Diagnostic Performance of Prehospital Point-of-Care Troponin Tests to Rule Out Acute Myocardial Infarction: A Systematic Review

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Abbreviations:
ACS: acute coronary syndrome
AMI: acute myocardial infarction
CK-MB: creatine kinase-myocardial band isoenzyme
cTn: cardiac troponin
ECG: electrocardiogram
ED: emergency department
HEAR: History, ECG, Age, and Risk Factors
HEART: History, ECG, Age, Risk Factors, and Troponin
HE-MACS: History and ECG-Only Manchester Acute Coronary Syndromes
NPV: negative productive value
POC: point-of-care
PPV: positive predictive value
QUADAS: Quality Assessment of Diagnostic Accuracy Studies
STEMI: ST-elevation myocardial infarction
T-MACS: Troponin-Only Manchester Acute Coronary Syndrome

Abstract

Introduction: Chest pain is one of the most common reasons for 999 calls and transfers to the emergency department (ED). In these patients, acute myocardial infarction (AMI) is often the diagnosis that clinicians are seeking to exclude. However, only a minority of those patients have AMI, causing a substantial financial burden to health services. Cardiac troponin (cTn) is the reference standard biomarker for the diagnosis of AMI. Several commercially available point-of-care (POC) cTn assays are portable and could feasibly be used in an ambulance. The aim of this paper is to systematically review existing evidence for the use of POC cTn assays in the prehospital setting to rule out AMI.

Methods: A systematic search was conducted on EMBASE, MEDLINE, and CINAHL Plus databases, reference lists, and relevant grey literature, including combinations of the relevant terms. Papers published in English language since the year 2000 were eligible for inclusion. A narrative synthesis of the evidence was then undertaken.

Results: The initial search and cross-referencing revealed a total of 350 papers, of which 243 were excluded. Seven papers were included in the systematic literature review.

Conclusion: Current evidence does not support the use of POC troponin assays to exclude AMI due to issues with diagnostic accuracy and insufficient high-quality evidence.

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Introduction

Accurately "ruling out" and "ruling in" acute myocardial infarction (AMI) presents a huge challenge for both physicians and paramedics, especially for a patient presenting with recent onset of chest pain or discomfort without clear electrocardiogram (ECG) abnormalities.[1,2] A missed myocardial infarction has a substantial negative impact due to the high mortality and morbidity. However, timely treatment for AMI (such as revascularization) can improve the patient prognosis and decreases the risk of mortality. Despite the importance of early AMI recognition, it is difficult to do this in the prehospital environment. It remains time-consuming in the emergency department (ED) in those patients without clear ECG abnormalities.

The current literature demonstrates that cardiac troponin (cTn) assays have become essential for the diagnosis of AMI.[3] There is now the possibility of a transition to portable

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point-of-care (POC) cTn assays, as they are now commercially available and enable near-patient analysis of cardiac biomarkers taking less than 20 minutes. In comparison, central laboratory-based testing takes up to two hours (after accounting for sample logistics), is not mobile, and requires large capital investment with specialist technical skills. The rapid turnaround time of POC assays could help to expedite decision making and facilitate the provision of rapid treatment for patients with myocardial injury. This is particularly apparent in patients without evidence of ischemia on an ECG. Goodacre, et al demonstrated that POC testing could reduce the period of diagnostic uncertainty.[2] However, robust evidence for their diagnostic accuracy is required before clinical use.

This systematic review was conducted to evaluate the diagnostic accuracy and safety of using POC troponin assays for patients in the prehospital setting with suspected cardiac chest pain.

Methods

A systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and following Cochrane methodology for diagnostic test accuracy reviews. This systematic review was pre-registered on the PROSPERO database (reference CRD42019126564).

Search Strategy and Eligibility Criteria

Embase (Elsevier; Amsterdam, Netherlands), Medline (US National Library of Medicine, National Institutes of Health; Bethesda, Maryland USA), and CINAHL (EBSCO Information Services; Ipswich, Massachusetts USA) were searched on February 25, 2019. Only articles written in English and published after the year 2000 (first year when cTn was cited as the reference standard biomarker for diagnosing AMI) were considered for inclusion. The search strategies are provided in the Supplementary Material (available online only). The reference lists of all relevant paperers were hand searched.

