annually, a figure that is expected to rise with an aging population.⁴ When patients with chest pain (or other symptoms suggestive of ACS) present at an emergency department (ED), investigations are rapidly conducted to rule out ACS.

STEMI is diagnosed by specific electrocardiogram (ECG) findings and is associated with a high risk of cardiac death. NSTEMI and UA are typically caused by myocardial ischemia but of differing severity depending on the presence of myocardial infarction (MI) and are often clinically indistinguishable because of the similarity in symptoms and transient or non-specific ECG findings of ischemia at presentation. In 2000, the European Society of Cardiology and the American College of Cardiology jointly redefined myocardial necrosis to incorporate cardiac troponin assays as a diagnostic determinant.⁵ In 2007, the European Society of Cardiology, the American College of Cardiology, and the American Heart Association updated the definition of MI and advocated a “rise and/or fall” of cardiac troponin during a six to nine-hour time period using the 99th percentile in a reference population as the cut-off for classifying an acute and evolving MI.³ The time frame for the assessment of cardiac troponin levels, after the first measurement, has been reduced to three to six hours in the third universal of MI (2012).⁶ Therefore, in patients with suspected MI but without ECG STEMI criteria, the troponin level is the discriminating criterion between NSTEMI and UA.

In Canada, there are two cardiac troponin tests available: cardiac troponin T and cardiac troponin I. In 2012, the manufacturer of the troponin T reagent started to remove the conventional reagent and replace it with a high-sensitivity troponin T assay reagent. High-sensitivity troponin I is not yet available, but its introduction to the market is expected in the near future. The troponin assays available in Canada are provided in Table 1. In the emergency medicine community, such a change is generating concern. A higher-sensitivity assay, with its increased ability to detect small differences in cardiac troponin levels over time, will potentially result in an earlier identification of those individuals experiencing an MI (as well as possibly identifying those who can be safely discharged from the ED with no further investigations).⁶ However, high-sensitivity assays are associated with lower specificity. Such lower specificity could potentially result in higher rates of clinically relevant false-positive tests; that is situations where patients are incorrectly identified as having NSTEMI. Up to 2% of the general population has elevations of high-sensitivity troponin T above the 99th percentile; these persons usually have conditions such as stable coronary artery disease, heart failure, renal failure, or left ventricular hypertrophy. Other conditions such as chronic pulmonary hypertension and pulmonary embolism have also been associated with elevated troponin levels.⁶ Therefore, the use of high-sensitivity cardiac troponin assays could lead to conducting additional investigations and undertaking more vascular interventions (e.g., angiogram). These additional investigations and interventions carry the potential to increase the pressure on EDs, cardiology referrals, and possibly cardiac catheterization suites. These could result in additional costs to the health care system and cause increased anxiety to patients.

Preparing clinicians on how to best to apply the high-sensitivity cardiac troponin test results is another important issue raised by their introduction in clinical practice. Many clinical algorithms incorporating troponin test results commonly used to diagnose ACS in the ED are based on studies of conventional troponin assays. For example, it is often recommended that patients

with troponin levels above the 99th percentile be “ruled in” as having an MI. Whether these algorithms can continue to be used with high-sensitivity troponin assays is uncertain; continued use of the 99th percentile threshold value may lead to additional patients being diagnosed with MI, when they may actually have other causes of their slightly elevated cardiac troponin levels. Further research based on new data will define the best algorithms to apply to the use of high-sensitivity cardiac troponin assays in clinical practice. In the interim, the optimal threshold values, timing of troponin tests, degree of change of troponin values between samples, and other issues covered by clinical algorithms for interpreting troponin results and diagnosing ACS remain uncertain.⁷

Table 1: Troponin Assays Available in Canada		
Test	Manufacturer	Product
Conventional Assays		
Troponin I	Abbott	AxSYM ADV
	Abbott	ARCHITECT
	Abbott	i-STAT ^a
	Alere	Triage ^a
	Alere	Triage Cardio2
	Alere	Triage Cardio3
	Beckman	Access AccuTnl
	bioMérieux	Vidas Ultra
	Ortho	Vitros ECi ES
	Response	RAMP ^a
	Siemens	Centaur XP Ultra
	Siemens	Dimension RxL
	Siemens	Dimension Vista
	Siemens	Immulite 2500
Siemens	Stratus CS ^a	
Troponin T	Roche	Cobas H232 ^a
	Roche	Elecsys TnT Gen 4
	Roche	Cardiac Reader cTnT ^a
High-Sensitivity Assays		
Troponin I	Abbott	Architect ^b
	Beckman	Access ^b
	Siemens	Vista ^b
Troponin T	Roche	Cobas E
	Roche	Elecsys

^aNear-patient/point-of-care testing systems.

