Cardiac biomarker measurement by point of care testing - development, rationale, current state and future developments.

Professor Paul Collinson. Departments of Clinical Blood Sciences and Cardiology, St George’s University Hospitals NHS Foundation Trust and St George’s University of London, Cranmer Terrace London SW17 0QT, UK

Running title Cardiac POCT

Words 3040 words

Figures 1

Tables 2

Keywords

Cardiac troponin I

Cardiac Troponin T

B Type natriuretic peptide

Point of care testing

Acute Coronary Syndromes

Correspondence to: Professor Paul Collinson. Department of Clinical Blood Sciences, St George’s University Hospitals NHS Foundation Trust, Cranmer Terrace, London SW17 0QT, UK.

Tel 0208 725 5934 Fax 0208 725 5838

Email: [paul.collinson@stgeorges.nhs.uk](mailto:paul.collinson@stgeorges.nhs.uk); [paul.collinson@ntlworld.com](mailto:paul.collinson@ntlworld.com)

Abstract

Cardiac biomarker measurements are integral to the diagnosis and management of patients presenting with breathlessness and chest pain. Measurement of B type natriuretic peptide either directly or of the N-terminal portion of the prohormone although possible by point of care testing (POCT) has largely become a laboratory test. Measurement of the cardiac troponins cardiac troponin T (cTnT) and cardiac troponin I (cTnI) can easily and accurately be performed by POCT. The situation has been complicated by the development of high sensitivity assays for cTnT and cTnI and the subsequent development of rapid rule out algorithms allowing patient categorisation and discharge on admission and 1 to 2 hours following admission. This article reviews the development of POCT for cardiac biomarkers, the evidence base comparing POCT with central laboratory testing, its strengths and limitations, and how POCT fits into the world of high sensitivity troponin assays. It also discusses what evidence there is that POCT can form part of rapid decision-making strategies and how this applies in an era of algorithms based on and is derived from measurement of high sensitivity troponin in the central laboratory.

Non-standard abbreviations.

MACE Major Adverse Cardiac Events

ACS Acute Coronary Syndromes

CLT Central Laboratory Testing

ED Emergency Department

Cardiac biomarker measurement by point of care testing - development, rationale, current state and future developments.

Introduction.

The role of relatively tissue-specific biochemical testing for myocardial damage began in 1954 with the development of an assay for aspartate transaminase[1]. This was followed by assays for lactate dehydrogenase[2] and its isoenzymes[3], creatine kinase[4;5] and its MB isoenzyme (CK-MB) [6]. The role of laboratory testing was recognised in the original World Health Organisation definition of myocardial infarction[7]. Subsequent evolution was the development of immunoassay, initially for myoglobin[8] and CK-MB[9], then for the novel cardiac structural proteins, cardiac Troponin T (cTnT) [10]and cardiac troponin I (cTnI)[11] and for biomarkers of cardiac function such as B type natriuretic peptide (BNP)[12]. The role and perception of cardiovascular biomarkers has undergone a paradigm shift. Myocardial infarction was redefined with cTnT and cTnI core to the definition[13] and cardiac biomarker measurement became part of management pathways in acute coronary syndromes (ACS)[14] and heart failure[15].

Development of point of care testing (POCT) for cardiac biomarkers.

The rationale for POCT is that delivering a rapid turnaround time would result in more rapid clinical decision-making in the acute setting and hence expedite patient flow. It was therefore logical to developed POCT for cardiac biomarker measurement. Initial technology for POCT was based on conventional dry chemistry systems with measurement of CK and CK-MB[16;17]. The breakthrough development was the use of disposable lateral flow immunoassay systems[18]. The typical technology is illustrated in figure 1 below.