Studies Included

Titles and abstracts were independently screened by two reviewers (AhA and MA) and papers were shortlisted for further evaluation based on the following criteria: (1) adult patients (>18 years); (2) patients with chest pain who required an ambulance response because of symptoms suggestive of an acute coronary syndrome (ACS); (3) patients underwent POC cTn testing in the prehospital setting; and (4) the outcome was a diagnosis of AMI, which should be based on the universal definition of AMI.[4] Both reviewers then retrieved full-text papers and independently reviewed and screened the full texts for consideration of inclusion in the final synthesis. In case of any disagreement, a third reviewer (AbA) was consulted. The screening process was performed with bespoke digital forms.

Outcome Measures

The primary outcome is a diagnosis of AMI, which was required to be defined in a manner consistent with the universal definition of AMI. This required a rise and/or fall of cTn with at least one value above the 99th percentile upper reference limit in combination with at least one other piece of supporting information, such as ECG changes or symptoms compatible with myocardial ischemia.[4]

Methodological Quality Assessment

The methodological quality assessment of included articles identified was independently assessed by two reviewers (AbA and CR) using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.[5] Discrepancies between reviewers were solved by discussion and consensus.

Data Extraction

After selecting all eligible studies, two investigators (AbA and CR) then used a standardized data extraction form to extract relevant details concerning the study design, study population, inclusion period, and results relevant to the research questions in this systemic review. The quantitative data required to evaluate diagnostic accuracy (true positives, false positives, false negatives, and true negatives) were extracted at all relevant cTn thresholds reported. Subsequently, where possible, 2X2 tables were constructed for each study, enabling calculation of test characteristics. In the event of missing data, the corresponding author for the relevant studies was contacted.

Statistical Analysis

After extracting the relevant data, the appropriateness of meta-analysis to pool the sensitivity and negative productive value (NPV) was considered. Also, the heterogeneity between the studies using Cochrane Q chi-square test and the I^2 statistics were aimed to be evaluated. However, this was not possible as there was overt evidence of analytical and clinical heterogeneity between studies, missing or unreported (and unobtainable) data, the wide variation between POC assays, and inconsistency of cut-offs between studies. Thus, meta-analysis was deemed inappropriate. All statistical analyses were performed using MedCalc (version 17.9.7; MedCalc Software; Ostend, Belgium).

Result

In total, the searched identified 329 potentially relevant studies that were eligible for review. Of those, 297 papers were excluded after screening titles and abstracts. Out of the 32 remaining articles which underwent full-text review, 25 papers were excluded for the following reasons: historic reference standard (n = 5), published only as a letter with insufficient data for analysis (n = 1), conference poster with insufficient data available for analysis (n = 15), only a study protocol had been published (n = 1), non-prehospital settings (n = 2), and different study population (n = 1; Figure 1).

Study Characteristics and Methodological Quality Analysis

The studies included in the systematic review (Table 1) were conducted in four different countries: three in Denmark,[6-8] two in Canada,[9,10] one in Italy,[11] and one in United State of America.[12] As shown in Table 2, the POC assay characteristics for each individual study included sensitivity, specificity, NPV, and positive predictive value (PPV).

The original QUADAS-2 methodological quality assessment tool was used to assess the methodological quality of included studies. Two out of the seven studies were randomized controlled trials, and there were only three studies excluding patients with ST-elevation myocardial infarction (STEMI; Table 3).[9,10] Also, one study used qualitative POC troponin assays.[6] Various and non-prespecified troponin cut-offs were used across many studies, thus raising concern about risk of bias and applicability of the index test. As per the inclusion criteria, all studies used the appropriate universal definition of AMI at the time of the study. In all studies, AMI was adjudicated by independent investigators, except in two cases[7,11]

