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# Point-of-care testing with high-sensitivity cardiac troponin assays: the challenges and opportunities

Louise Cullen <sup>1</sup>, Paul O Collinson <sup>2</sup>, Evangelos Giannitsis<sup>3</sup>**Handling editor** Richard Body<sup>1</sup>Emergency and Trauma Centre, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia<sup>2</sup>Departments of Clinical Blood Sciences and Cardiology, St George's University of London, London, UK<sup>3</sup>Medical Department III, University Hospital Heidelberg, Heidelberg, Germany**Correspondence to**Dr Louise Cullen, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia; [louise.cullen@health.qld.gov.au](mailto:louise.cullen@health.qld.gov.au)

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**ABSTRACT**

Methods to improve the safety, accuracy and efficiency of assessment of patients with suspected acute coronary symptoms have occupied decades of study and have supported significant changes in clinical practice. Much of the progress is reliant on results of laboratory-based high-sensitivity cardiac troponin assays that can detect low concentrations with high precision. Until recently, point-of-care (POC) platforms were unable to perform with similar analytical precision as laboratory-based assays, and recommendations for their use in accelerated assessment strategies for patients with suspected acute coronary syndrome has been limited. As POC assays can provide troponin results within 20 min, and can be used proximate to patient care, improvements in the efficiency of assessment of patients with suspected acute coronary syndrome is possible, particularly with new high-sensitivity assays.

This manuscript evaluates the point-of-care (POC) testing of cardiac troponin (cTn) including new high-sensitivity (hs) assays, highlights current clinical assessment practices for patients with possible acute coronary syndromes (ACS) and forecasts future opportunities with use of such assays.

The high burden of cardiovascular disease, and that of ACS in particular, within society has significant impact on patients, clinicians and healthcare services. Symptoms of chest pain, indicative of possible acute myocardial infarction (AMI), are one of the most common causes for ED presentations worldwide, with suspected patients with ACS accounting for approximately 10% of all emergency visits.<sup>1</sup> Decades of investigation into methods to improve the safety, accuracy and efficiency of assessment practices for patients with chest pain and suspected ACS have supported significant change in clinical practice.<sup>2,3</sup>

Many of the advances in clinical care are reliant on laboratory-based hs-cTn assays,<sup>3</sup> with the greatest benefits realised in hospital-based care in large institutions.<sup>4</sup> These cTn assays, used for the detection of myocardial injury,<sup>2</sup> allow the detection of low concentrations with high precision.<sup>5</sup> POC platforms are available, yet until recently the ability for this modality to perform with the accuracy and precision of laboratory-based cTn assays has been unattainable.<sup>6-9</sup> This paper reviews the state of the art of POC cTn assays, highlights current clinical assessment practices for patients with possible ACS and forecasts future opportunities with true hs POC assays.

**THE ROLE OF TROPONIN AND USE OF TROPONIN ASSAYS**

To understand the significant changes in this practice area, it is important to be aware of two key events that occurred following the introduction and subsequent development of cTn assays. First, the change from diagnosis using creatine kinase MB to cTn increased the risk of a biochemical false-positive from 0.044% (classified as abnormal when more than twice the 97.5th reference limit) to 1% (abnormal when above the 99th percentile).<sup>10-12</sup> The second is the improvement in troponin assays. Early assays had inadequate sensitivity for detection of troponin. Progressive improvements in assay sensitivity combined with the use of the 99th percentile resulted in previously undiagnosed myocardial injury being detectable in a range of clinical conditions.<sup>2</sup> Currently, hs-cTn assays are in routine clinical use in many laboratories and are defined by two criteria. First, the coefficient of variation (CV) at the 99th percentile upper reference limit should be  $\leq 10\%$ , and second that measurable concentrations should be attainable at a concentration at or above the assay's limit of detection (LoD) for  $>50\%$  of healthy individuals.<sup>13</sup> Hence, hs-cTn assays represent the reference analytical standard against which diagnostic strategies must now be compared.