A range of lateral flow immunoassay tests were developed for cTnT, cTnI, CK-MB and myoglobin[19-22]. These assays were originally visually read and hence qualitative. Qualitative measurement was superseded by quantitative measurement by reflectance[23]. A dedicated system that was machine read only, as it was a fluorescence immunoassay based on lateral flow, was also developed[24]. Of these devices, only 2 qualitative lateral flow immunoassays remain in current clinical use. The alternative strategy was to develop small laboratory type instruments that would take a whole blood samples that were suitable for use in a dedicated point of care area in the acute care setting. The earliest example of this type of instrument was the Stratus CS[22]. It is interesting to note that the rapid cTnT test was developed to bridge the gap before a compact stat immunoassay platform was available for cTnT. Immunoassay for cTnI began with such a platform[25]. Since then a number of different instruments have been developed utilising either a conventional approach using reagent wells or cartridges incorporating microfluidic designs[26]. The reported analytical performance of the current POCT system routinely available is summarised on the International Federation of Clinical Chemists website <https://www.ifcc.org/ifcc-education-division/emd-committees/committee-on-clinical-applications-of-cardiac-bio-markers-c-cb/>.

Independent analytical validation of a number of these instruments has been performed (table 1). Table 1 illustrates the evolution of such systems from qualitative to quantitative and with progressive improvement in analytical performance. It also illustrates the problem with the shift in expectation with improvement in analytical performance of central laboratory testing (CLT) and changes in the clinical diagnostic criteria used. The impact of such changes will be discussed in more detail below.

Table 1 Analytical evaluation studies of cardiac Troponin

|  |  |  |
| --- | --- | --- |
| Technology | Result | Reference |
| Multicentre evaluation of a Boehringer Mannheim qualitative lateral flow cTnT immunoassay. | Diagnostic equivalence with central lab ELISA (WHO criteria) Diagnostic cut off 0.3 µg/L. | [27] |
| Comparative evaluation of Stratus CS cTnI analyser (Dade-Behring). | Detection limit 0.01 µg/L, CV 4.5% 0.1 µg/L diagnostic threshold 0.15 µg/L (WHO criteria) | [28] |
| Triage qualitative lateral flow fluorescent sandwich immunoassay (Biosite). | Detection limit 0.19 µg/L CV 12% (WHO criteria). | [24] |
| Roche cardiac reader quantitative cTnT measurement (Roche diagnostics). | Diagnostic cut off 0.1 µg/L imprecision 10-12% 0.16-1.24 µg/L. Equivalent analytical and clinical performance to laboratory analyses (WHO criteria). | [23] |
| iSTAT (iSTAT) | Detection limit 0.02 mcg/L, 10% CV 0.09 µg/L 99th percentile 0.08 µg/L. | [29] |
| RAMP (Response Biomedical) | Limit of detection 0.03 µg/L, 10% CV 0.21 µg/L, 99th percentile 0.12 µg/L. Equivalent diagnostic efficiency to central lab testing (ESC criteria) | [30] |
| AQT90.(Radiometer) | 99th percentile 19 ng/L, 10% imprecision 22 ng/L for cTnI | [31] |
| Minicare (Phillips) | LOD 18 ng/L, 20% CV 38 ng/L, 99th percentile 39 ng/L. | [32] |
| PATHFAST (LSI Medience) | LOD 2.3 ng/L CV 6.1% at 29 ng/L 99th percentile 28ng/L | [33] |
| Evaluation of Konica Minolta high sensitivity troponin assay | LOD 0.60 ng/L 10% CV 3.9 ng/L 99th percentile 12.2 ng/L | [34] |

LOD, limit of detection; CV, coefficient of variation.