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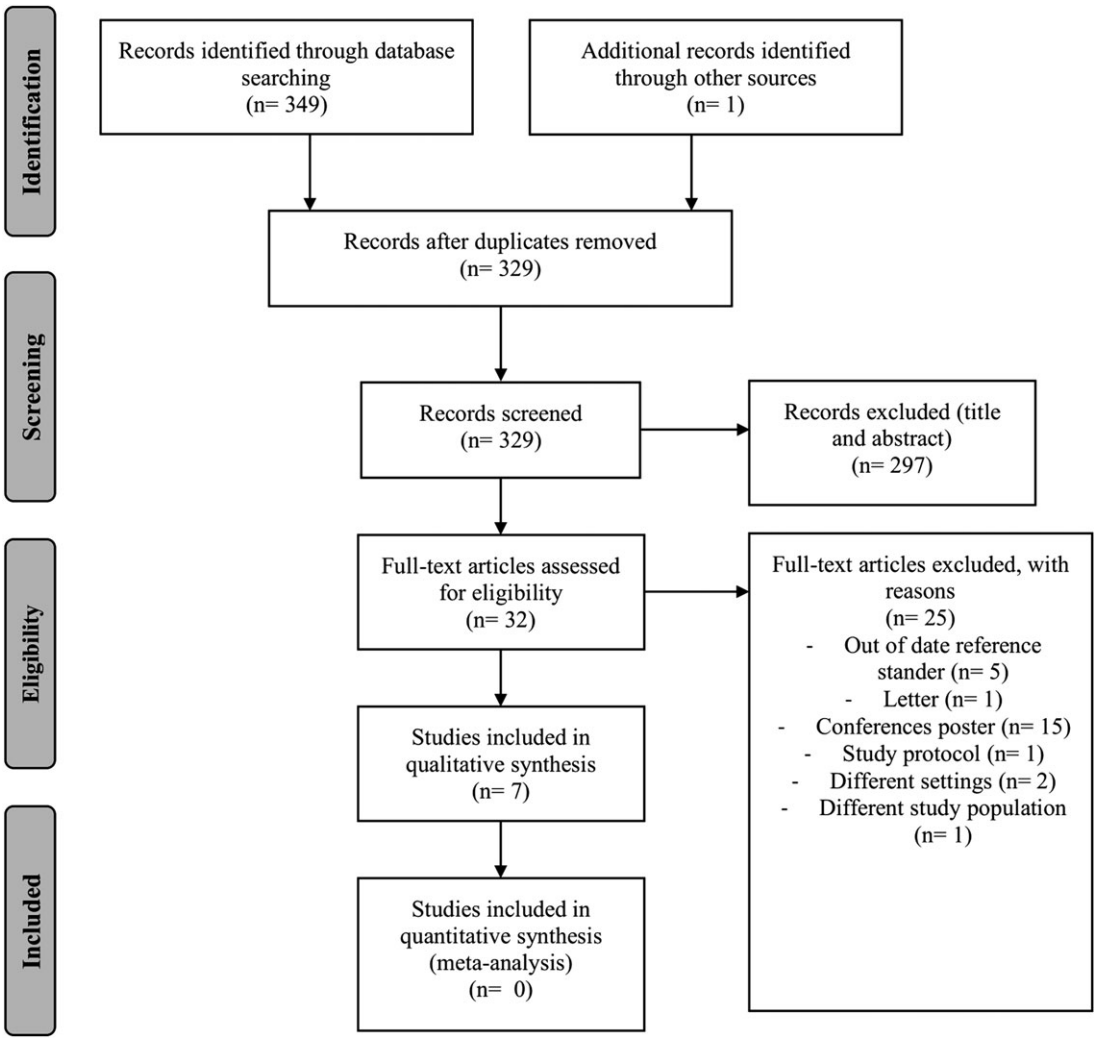

Figure 1. Flow Diagram of the Study Selection.

where the final diagnosis was used. A summary of the quality assessment results across all four QUADAS-2 domains was reported in Figure 2. Studies weaknesses were presented in Table 4.