^bHigh-sensitivity troponin I assays not commercially available in Canada.

Because of the availability of newer cardiac troponin assays, there is a need to independently compare the performance of high-sensitivity troponin T with conventional troponin T, conventional troponin I, and high-sensitivity troponin I as well as determine the comparative clinical and economic impact of using these tests.

Evidence-informed recommendations on the use of cardiac troponin for the rapid diagnosis of ACS in the ED were developed by the Health Technology Expert Review Panel (HTERP) to address the following policy questions:

- **Question 1:** In light of the discontinuation of the conventional cardiac troponin T assay and the development of high-sensitivity cardiac troponin assays to determine cardiac ischemia in patients presenting in the ED with chest pain, which of the other troponin assays should hospitals adopt? Does one of the troponin assays offer an advantage as compared with the others when used in the ED setting?
- **Question 2:** Are there evidence-based strategies available to optimize the use of troponin tests in the ED setting? For a particular troponin test, does one of these strategies result in better outcomes?

The clinical and economic evidence used for developing recommendations was derived from the following CADTH reports:

- The CADTH Optimal Use report: *High-Sensitivity Cardiac Troponin for the Rapid Diagnosis of Acute Coronary Syndrome in the Emergency Department: A Clinical and Cost-Effectiveness Evaluation*, consisting of a systematic review of clinical evidence and a primary economic model.
- A CADTH Rapid Response report summarizing and appraising information on point-of-care troponin testing.
- A CADTH Rapid Response report summarizing and appraising current clinical practice guidelines.
- A CADTH Environmental Scan describing current Canadian test use.

HTERP considered the evidence and its limitations from a population-based perspective. The anticipated benefits, harms, and cost-effectiveness of the various cardiac troponin assays were considered to be fundamental in the development of system-level recommendations.

2 SUMMARY OF THE EVIDENCE

2.1 Clinical Evidence

HTERP considered the results of a systematic review conducted to assess the accuracy of conventional and high-sensitivity troponin assays for the diagnosis of ACS in the ED. Diagnostic accuracy measures were estimated for the comparison between four possible tests: high-sensitivity troponin T, high-sensitivity troponin I, conventional troponin T, and conventional troponin I assays. Direct and indirect comparison methods were used.

The clinical evidence suggests that:

- Despite different assays and different cut-off points, the sensitivity values of high-sensitivity troponin tests were consistently higher than those of conventional troponin tests.
- Conventional troponin tests had lower sensitivity, but relatively higher specificity values; whereas, high-sensitivity troponin tests had higher sensitivity but lower specificity.
- High-sensitivity troponin I yielded the highest sensitivity for diagnosis of acute MI and conventional troponin T had the highest specificity.
- Patients' risk of MI at baseline or their previous history of ischemic heart disease had no effect on the sensitivity of high-sensitivity troponin T.
- At the 99th percentile cut-off point, high-sensitivity troponin T is overall statistically less accurate than high-sensitivity troponin I, conventional troponin T, and conventional troponin I.
- At the 99th percentile cut-off point, high-sensitivity troponin I is statistically more accurate than high-sensitivity troponin T, but not conventional troponin T and conventional troponin I. HTERP noted that the clinical relevance of this difference is likely marginal.
- No information of the effects of the various troponin tests on quality of life, readmission rates, and ED time until the diagnosis of MI was identified.

2.2 Economic Evidence

HTERP considered the results of a cost-utility analysis with high-sensitivity troponin T, high-sensitivity troponin I, and conventional troponin I, compared in terms of incremental cost per quality-adjusted life-year (QALY) gained. The population cohort entering the model were 65-year-old patients presenting to an ED with ischemic chest pain without ST-segment elevation ECG who require troponin testing for the diagnosis of NSTEMI. The analysis was taken from the perspective of a publicly funded health care system. The cost of drugs that are covered in the provincial formularies for eligible patients, in-patient costs, and physician fees for services that are covered in provincial fee schedules were included in the analysis. A lifetime horizon approach was used in the model.