The situation for immunoassays of BNP is slightly more complicated. BNP assays were available only in research laboratories until the launch of the triage BNP assay[35]. The subsequent publication of the landmark Breathing Not Properly study[36] catapulted the role of BNP testing from research into routine clinical practice. However, for a substantial period, BNP measurements were being performed by a POCT instrument but measurements were occurring in the central laboratory. Introduction of BNP measurements into the central laboratory on high throughput immunoassay platforms occurred subsequently. Measurement of BNP by measurement of the N-terminal fragment of the prohormone, NT-proBNP, commenced as a laboratory test[37] and was subsequently developed for point of care[38]. Unlike cTnT and cTnI, the analytical range of BNP and NT-proBNP assays by POCT and CLT were congruent. All assays for BNP (POCT or CLT) have an effective harmonisation at the clinical cut-off of 100 ng/L although there are differences above and below this point between different methods[39]. The decision to license NT-proBNP has meant that NT-proBNP can be measured in the central laboratory or by POCT with equivalent results. The analytical performance of BNP and NT-proBNP assays is available on the website cited above. In addition, there have been a number of external evaluations of assay performance[35;38;40-43].

As well as the questions of reliable analytical performance for POCT there are additional factors that will affect real-life in use performance. Staff training and quality assurance are well understood from experience with other POCT systems. Connectivity supports operator identification, system monitoring and quality assurance as well as overcoming the problem of incorporating results into the electronic patient record. However, there may be other factors to consider such as inter-observer variability for qualitative systems [44]and use of different sample matrices. The use of capillary sampling has variously been reported to have an effect[45] or not have an effect [32;43] on biomarker results by POCT.

Clinical applications of POCT testing for cardiovascular biomarkers and the impact of changes in central laboratory testing methods.

The clinical utility of POCT has to be seen in the context of the comparator CLT method. From the beginning, CK, CK-MB, myoglobin and BNP/NT-proBNP measurements showed comparable results whether by POCT or CLT. BNP began as a POCT test but the majority of BNP testing is now laboratory-based although there is a small residual POCT group within the laboratory rather than as a true POCT test[46]. Currently in the UK of all those participating in external quality assessment for B type natriuretic peptide testing (all methods), only 8/48 (16.7%) of BNP and 6/170 (3.5%) of NT-proBNP measurements are performed by POCT. Hence the majority of B type natriuretic peptide measurements are performed (93.6%) by the central laboratory (Alan Reid, personal communication).

Although superficially measurement of BNP or NT-proBNP could be performed either by POCT or the central laboratory, there is very little published evidence for POCT measurement in clinical practice and no randomised controlled trials. In primary care measurement of BNP or NT-proBNP is typically only one of a number of tests required in assessing the patient with chronic breathlessness. In addition, such cases are not perceived as immediately life-threatening but as management of a suspected chronic condition with referral to a specialist centre. The lack of evidence for serial measurement of BNP/NT-proBNP for monitoring is probably another contributing factor. Although measurement may be useful in situations where access to the central laboratory is geographically constrained [47]there seems to be little evidence of widespread adoption of POCT for BNP/NT-proBNP measurements.

The situation with cTnT and cTnI is more complicated. The initial troponin assays were relatively insensitive. However, the diagnostic gold standard at this point was the WHO criteria for myocardial infarction which stipulated biomarkers twice the upper reference limit[7]. Early studies with troponin showed unequivocally that approximately one third patients categorised as unstable angina by WHO criteria had detectable troponin. An elevated troponin in this patient group was associated with an increased incidence of subsequent major adverse cardiac events (MACE) when the patient was followed up, readmission with myocardial infarction, need for emergency revascularisation or death (cardiac death or total death)[48;49]. Troponin elevation in unstable angina predicting an adverse outcome was a consistent research finding and lead initially to a consensus conference[50] and ultimately the redefinition of MI[13] and the universal definition of MI [51]using troponin as gold standard biomarker of cardiac damage. There were two consequences for clinical practice and research. First, the definition of myocardial infarction in studies shifted progressively from one using WHO criteria for MI to the redefinition/universal definition of MI. Use of the redefinition produced an increase in the number of cases of MI detected when troponin was used as biomarker [52]. Second, the redefinition stated that the coefficient of variation (CV) of cTnT and cTnI assays should be 10% or lower at the 99th percentile. This quality specification began a process of progressive improvement in the analytical quality of assays which has ultimately produced high sensitivity troponin assays[53]. It is important to remember that high sensitivity troponin assays are not measuring a different form of troponin and the term “high sensitivity” refers solely to the analytical performance. The routine use of high sensitivity troponin assays has generated two analytical features.