Discussion

The systematic review suggests that the use of POC troponin assays alone are insufficiently sensitive to rule out AMI in the prehospital settings. Six studies that evaluated the diagnostic accuracy of POC cTn testing in the prehospital settings were found. These findings show that prehospital troponin testing has a sensitivity ranging from 26.5% to 91.0% and NPV up to 94.9% for the diagnosis of AMI.[6-12]

One of the most challenging tasks for paramedics in the prehospital setting is the diagnosis of AMI. Treatment for ACS or "rule out" could be initiated in the prehospital setting based on the ECG, the patient history of risk factors, blood pressure, and heart rate. Different prehospital studies show only 5%-18% of initial prehospital ECGs demonstrate STEMI.[11,13-16] This might lead to missed or delayed diagnosis of non-ST-elevation AMI, leading to treatment delay and poorer outcomes. Previously, many studies have evaluated cTn testing in the prehospital setting. These studies have focused on different aspects rather than the diagnostics accuracy of it, such as prognostication, and the association between the elevation of creatine kinase-myocardial band isoenzyme (CK-MB) or cTn and ST-segment elevation or ACS.[13,17,18] Interestingly, those studies reported that STEMI was strongly associated with elevation of CK-MB and cTn, which is significantly related to both ACS and AMI.[13,17] In addition, three studies were conducted to evaluate the feasibility and reliability of prehospital troponin POC.[6,8,11,19] The authors of these studies showed that POC troponin testing by paramedics is feasible, reliable, and recommended, implementing POC troponin testing in the prehospital emergency settings by paramedics to facilitate triage and risk stratify with a suspected AMI patient. So far, there is no solid evidence to show the effect on treatment and outcome for patients with suspected AMI when using biomarker values to triage and initiate treatment in the prehospital emergency environment.[6,13,20] Also, there are further troponin studies in the prehospital setting; however, in those studies, blood samples were obtained by paramedics in ambulances but only tested later in the hospital using central laboratory high-sensitivity assays.[21-24]

This systematic review focused on evaluating the diagnostic accuracy of POC cTn assays when used in the prehospital setting. An earlier systematic review by Nehme, et al[25] aimed to evaluate the

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Study	Year	Country	Study Design	N	Sites	Study Period
Di Serio, et al[11]	2006	Italy	Prospective observational diagnostic accuracy	53	NA	NA
Sorensen, et al[6]	2011	Denmark	Prospective observational diagnostic accuracy	4905	70 ambulances	June 2008 - September 2009
Stengaard, et al[8]	2013	Denmark	Prospective observational diagnostic accuracy	985	25 ambulances	May 2010 - May 2011
Ezekowitz, et al[10]	2014	Canada	Randomized controlled trial	491	25 ambulances	November 2011 - December 2012
Ezekowitz, et al[9]	2015	Canada	Randomized controlled trial	601	25 ambulances	July 2013 - February 2015
Rasmussen, et al[7]	2017	Denmark	Observational population-based follow-up study	19,615 cases (16,449 individual patient)	68 ambulances	June 2012 - November 2015
Stopyra, et al[12]	2020	United States	Prospective observational diagnostic accuracy	506	Three EMS systems	December 2016 - January 2018

Table 1. Characteristics of Included Studies
Abbreviation: EMS, Emergency Medical Services.

Study	N	Assay, (marker)	Cut-offs (μg/L)	Outcome	Sen%	Spe %	NPV %	PPV%
Di Serio, et al[11]	53	i-Stat	0.09	AMI	91	87	93	83
Sorensen, et al[6]	928	Qualitative Roche trop t sensitive	0.10	AMI	31	99	84	91
Stengaard, et al[8]	985	Cobas h232	0.05	AMI	39	95	86	68
Ezekowitz, et al[10]	227	Triage device Alere Cardio2 cTnI	0.03	AMI	NA	NA	NA	NA
Ezekowitz, et al[9]	305	Triage device Alere Cardio2 cTnI	0.03	AMI	NA	NA	NA	NA
Rasmussen, et al[6]	18712	Cobas h232	0.05	AMI	44	93	93	45
Stopyra, et al[12]	421	i-Stat	0.01	AMI	79.4	74.2	94.9	37.2
			0.08		26.5	99.2	87.5	85.7