To date, in each clinical situation where troponin elevation has been detected and where myocardial infarction (MI) or ACS is not suspected, the troponin elevation has been shown to be prognostic. More troponin is worse than less troponin and no troponin is better than any troponin. Troponin measurement remains an excellent rule-out test. Use of the term 'troponinitis' is trivialising and clinically dangerous.<sup>14</sup> Any elevated troponin requires explanation, yet not necessarily catheterisation or a cardiologist review.

Evidence for the clinical use of hs-cTn assays in patients presenting with chest pain has recently been reviewed and recommended for the early rule-out of MI.<sup>3, 15</sup> Such assays have also been described within rapid predictive algorithms by the European Society of Cardiology<sup>3</sup> and although data are included about POC hs-cTn assays, the recommendations at the time of writing are for use of laboratory-based assays. This is congruent with recommendations from the National Institute for Health and Care Excellence guidelines<sup>15</sup> that suggest further evaluation of the performance of POC cTn assays using whole blood samples (rather than stored plasma samples) is required before clinical use.



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**Table 1** Performance characteristics of POCT troponin assays<sup>8 16 18</sup>

Assay	Platform	Company	Concentration at 10% CV	Specimen type	99th percentile	Per cent normals measured $\geq$ LoD	Assay type/device
hs-cTnI	Atellica VTLi	Siemens	NP (20% CV 6.7 ng/L)	Li-heparin plasma	Overall: 23 ng/L F: 18 ng/L M: 27 ng/L	Overall: 83.7% F: 79.7% M: 87.3%	hs; cds
hs-cTnI/cTnI-II	PATHFAST	LSI Medience (formerly Mitsubishi)	15 ng/L	Heparin-Na, heparin-Li or EDTA whole blood or plasma	Overall: 27.9 ng/L F: 20.3 ng/L M: 29.7 ng/L	Overall: 66.3% F: 52.8% M: 78.8%	hs; cds
hs-cTnI	TriageTrue	Quidel/Alere	4.4–8.4 ng/L (plasma) 5.8–6.2 ng/L (whole blood)	EDTA whole blood or plasma	Overall: 20.5 ng/L F: 14.4 ng/L M: 25.7 ng/L	Overall: $\geq$ 50%	hs; bls
cTnI test pack	STRATUS CS Acute Care	Siemens	0.06 $\mu$ g/L	Whole blood (Li or NP heparin) or plasma Li or Na heparin	Overall: 0.07 $\mu$ g/L		cs; bls
TnI	AQT90 FLEX	Radiometer	0.027 $\mu$ g/L	EDTA and heparinised whole blood and plasma	Overall: 0.023 $\mu$ g/L		cs; bls
TnT	AQT90 FLEX	Radiometer	0.026 $\mu$ g/L	EDTA and heparinised whole blood and plasma	Overall: 0.017 $\mu$ g/L		cs; bls
Troponin I	RAMP	Response Biomedical	0.21 $\mu$ g/L	Only EDTA whole blood	Overall: <0.10 $\mu$ g/L		Non-hs/cs; bls
cTnI	i-STAT	Abbott	0.1 $\mu$ g/L	Na and Li heparinised whole blood and plasma	Overall: 0.08 $\mu$ g/L		Non-hs/cs; cds
Cardiac POC troponin T	Cobas h 232	Roche	9.3% between 0.04 and 0.2 $\mu$ g/L	Heparinised whole blood	NP		Non-hs/cs; cds

Adapted from the International Federation of Clinical Chemistry and Laboratory Medicine—Clinical Applications of Cardiac Bio-Markers Updated tables (<https://www.ifcc.org/media/477653/point-of-care-cardiac-troponin-i-and-t-assay-analytical-characteristics-designated-by-manufacturer-v012019.pdf>).  
bls, bedside use; cds, compact desktop systems; cs, contemporary sensitivity; CV, coefficient of variation; hs-cTnI, high-sensitivity cardiac troponin I; Li, lithium; Na, sodium; NP, not provided; POCT, point-of-care test; TnI, troponin I; TnT, troponin T.