The economic evidence suggests that:

- Among the test strategies, the model predicts high-sensitivity troponin T to have the highest expected per patient costs (\$2,186), followed by high-sensitivity troponin I (\$2,082) and conventional troponin I (\$2,018).
- The expected discounted number of QALYs was highest for high-sensitivity troponin T (8.1399) followed by high-sensitivity troponin I (8.1389) and conventional troponin I (8.1385).
- The base-case economic analysis estimated the incremental cost-effectiveness ratio of high-sensitivity troponin T compared with conventional troponin I to be \$119,377 per QALY.
- The testing strategy of high-sensitivity troponin I was extendedly dominated by conventional troponin assays and high-sensitivity troponin T.
- The analysis was sensitive to NSTEMI prevalence; NSTEMI one-year mortality; and mortality differences between patients treated early, late, and not at all. The analysis was also sensitive to assumptions on the proportion of initial positive patients that would be admitted to hospital, the cost of a false-positive hospitalization, and the proportion of patients with initial false-negative results that would become true positives with the second troponin tests.
- Findings were not sensitive to the cost per high-sensitivity troponin T assay.
- The economic evaluation did not account for the capital costs of the analyzers needed to conduct the various assays. These capital costs can be substantial and laboratories are often bound by time-specific contracts with manufacturers. HTERP therefore noted that there may be constraints on switching to a different troponin test that requires the purchase of a new analyzer.

3 SUMMARY OF RECOMMENDATIONS

Recommendation 1: HTERP recommends conventional cardiac troponin I when considering the selection of a cardiac troponin assay, in institutions using clinical algorithms based on conventional troponin data.

Recommendation 2: HTERP recommends that at this time institutions using conventional cardiac troponin I do not change their assay.

Recommendation 3: HTERP recommends that at this time institutions using high-sensitivity cardiac troponin T do not change their assay.

Statement: HTERP encourages further research exploring different clinical algorithms to optimize patient and health system outcomes associated with high-sensitivity cardiac troponin testing.

Detailed information regarding the reasons for the HTERP recommendations and statement is provided below. To assist with the interpretation of the recommendations and provide commentary relating to the evidence, key points from HTERP deliberations are noted in Appendix 2.

1. HTERP recommends conventional cardiac troponin I when considering the selection of a cardiac troponin assay, in institutions using clinical algorithms based on conventional cardiac troponin data.

Reasons for Recommendation 1:

- Based on indirect comparisons, the overall diagnostic accuracy of the high-sensitivity cardiac troponin T assay at the 99th percentile is statistically lower than that of both conventional cardiac troponin T and conventional cardiac troponin I assays.
- Based on indirect comparisons, the overall diagnostic accuracy of the conventional cardiac troponin I at the 99th percentile is statistically higher than that of the high-sensitivity cardiac troponin T.
- With the clinical algorithms currently in clinical use, the conventional troponin I assay appears to be the most cost-effective when compared with high-sensitivity cardiac troponin I and troponin T assays.
- Commonly used algorithms are based on conventional troponin data. Further research is required to define the best algorithms to apply to the use of high-sensitivity cardiac troponin assays in clinical practice.

2. HTERP recommends that at this time institutions using conventional cardiac troponin I do not change their assay.

Reasons for Recommendation 2:

- Based on indirect comparisons, the overall diagnostic accuracy of the conventional cardiac troponin I at the 99th percentile is statistically higher than that of the high-sensitivity cardiac troponin T.
- The difference in the overall diagnostic accuracy between the conventional cardiac troponin I and the high-sensitivity cardiac troponin I assays is not statistically significant.
- Using the current clinical algorithms, the conventional cardiac troponin I assay appears to be the most cost-effective assay when compared with high-sensitivity cardiac troponin I and troponin T assays.

3. HTERP recommends that at this time institutions using high-sensitivity cardiac troponin T do not change their assay.

Reasons for Recommendation 3:

- Based on indirect comparisons, the overall diagnostic accuracy of the high-sensitivity cardiac troponin T assay at the 99th percentile is statistically lower than that of both the conventional cardiac troponin T and conventional cardiac troponin I assays; however, the clinical significance of this difference is likely marginal, and therefore, there is no advantage to replacing high-sensitivity cardiac troponin T at this time.
- The high-sensitivity cardiac troponin T does not appear to be cost-effective when compared with the conventional troponin I assay; however, the economic evaluation did not consider the cost of implementing new instrumentation for the replacement troponin assay, which may be associated with increased costs.
- If other factors indicate the possibility of changing assays (i.e., reaching the end of a capital equipment change cycle), Recommendation 1 would apply.

4. Statement: HTERP encourages further research exploring different clinical algorithms to optimize patient and health system outcomes associated with high-sensitivity cardiac troponin testing.

Reasons for statement:

- Peer-reviewed, published evidence regarding optimal clinical algorithms for high-sensitivity cardiac troponin testing was identified as a research gap.
- No evidence was available to HTERP on different testing algorithms; however, they noted that such evidence may exist but did not meet the criteria for inclusion in the systematic review.
- There is a lack of consensus in clinical practice guidelines on the optimal use of troponin tests.
- There are no recent Canadian guidelines on the use of cardiac troponin tests.
- Optimized testing algorithms, as opposed to those currently used, may affect the cost-effectiveness of high-sensitivity troponin tests.