1. The ability to measure very low levels of cTnT and cTnI, towards the lower end, often near the bottom, of the reference interval of a healthy population.

2. The ability to measure very low levels with low imprecision, of the order of 2-5%. This means that repeat sampling across short time intervals is possible, hence use of the patient as their own reference.

These two features have been exploited clinically. The ability to measure very low levels has resulted in a series of studies which have demonstrated that measurement of cTnT[54] or cTnI[55] on a sample taken at first presentation can be used to predict a low risk of subsequent myocardial infarction or MACE over 30 days in patients admitted with chest pain ?ACS. These patients require no further repeat troponin measurement so can be immediately discharged. Single sample measurement on admission for the management of chest pain patients is highly attractive to Emergency Department (ED) physicians. It is referred to as “one and done” and allows immediate discharge of low risk patients. The second is the use of repeat measurements with the first measurement on admission and the second 1-3 hours later. The calculation of a delta value allows earlier identification of patients for rule in suspected myocardial infarction or rule out. The use of a combined admission and early rule out has been endorsed by the European Society of Cardiology (ESC) [56]. Such rapid decision-making algorithms are derived from and predicated on the use of high sensitivity troponin measurements performed by CLT.

Role of POCT in acute cardiac care - assessing the evidence.

The rationale for POCT is that rapid provision of test results would improve patient flows in the ED or on the coronary care unit (CCU). When evaluating published studies involving POCT the following questions need to be asked.

1. What was the reference standard used, diagnosis or outcome. If diagnosis was used with WHO criteria for myocardial infarction, then the applicability to current approaches may be limited. If however outcome measures such as MACE were used there may be some utility although this will be limited when the definition includes readmission with myocardial infarction based on WHO criteria. However, there will definitely be utility if cardiac death or total mortality was used as the outcome measure.

2. What was the predicate CLT cTnI or cTnT method? If it supported diagnosis based on the 99th percentile (even with a CV at the 99th percentile up to 20%[57]) then the comparison is currently valid.

The majority of clinical studies of POCT have been observational. Early studies showed diagnostic equivalence to CLT using less sensitive laboratory methods and WHO criteria for MI[58]. Comparison of a POCT method which does not meet the criteria for high sensitivity with a CLT method that does however illustrates that there is a lack of equivalent diagnostic utility[59]. The situation is more complex if the POCT method meets the criteria of “clinically usable” (imprecision at the 99th percentile in the range 10-20%) and the prior probability of myocardial infarction in the population is a low. Comparison of such a POCT with a conventional sensitive CLT method, but using an optimised cut-off derived from receiver operating characteristic curve analysis for a the POCT method (rather than the 99th percentile) can demonstrate diagnostic equivalence even when universal definition of MI criteria are used[60]. Such a study may not be sufficiently powered to demonstrate true differences between methods. However, for POCT methods which have or approach high sensitivity, diagnostic equivalence with high sensitivity central laboratory testing has been demonstrated[61;62].

3. What is the decision making algorithm undergoing evaluation? Distinction must be made between low-level measurement on admission, use of serial sampling with short time intervals (0-1 or 0-2 hour sampling) and measurement on admission and at 3 or 6 hours (or longer) from admission. It is then important to determine whether diagnostic decision-making was based on diagnostic thresholds, the combination of a diagnostic threshold and a delta change value or utilised the 99th percentile, with or without a delta change value.