### POINT-OF-CARE TROPONIN ASSAYS

The performance characteristics of point-of-care test (POCT) troponin assays is summarised in [table 1](#),<sup>16</sup> including newer assays that reach the analytical classification of hs assay. In addition to classification based on analytical performance, they can also be divided into compact desktop systems aimed solely at bedside use, and larger systems suitable for close to patient operation or use in an emergency testing facility. The analytical and clinical performance characteristics of these systems have been examined in independent evaluations.<sup>6–9 17 18</sup> Evaluation has occurred using the same criteria as laboratory-based assays to a predicate method of comparable analytical sensitivity. In addition, three new prototype systems have been documented that have the potential for clinical use.<sup>18–20</sup>

Most evaluations of POCT troponin assays have been based on the ability to achieve comparable diagnostic classification for MI in comparison with laboratory-based assays, with diagnosis based on being able to detect troponin above the 99th percentile 3–6 hours from presentation. POCT assays meeting contemporary sensitive criteria are reliable for ruling in AMI on admission for samples exceeding the 99th percentile,<sup>9</sup> yet may require sampling up to 6 hours postadmission for safe rule-out.<sup>21</sup>

### Laboratory-based assays and accelerated diagnostic pathways

Clinical studies of POC testing can be divided into those evaluating clinical diagnostic performance and those assessing the

impact of these tests on patient flow and cost economics. The early POC studies, including Randomised Assessment of Treatment using Panel Assay of Cardiac markers (RATPAC) and Asia Pacific Evaluation of Chest pain Trial (ASPECT), evaluated older multimarker approaches incorporating creatine kinase, myoglobin and troponin.<sup>22 23</sup> These protocols enabled safe identification of low-risk patients who could be discharged early from hospital-based care. The subsequent introduction of laboratory-based troponin assays with higher analytical sensitivity and precision, enabled more accurate detection of small infarcts as well as faster diagnosis, and saw the interest in multimarker POC platforms falter. However, contemporary POC assay results incorporated into strategies with risk scores have been shown to be safe and accurate when compared with laboratory-based hs assay strategies. For example, the Troponin-only Manchester Acute Coronary Syndromes decision aid using POC cTnT results may enable one-third of ED patients to have ACS ruled out within 3 hours.<sup>24</sup> Additionally, the early measurement and detection of significant troponin elevation to rule-in MI using POC assays, including less sensitive systems has been shown.<sup>25</sup> Overall, however, the efficiency of contemporary POC clinical strategies cannot compete with the optimised laboratory-based hs-cTn protocols.

As there are no guideline-recommended accelerated diagnostic pathways using either contemporary or hs POC assays<sup>215</sup> to consider the benefits, an understanding of the utilisation of laboratory-based hs-cTn assays is crucial. Very low hs-cTn concentrations at admission,

**Table 2** Overview on the performance of fast rule-out strategies based on single and serial blood draw at 0 hour/1 hour

Test principle	Company	Meta-analysis cohorts	Troponin (ng/L)	Sensitivity (pooled)	NPV (pooled)	Proportion eligible for rule-out	Event rate after rule-out		
							MACE	Death	MI
<b>0-hour rule-out: single hs-cTnT &lt;LoD (SMS)</b>									
Pickering, <i>et al</i> <sup>29</sup>	hs-cTnT	11 cohorts 9241 patients	<LoD (<5 ng/L)	98.7% (96.6 to 99.5)	99.3% (97.3 to 99.8)	30.60%	21/8059	1.30%	14/8059
<b>ESC 0/1 hour: either very low 0 hour &lt;LoD or low hs-cTn and small <math>\delta</math> between 0 and 1 hour</b>									
Chiang, <i>et al</i> <sup>28</sup>	hs-cTnI	Abbott	4 cohorts	98.1% (94.6 to 99.3)	99% (96.0 to 100)	50.00%	NA	0.10%	NA
15 cohorts: 11 014 patients	hs-cTnI	Siemens	4 cohorts	98.7% (97.3 to 99.3)	100% (99 to 100)	51.00%	NA	0.10%	NA
	hs-cTnT	Roche	7 cohorts 7744 patients	98.4% (95.1 to 99.5)	99.6% (99.0 to 99.9)	55.00%	NA	0.10%	NA