Table 2. Diagnostic Characteristics of Studies that Used POC Troponin in the Ambulance
Abbreviations: AMI, acute myocardial infarction; FN, false negative; FP, false positive; NA, not available; NPV, negative predictive value; POC, point-of-care; PPV, positive predictive value; Sen, sensitivity; Spe, specificity; TN, true negative; TP, true positive.

diagnostic accuracy of clinical prediction rules for potential use in a prehospital emergency environment, using data that "were not reliant on tests unavailable out of the hospital," but found no evidence of any rules that could be used in practice. Since that time, studies have evaluated the History, ECG, Age, Risk Factors, and Troponin (HEART) score, a modified HEART score, and a History, ECG, Age, and Risk Factors (HEAR) score (the HEART score without requiring cTn testing) in the prehospital setting, albeit without using a POC cTn device to test prehospital blood samples.

A study by Stopyra, et al[26] evaluated the diagnostic accuracy of modified HEART score in which the H-E-A-R components of the score were collected by paramedics in the ambulance and the T (for troponin) was based on the initial contemporary troponin concentration from the ED. The primary outcome was the occurrence of major adverse cardiac events within 30 days.[26] In addition, van Dongen, et al[27,28] have evaluated both the HEART and HEAR scores in the prehospital setting. The primary outcome for both papers was major adverse cardiac events within 35 days. Despite the great work to evaluate and validate the HEART,

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Study	Population	AMI Prevalence	Target Condition
Di Serio, et al[11]	Patient with chest pain and non-ST-elevation AMI	41.5	AMI
Sorensen, et al[7]	Patients with suspected acute coronary syndrome	21.8	AMI
Stengaard, et al[8]	Ongoing or prolonged periods of chest pain or discomfort within the past 12 hours, acute dyspnea	20.3	AMI
Ezekowitz, et al[10]	Adults >18 years old who activated EMS for acute chest discomfort or dyspnea for which acute cardiovascular disease was deemed to be the most probable diagnosis by EMS personnel	9	Time from first medical contact to final disposition in the ED.
Ezekowitz, et al[9]	Adults over age 30 years of age with symptoms of acute chest discomfort for which acute cardiovascular disease was deemed to be the most probable diagnosis by EMS personnel	13.6	Time from first medical contact to final disposition in the ED.
Rasmussen, et al[7]	Patients who presented with symptoms suggestive of an AMI in the prehospital setting, and who underwent prehospital POC cTn testing before hospital admission (19,615 cases with 18,712 POC cTn)	11.7	AMI
Stopyra, et al[12]	Adult patients over 21 years of age with acute, non-traumatic chest pain, without evidence of STEMI on ECG	16.2	AMI

Table 3. Study and Patient Characteristics of all Studies Included in the Systematic Review
Abbreviations: AMI, acute myocardial infarction; cTn, cardiac troponin; ECG, electrocardiogram; ED, emergency department; EMS, Emergency Medical Services; POC, point-of-care; STEMI, ST-elevation myocardial infarction.

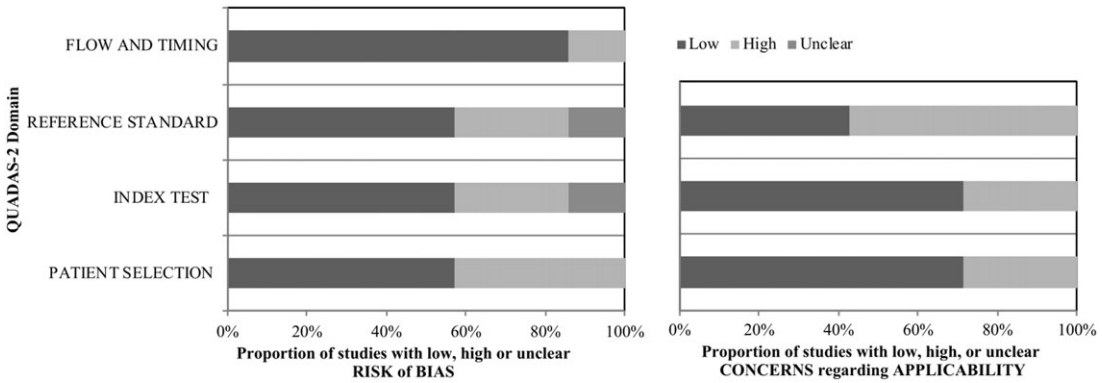

Figure 2. QUADAS-2 Assessment of Eligible Studies.
Abbreviation: QUADAS, Quality Assessment of Diagnostic Accuracy Studies.

modified HEART, and HEAR scores in the prehospital setting, the sensitivity and NPV ranged from 78% to 95% and 92% to 97%, respectively. This introduces an unacceptable risk of missed diagnosis in the prehospital setting.