The majority of clinical studies which have evaluated POCT, utilised the universal definition of myocardial infarction and used high sensitivity troponin assays as diagnostic comparator, have not evaluated rapid diagnostic algorithms. They have used serial sampling on admission then at least 3 hours later and often for longer periods. They also use the 99th percentile as the diagnostic criterion for comparative evaluation [60-64]. Direct comparison of a range of POCT and CLT methods found only assays meeting high sensitivity criteria supported rule out based on admission measurement, with maximal diagnostic efficiency for 0-3 hour protocols[65]. To date there are only two studies which have looked at a high sensitivity POCT cTnI assay and evaluated rapid diagnostic algorithms[66;67].

Clinical trials of POCT versus CLT.

The rationale for POCT is that rapid provision of test results should translate into clinical benefit. This has been difficult to demonstrate in clinical practice. There have been a small number of trials of POCT versus CLT. These are summarised in table 2. When these trials were performed there was analytical equivalence between POCT and central laboratory testing (CLT). It is therefore worth reviewing the evidence that POCT will deliver improved workflow.

Table 2 Clinical trials of Point of Care testing

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Type | Methodology | Cut off | Location | Outcome | Result | Author |
| Single centre RCT | Roche cTnT CLT vs POCT | 0.2 µg/L | ED referrals to CCU | Length of stay in pre-specified rule out subgroup | Reduction of length of stay in POCT group | Collinson et al[68] |
| Multicentre RCT | iSTAT cTnI |  | ED | Time to discharge home or transfer | Reduction in one site and increase in another | Ryan et al [69] |
| Single centre RCT | Stratus CS vs Dimension RxL | 0.1 µg/L | ED | Time to treatment  Length of stay in the ED | Reduced time to treatment  No reduction in ED stay | Renaud et al[70] |
| 3 centres prospective observational study | Triage cardiac panel vs Dimension RXL | 0.4 µg/L | ED | Retrospective review of diagnostic accuracy  Length of stay | Improved diagnostic accuracy of multimarker strategy  Increased number of discharges <24 hours compared with historical data | Straface et al[71] |
| 2 Centre Cluster randomised controlled trial | iStat vs Beckman Coulter Accu I | ns | ED | Length of ED stay | Not significant | Loten et al[72] |
| 6 centre RCT | Stratus CS vs Central Lab | 0.7 µg/L | ED | Discharges <4 hour  Length of hospital stay  MACE | Increased discharge <4 hours with less admissions  MACE was equivalent in POCT and CLT groups | Goodacre et al[73;74] |
| Cluster RCT | Roche cardiac reader | 0.1 µg/L | 68 rural primary care centres | Clinical diagnosis | Improved diagnostic accuracy | Tomonaga et al[75] |
| Single centre RCT | AQT Flex vs hs cTnT | 14 ng/L | ED | MACE at 3 months | No significant differences | Asha et al[76] |

Abbreviations: RCT, randomised controlled trial; cTnT, cardiac troponin T; cTnI, cardiac troponin I; ED, emergency department; CCU, Coronary Care Unit; MACE, major adverse cardiac events; ns , not stated.

# 6 trials examined the impact of rapid provision of laboratory tests on clinical decision-making in the acute care environment as judged by length of stay (LOS). The results are not consistent. 3 studies demonstrated improved throughput while 2 did not. One study showed inconsistency between trial sites with reduction in LOS one site and increase in another. It is likely that this is due to the impact of individual patient pathways within different institutions. In order to achieve clinical impact by POCT, the provision of test results must be the time critical component of the patient pathway. This was also the conclusion of an evidence-based review of POCT[77]. The effect of process is supported by the site specific analysis of the RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial which showed marked differences in length of stay between sites which could be directly attributed to the patient pathways in use[78].

Current strategies for management of chest pain.