ESC, European Society of Cardiology; hs-cTnI, high-sensitivity cardiac troponin I; LoD, limit of detection; MACE, major adverse cardiac events; MI, myocardial infarction; NA, not available; NPV, negative predictive value; SMS, single marker strategy.

defined as hs-cTn close to or below the LoD in patients presenting more than >2 hours after onset of symptoms, may rule-out an MI without the need for re-testing.<sup>3</sup> The option to rule-out an MI using a single, very low hs-cTn concentration is particularly interesting for accelerating assessment and enabling discharge of low-risk patients from busy EDs.<sup>26 27</sup> Strong evidence supporting the safety and efficacy of instant and early rule-out protocols using laboratory-based assays exists (table 2).<sup>28 29</sup> Care is needed in utilisation of such strategies though, as some patients are not able to precisely state the onset of their symptoms or to recall the exact time of the last chest pain episode. The proportion of patients who qualify for the 0-hour rule-out option is around 30% in a meta-analysis that included 11 cohorts with a total of 9241 participants.<sup>29</sup>

For patients not meeting the criteria for single troponin testing, the interval between serial measurements should be long enough to overcome the troponin-blind period that is typically seen following the early hour(s) of an MI.<sup>3</sup> Validated algorithms that allow for an earlier detection of an MI with re-testing using a hs assay after 1, 2 or 3 hours instead of 6–9 hours that were recommended with less-sensitive troponin assays.<sup>3</sup> At this stage, the algorithms are used to predict either a low probability (rule-out) or a high probability (rule-in) of a diagnosis of MI on follow-up and do not use the 99th percentile upper limit of normal.<sup>3</sup> They use lower thresholds and concentration changes optimised to rule-out MI with a sensitivity of >99% or higher thresholds to rule-in with a specificity of >75%. When diagnosis is uncertain, patients are classified to an intermediate risk zone and subsequent testing is recommended.

Serial testing of troponin is also required to detect a relevant rise or fall, a key principle to discriminate acute from chronic myocardial injury.<sup>2</sup> Serial testing of troponin within 3 hours after the initial blood sample helps to establish an earlier diagnosis (rule-in) of non-ST-segment elevation myocardial infarction (NSTEMI), provided an hs-cTn assay is being used. Several strategies exist, with the 2020 European Society of Cardiology Guidelines on NSTEMI-ACS<sup>4</sup> recommending the 0-hour to 1-hour algorithm in preference to the 0-hour to 3-hour algorithm. The 0-hour to 2-hour algorithm is recommended as an alternative. Faster diagnostic algorithms seem to perform reliably in patients with pre-existing structural heart disease, chronic kidney disease and older adults, although

proportion of patients who qualify for early rule-out MI decline, due to the high prevalence of chronic elevation of troponin.

### Accuracy of POC hs-cTn

Recent studies suggest that new POC hs-cTn assays are comparable to laboratory-based assays and that early assessment strategies (0-hour and 0-hour to 1-hour protocols) may also be achievable (table 3).<sup>6 7</sup> These studies have reported potential benefits, although used stored, rather than whole, blood.<sup>6 7 20</sup> These studies show promise in that early rule-out using single samples and serial sampling strategies may be able to safely manage emergency patients with suspected ACS. However, a criticism of all these studies is that they have been performed using stored serum or plasma in controlled environments. Although studies demonstrate comparable diagnostic performance with laboratory-based assay they have not been performed using whole blood in the POC ED environment. However, one recent study of an hs-cTn POC assay has compared results using both whole blood and plasma has shown results that are analytically equivalent.<sup>30</sup> The theoretical health service benefits of rapid assessment strategies using POC hs-cTn assays described now require evaluation when implemented into clinical practice.