4 REFERENCES

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APPENDIX 1: EXPERT PANEL AND CONTRIBUTORS

HTERP consists of five Core Members appointed to serve for all topics under consideration during their term of office, and up to four Specialist Members appointed to provide their expertise for a specific topic. For this project, three Specialist Experts were appointed; their expertise included cardiology, emergency medicine, and medical biochemistry. The Core Members include individuals with qualifications in evidence-based medicine and/or critical appraisal, including a Chair, an ethicist, a health economist, a health care practitioner, and one Public Member who represents the broad public interest.

HTERP is an advisory body to CADTH and is convened to develop guidance or recommendations on non-drug health technologies to inform a range of stakeholders within the Canadian health care system.

HTERP Members

Dr. Devidas Menon, Chair
Professor and Interim Chair
Department of Public Health Sciences
School of Public Health
University of Alberta

Dr. Stirling Bryan
Director, Centre for Clinical Epidemiology & Evaluation
Vancouver Coastal Health Research Institute
Professor, School of Population & Public Health
University of British Columbia

Dr. Charlotte Moore Hepburn
Pediatrician, The Hospital for Sick Children
Assistant Professor, Department of Pediatrics
University of Toronto

Ms. Anita Fineberg
Public Member

Dr. Lisa Schwartz
Arnold L. Johnson Chair in Health Care Ethics
Department of Clinical Epidemiology and Biostatistics
Centre for Health Economics and Policy Analysis
McMaster University

Specialist Members

Dr. Ron Booth
Clinical Biochemist, Division of Biochemistry
The Ottawa Hospital
Assistant Professor, Department of Pathology and Laboratory Medicine
University of Ottawa

Dr. Steve Clark
Emergency Physician
Division of Emergency Medicine
Alberta Health Services, Calgary Zone Adult Sites
Clinical Lecturer, University of Calgary

Dr. James Tam
Chief of Cardiology
University of Manitoba

Conflict of Interest

No members declared any conflicts of interest. *Conflict of Interest Guidelines* are posted on the CADTH website.

APPENDIX 2: KEY POINTS FROM HTERP DELIBERATIONS

During deliberation, HTERP noted:

- When comparing conventional troponin I testing with high-sensitivity troponin T testing for the diagnosis of ACS at a single cut-off point of the 99th percentile, high-sensitivity troponin T does not appear to be cost-effective. This conclusion is even more apparent when comparing conventional troponin I with high-sensitivity troponin I.
- There are potential patient risks associated with both the conventional and high-sensitivity tests. Lower sensitivity of the conventional troponin assays may result in sending home symptomatic patients without a diagnosis. However, the lower specificity of the high-sensitivity test may lead to increased follow-up testing and procedures for patients with false-positive tests, leading to unnecessary risk and anxiety for patients (i.e., ionizing radiation), increased costs, and increased utilization of limited resources.
- There are non-ACS causes of troponin elevation. Some patients who falsely test positive for ACS may still have a different condition that needs to be treated. HTERP chose not to address this in the recommendations because it was outside the scope of the systematic review.
- The clinical and cost-effectiveness analyses were based on current serial (test/re-test) testing algorithms at a single cut-off of the 99th percentile. It was noted that high-sensitivity tests may be able to replicate conventional assay results by adjusting the cut-off or threshold value to avoid the consequences of poor test specificity. It was suggested that with improved diagnostic testing algorithms and clinical practices to reduce the risks and costs associated with non-ACS related troponin elevations, high-sensitivity troponin T may be the preferred assay.
- While the Optimal Use troponin science report included a cost-effectiveness analysis, the financial impact of switching troponin assays, including the capital cost of acquiring new instruments, was not considered.
- The ability of hospitals to switch assays may be limited by such factors as existing vendor contracts and the fact that multiple tests, other than troponin assays, are conducted with a single analyzer.
- There is no compelling reason for hospitals to make an immediate change in troponin assay choice, if outside a capital equipment change cycle. When evaluating a new instrument, then HTERP's Recommendation 1 should be considered.

APPENDIX 3: ABBREVIATIONS

ACS	acute coronary syndrome
ECG	electrocardiogram
ED	emergency department
HTERP	Health Technology Expert Review Panel
MI	myocardial infarction
NSTEMI	non-ST-segment elevation myocardial infarction
QALY	quality-adjusted life-year
STEMI	ST-segment elevation myocardial infarction
UA	unstable angina