The current recommendations from the European Society of Cardiology for the investigation and management of patients with chest pain?ACS and suspected NSTEMI endorse the use of troponin measurement on admission followed by serial measurement and calculation of a delta change over a short time interval, typically 1 or 2 hours. High sensitivity troponin assays are specifically recommended. The majority of POCT does not meet the specification and sampling at 3 or 6 hours from presentation is required. Even assuming a pessimistic turnaround time of 1 hour for CLT, the ability to categorise the majority of patients within 2-3 hours is superior to waiting 3-6 hours even with a 15 minute analytical turnaround time. Current guidelines do not recommend POCT for cTnT or cTnI measurement. Although there are POCT methods which meet high sensitivity criteria and have been evaluated in rapid diagnostic algorithms [66;67], there are no in use prospective studies that have utilised whole blood and been performed in the ED environment.

Access to high sensitivity CLT troponin testing is confined to urban environments. There are rural environments where there is a choice of POCT troponin testing or none. In this situation POCT can have a significant positive impact [75;79]. However, the use of testing that is less sensitive can mean that there is a delay before results are obtained[80] or misdiagnosis made[81]. Finally the situation can become even more complicated if there is a mixed economy of POCT plus high sensitivity CLT. Under the circumstances there will be diagnostic discordance between POCT and CLT. Although the results can be harmonised by increasing the diagnostic threshold used for the CLT method to a value similar to POCT methods in use, this is achieved at the expense of missed diagnoses[82;83].

New generation POCT.

The technology for POCT and the available technology are undergoing constant evolution. The use of solid state devices ”Lab on a chip” and new technologies promise improved diagnostic sensitivity with lower unit costs[84-86]. In addition, novel sensor technology or immuno-concentration techniques may be combined with lateral flow. A range of potential high sensitivity troponin technologies are summarised in supplementary table 1.

Conclusions

POCT has the potential to significantly improve patient flow through the emergency department when combined with a rapid rule out algorithm and if implemented as part of a decision making protocol. The requirement is for the analytical performance of the POCT system to match CLT. There is encouraging but preliminary evidence that the analytical performance of POCT is approaching central laboratory methods. However, there are as yet no published studies that have independently documented high sensitivity performance using whole blood as the sample matrix and no in-use real life clinical studies. But what we are looking for is randomised controlled clinical trials.

# Declarations of interest

# The author is a consultant to and a member of the International Federation of Clinical Chemists Committee on Clinical Applications of Cardiac Bio-Markers (C-CB) and the European Federation of laboratory medicine task group - cardiac markers (EFLM – CM).

Provenance

This article was suggested as a contribution to the special issue. The author takes full responsibility for the conception, writing and content of the article.

Table 1 Analytical evaluation studies of cardiac Troponin

|  |  |  |
| --- | --- | --- |
| Technology | Result | Reference |
| Multicentre evaluation of a Boehringer Mannheim qualitative lateral flow cTnT immunoassay. | Diagnostic equivalence with central lab ELISA (WHO criteria) Diagnostic cut off 0.3 µg/L. | [27] |
| Comparative evaluation of Stratus CS cTnI analyser (Dade-Behring). | Detection limit 0.01 µg/L, CV 4.5% 0.1 µg/L diagnostic threshold 0.15 µg/L (WHO criteria) | [28] |
| Triage qualitative lateral flow fluorescent sandwich immunoassay (Biosite). | Detection limit 0.19 µg/L CV 12% (WHO criteria). | [24] |
| Roche cardiac reader quantitative cTnT measurement (Roche diagnostics). | Diagnostic cut off 0.1 µg/L imprecision 10-12% 0.16-1.24 µg/L. Equivalent analytical and clinical performance to laboratory analyses (WHO criteria). | [23] |
| iSTAT (iSTAT) | Detection limit 0.02 mcg/L, 10% CV 0.09 µg/L 99th percentile 0.08 µg/L. | [29] |
| RAMP (Response Biomedical) | Limit of detection 0.03 µg/L, 10% CV 0.21 µg/L, 99th percentile 0.12 µg/L. Equivalent diagnostic efficiency to central lab testing (ESC criteria) | [30] |
| AQT90.(Radiometer) | 99th percentile 19 ng/L, 10% imprecision 22 ng/L for cTnI | [31] |
| Minicare (Phillips) | LOD 18 ng/L, 20% CV 38 ng/L, 99th percentile 39 ng/L. | [32] |
| PATHFAST (LSI Medience) | LOD 2.3 ng/L CV 6.1% at 29 ng/L 99th percentile 28ng/L | [33] |
| Evaluation of Konica Minolta high sensitivity troponin assay | LOD 0.60 ng/L 10% CV 3.9 ng/L 99th percentile 12.2 ng/L | [34] |