### Potential role of POC assays

A key benefit of POC assays is the short turnaround time with most reporting <20 min from testing to results.<sup>6–9 19 20</sup> With the need for serial cTn testing, older POC cTn assays have shown conflicting results in terms of reduced ED length of stay and economic benefits,<sup>31–33</sup> yet have been shown to improve the speed with which patients with AMI are identified.<sup>34</sup> Indeed the recent Providing Rapid Out of Hospital Acute Cardiovascular Treatment 4 (PROACT-4) trial, where POC troponin was tested in the ambulance setting, reported only modest time-savings (0.3 hour) from first medical contact to discharge from ED or admission.<sup>35</sup> As no studies have reported the impact of utilisation of POC hs-cTn assays in actual patient care (due to the newness of this technology), our understanding of the effects of accelerated risk stratification on health systems is also derived from reports using laboratory-based assays. Patient risk stratification and management practices vary

**Table 3** Results from diagnostic accuracy studies of POCT hs-cTn assays at presentation for the diagnosis of AMI

POC assay	AUC (95% CI)	Comparator assay	AUC (95% CI)	Patients	AMI rate
PATHFAST POC hs-cTn <sup>7</sup> (plasma)	0.91 (0.89 to 0.93)	cTnI-Architect (fresh serum or plasma)	0.90 (0.87 to 0.92)	1279	134 (20%)
i-STAT TnI-Nx <sup>20</sup> * (plasma)	0.97 (0.96 to 0.99)	cTnI-Architect (plasma)	0.97 (0.95 to 0.99)	354	57 (16%)
Minicare POC hs-cTn <sup>9</sup> (whole blood)	0.88 (0.83 to 0.94)	cTnI-Architect (serum or plasma)	0.91 (0.87 to 0.95)	450	72 (16%)
		I-Stat POC cTnI	0.88 (0.82 to 0.94)		
Triage True POC hs-cTn <sup>6</sup> (plasma)	0.95 (0.93 to 0.96)	cTnT Elecsys (serum or plasma)	0.94 (0.93 to 0.96)	1261	178 (14%)
		cTnI-Architect (serum or plasma)	0.92 (0.90 to 0.93)		

\* Analytical studies of this assay are pending.  
AMI, acute myocardial infarction; AUC, area under the curve; hs-cTnI, high-sensitivity cardiac troponin I; POCT, point-of-care test.

considerably between hospitals, countries and continents. Adoption of accelerated assessment strategies has been shown to have significant benefits for health services internationally, including sites in Europe and Australia.<sup>4 26 27 36</sup> Rates of major adverse cardiovascular events at 30 days in low-risk patients postadoption of strategies remain low (<1%).<sup>36</sup> The effects of implementation of a 0-hour to 1-hour algorithm was evaluated by two registries reporting that more patients could be discharged, with shorter lengths of stay in the ED, and without an excess of resources for work-up compared with the 0-hour to 3-hour protocol.<sup>26 27</sup> Notably, rates of coronary angiography and functional testing remained consistently low after implementation of the 0-hour to 1-hour protocol instead of the 0-hour to 3-hour protocol. A similar finding has been reported in the High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome (High-STEACS) and High-Sensitivity Cardiac Troponin on Presentation to Rule Out Myocardial Infarction (HiSTORIC) trials.<sup>37 38</sup> In contrast, the randomised Rapid Assessment of Possible ACS in the Emergency Department With High-Sensitivity Troponin T (RAPID-TnT) study evaluating a 0-hour to 1-hour protocol and 0-hour to 3-hour protocol showed the use of invasive coronary investigation was increased among patients with newly identified low-concentration troponin elevations.<sup>36</sup>

Although diagnostic protocols are getting faster and demonstrate additional benefits including safety of discharge, reduction of the length of ED stay and cost-effectiveness, the global implementation rate of hs troponin assays is far behind expectations. A 2019 survey<sup>39</sup> found that only 41% of hospitals worldwide use hs-cTn assays and <10% implement a 0-hour/1-hour or 0-hour/2-hour protocol. Possible reasons for this include infrastructural barriers that hinder embracing the benefits of shorter turnaround times for results, which may be negated by access to hs POC assays.