Another clinical decision rule, the History and ECG-Only Manchester Acute Coronary Syndromes (HE-MACS) decision aid, has been derived and validated in the ED environment based on variables that are obtainable in the prehospital setting. The HE-MACS uses that data to calculate the probability of ACS based on six variables. The algorithm then risk stratifies patients into four groups: "very low risk" (possible immediate rule out), "low risk," "moderate risk," and "high risk" (potentially rule in ACS).[29] However, the accuracy this decision aid when used by paramedics in the prehospital environment has not yet been studied.

Future Research

Given the limited sensitivity of contemporary POC cTn assays, future work should focus on the evaluation of the accuracy of new, more sensitive assays as and when they become available; as well as on the combination of cTn concentrations with other clinical information as part of clinical decision aids (eg, the HEART score or Troponin-Only Manchester Acute Coronary Syndromes [T-MACS] decision aid).

Recently, the accuracy of the i-STAT (Abbott Point of Care; Priceton, New Jersey USA) POC troponin assay was validated in the ED setting with T-MACS decision rule and the HEART score.[30] Although those aids can be used in the prehospital emergency environment, the feasibility of data collection and diagnostic accuracy must now be evaluated when they are specifically used in that environment by paramedics. The anticipated

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Study	Study Weaknesses
Di Serio, et al[11]	Small sample size; Unclear adjudication process for AMI; Unclear cut-off for diagnosing AMI in hospital.
Sorensen, et al[7]	Only 958 patients of 4905 had POC test; Prehospital POC cTnT concentrations considered when adjudicating diagnoses (incorporation bias).
Stengaard, et al[8]	Unclear protocol for reference standard troponin testing.
Ezekowitz, et al[10]	The trial was stopped early as the enrolment rate was less than expected without any significant difference in the primary outcome; Diagnostic accuracy was not primary objective and included dyspnea, primary end point was time to finalized ED plan.
Ezekowitz, et al[9]	Broad inclusion criteria, which could lead to the inclusion of patients without cardiac disease; Diagnostic accuracy was not primary objective and included Dyspnea, primary end point was time to finalized ED plan.
Rasmussen, et al[7]	Unclear reference standard; Final clinical diagnoses retrieved but the proportion of patients undergoing laboratory troponin testing and its timing are not stated; Clinicians were not blinded to POC cTnT results, meaning that the study may be subject to important verification and incorporation bias.
Stopyra, et al[12]	Single center study, and selection bias; High error of POC assay.

Table 4. Studies Weaknesses
Abbreviations: AMI, acute myocardial infarction; cTn, cardiac troponin; ED, emergency department; POC, point-of-care.

results of the Prehospital Evaluation of Sensitive Troponin (PRESTO) study will help to address that evidence gap.[31] Validation of decision rules that do not require cTn testing (eg, HEAR and HE-MACS) is also required in order to determine the potential value of prehospital POC cTn testing.

Limitations

In this systematic literature review, some relevant papers may have been missed as only included non-English-language papers were excluded. However, an extensive hand and literature searcher was conducted to minimize this. Unfortunately, a meta-analysis was not conductible as there was three different POC troponin assays with different cut-off and analytical properties.

Conclusion

This systematic review of the literature shows that, based on current evidence, clinical use of POC cTn assays in the prehospital environment to rule out AMI cannot be justified. The limited available evidence suggests that alone, POC troponin assays are insufficiently sensitive to rule out AMI in the prehospital settings. Future research should focus on evaluating the diagnostic accuracy of using a validated decision aid in the prehospital settings to rule out AMI.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1049023X20000850

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