LOD, limit of detection; CV, coefficient of variation.

Table 2 Clinical trials of Point of Care testing

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Type | Methodology | Cut off | Location | Outcome | Result | Author |
| Single centre RCT | Roche cTnT CLT vs POCT | 0.2 µg/L | ED referrals to CCU | Length of stay in pre-specified rule out subgroup | Reduction of length of stay in POCT group | Collinson et al[68] |
| Multicentre RCT | iSTAT cTnI |  | ED | Time to discharge home or transfer | Reduction in one site and increase in another | Ryan et al [69] |
| Single centre RCT | Stratus CS vs Dimension RxL | 0.1 µg/L | ED | Time to treatment  Length of stay in the ED | Reduced time to treatment  No reduction in ED stay | Renaud et al[70] |
| 3 centres prospective observational study | Triage cardiac panel vs Dimension RXL | 0.4 µg/L | ED | Retrospective review of diagnostic accuracy  Length of stay | Improved diagnostic accuracy of multimarker strategy  Increased number of discharges <24 hours compared with historical data | Straface et al[71] |
| 2 Centre Cluster randomised controlled trial | iStat vs Beckman Coulter Accu I | ns | ED | Length of ED stay | Not significant | Loten et al[72] |
| 6 centre RCT | Stratus CS vs Central Lab | 0.7 µg/L | ED | Discharges <4 hour  Length of hospital stay  MACE | Increased discharge <4 hours with less admissions  MACE was equivalent in POCT and CLT groups | Goodacre et al[73;74] |
| Cluster RCT | Roche cardiac reader | 0.1 µg/L | 68 rural primary care centres | Clinical diagnosis | Improved diagnostic accuracy | Tomonaga et al[87] |
| Single centre RCT | AQT Flex vs hs cTnT | 14 ng/L | ED | MACE at 3 months | No significant differences | Asha et al[76] |

Abbreviations: RCT, randomised controlled trial; cTnT, cardiac troponin T; cTnI, cardiac troponin I; ED, emergency department; CCU, Coronary Care Unit; MACE, major adverse coronary events; ns , not stated

Figure 1 Lateral flow assay principles. (Illustration from NASA, non-copyright)

Reference List

1. Ladue JS, Wroblewski F, Karmen A. Serum glutamic oxaloacetic transaminase activity in human acute transmural myocardial infarction. Science 1954; 120:497-9.

2. Wroblewski F, Ladue JS. Lactic dehydrogenase activity in blood. Proc Soc Exp Biol Med 1955; 90:210-3.

3. Bearn AG, Vesell ES. Localization of lactic acid dehydrogenase activity in serum fractions. Proc Soc Exp Biol Med 1957; 94:96-9.

4. Dreyfus JC, Schapira G, Resnais J, Scebat L. [Serum creatine kinase in the diagnosis of myocardial infarct]. Rev Fr Etud Clin Biol 1960; 5:386-7.

5. Rosalki SB. An improved procedure for serum creatine phosphokinase determination. J Lab Clin Med 1967; 69:696-705.

6. Roberts R, Henry PD, Witteeveen SA, Sobel BE. Quantification of serum creatine phosphokinase isoenzyme activity. Am J Cardiol 1974; 33:650-4.