### The future of POC troponin assays

Within the busy ED, opportunities to safely improve the efficiency of assessment of patients are welcomed. POC analysis of key biomarkers enables clinicians to have results proximate to care, assisting in diagnosis and disposition planning. With the advent of POC hs-cTn assays, the potential of a single analysis of cTn (0 hour only) with the ability to immediately rule-out an AMI for some patients needing evaluation for possible MI is attractive, and may improve efficiency in assessment if this strategy is adopted into clinical care.<sup>3</sup> A key dependency on the impact of POC devices is confidence that results are reliable and accurate, and that all pathology investigations that are required are available. Consideration of the

entire process of assessment is paramount for effective utilisation of POC testing. For example, without additional investigation results, such as haemoglobin, electrolytes and creatinine being readily available, POC hs-cTn assays may not have a significant impact on ED efficiency. The literature to date illustrates that it is not the provision of rapid cTn results alone that is important but their inclusion within a clinical decision-making pathway.<sup>32</sup> Widespread adoption of change also requires systematic clinical redesign of assessment pathways to achieve maximum impact.<sup>4</sup>

Currently, most patients with proximate symptoms of suspected ACS are referred to places where definitive risk stratification can occur. Access to POC hs-cTn assays may change this, yet this would be reliant on several key issues being addressed. These issues include the availability of POC hs-cTn, a proven record of safety and accuracy in ruling out AMI on a single blood draw, and potentially that samples are able to be performed using finger stick (rather than a technically more complex venepuncture) to enable less skilled personnel to accurately test. If these issues are addressed, primary care physicians (who in many places around the world currently perform and report ECGs) would also be able to assess and rule-out the need for patients at low risk of an MI being referred to local EDs. Such use of in the primary care setting may be highly beneficial to safely identify low-risk patients due to the lower prevalence of ACS in this cohort. A similar strategy may be supported in cardiologists' rooms or outpatients where at-risk patients may be seen.

Correct identification of higher risk patients for NSTEMI in the prehospital setting may also prove valuable.<sup>40</sup> Variation in the in-hospital management of patients with AMI occurs, correlating with the availability of cardiac procedures<sup>41</sup> and patients with NSTEMIs or other acute cardiac conditions are ideally managed with specialist cardiac care. The ability to identify patients suspected of having ACS early with elevated troponin values in the prehospital phase of care may support the correct disposition of patients and avoid the need for secondary transfer<sup>42</sup> reducing burden on healthcare and ambulance services. The results of studies into prehospital use of POC assays currently underway are eagerly awaited, including those from the Acute Rule out of non ST-segment elevation acute coronary syndrome in the (pre)hospital setting by HEART score assessment and a single point of Care troponin (ARTICA)<sup>43</sup> and Pre-hospital Evaluation of Sensitive Troponin (PRESTO)<sup>44</sup> trials.

### CONCLUSION

The evolution of troponin assays continues, and POCT hs-cTn assays soon will become more widely accessible. Evidence is required to ensure that emerging POCT hs-cTn assays meet both analytical and

clinical needs, and robust redesign of models of care will be needed to maximise the potential benefits. Randomised controlled trials incorporating POCT hs-cTn are required to identify the impact on assessment of patients with suspected ACS in emergency, prehospital and primary care settings.

**Twitter** Louise Cullen @louiseacullen

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#### ORCID iDs

Louise Cullen <http://orcid.org/0000-0001-6611-8229>

Paul O Collinson <http://orcid.org/0000-0002-7000-5996>

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