7. Nomenclature and criteria for diagnosis of ischemic heart disease. Report of the Joint International Society and Federation of Cardiology/World Health Organization task force on standardization of clinical nomenclature. Circulation 1979; 59:607-9.

8. Kubasik NP, Guiney W, Warren K, D'Souza JP, Sine HE, Brody BB. Radioimmunoassay of serum myoglobin: evaluation and modification of a commercial kit and assessment of its usefulness for detecting acute myocardial infarction. Clin Chem 1978; 24:2047-9.

9. Vaidya HC, Maynard Y, Dietzler DN, Ladenson JH. Direct measurement of creatine kinase-MB activity in serum after extraction with a monoclonal antibody specific to the MB isoenzyme. Clin Chem 1986; 32:657-63.

10. Katus HA, Remppis A, Looser S, Hallermeier K, Scheffold T, Kubler W. Enzyme linked immuno assay of cardiac troponin T for the detection of acute myocardial infarction in patients. J Mol Cell Cardiol 1989; 21:1349-53.

11. Cummins B, Auckland ML, Cummins P. Cardiac-specific troponin-I radioimmunoassay in the diagnosis of acute myocardial infarction. Am Heart J 1987; 113:1333-44.

12. Takeyama M, Yasunaga F, Otaka A, Fujii N, Yajima H. Microenzyme immunoassay for the measurement of brain natriuretic peptide (BNP)-like immunoreactivity in porcine plasma. J Immunol Methods 1990; 130:217-22.

13. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. Eur Heart J 2000; 21:1502-13.

14. Bertrand ME, Simoons ML, Fox KA et al. Management of acute coronary syndromes: acute coronary syndromes without persistent ST segment elevation. Recommendations Of the task force of the european society of cardiology. Eur Heart J 2000; 21:1406-32.

15. Nieminen MS, Bohm M, Cowie MR et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005; 26:384-416.

16. Ng RH, Altaffer M, O'Neill M, Mukadam H, Statland BE. Measurement of six enzymes with the Kodak DTSC Module, a physician's office analyzer. Clin Chem 1987; 33:1911-3.

17. Ramhamadany EM, Collinson PO, Evans DH, Fink RS, Baird IM. Reliability of the Ames Seralyser for creatine kinase measurement in the coronary care unit. Clin Chem 1988; 34:1914.

18. Koczula KM, Gallotta A. Lateral flow assays. Essays Biochem 2016; 60:111-20.

19. Collinson PO, Thomas S, Siu L, Vasudeva P, Stubbs PJ, Canepa-Anson R. Rapid troponin T measurement in whole blood for detection of myocardial damage. Ann Clin Biochem 1995; 32 ( Pt 5):454-8.

20. Panteghini M, Pagani F. Characterization of a rapid immunochromatographic assay for simultaneous detection of high concentrations of myoglobin and CK-MB in whole blood. Clin Chem 1996; 42:1292-3.

21. Brogan GX, Jr., Bock JL, McCuskey CF et al. Evaluation of cardiac STATus CK-MB/myoglobin device for rapidly ruling out acute myocardial infarction. Clin Lab Med 1997; 17:655-68.

22. Heeschen C, Goldmann BU, Moeller RH, Hamm CW. Analytical performance and clinical application of a new rapid bedside assay for the detection of serum cardiac troponin I. Clin Chem 1998; 44:1925-30.

23. Muller-Bardorff M, Rauscher T, Kampmann M et al. Quantitative bedside assay for cardiac troponin T: a complementary method to centralized laboratory testing. Clin Chem 1999; 45:1002-8.

24. Apple FS, Christenson RH, Valdes R, Jr. et al. Simultaneous rapid measurement of whole blood myoglobin, creatine kinase MB, and cardiac troponin I by the triage cardiac panel for detection of myocardial infarction. Clin Chem 1999; 45:199-205.

25. Adams JE, III, Bodor GS, Davila-Roman VG et al. Cardiac troponin I. A marker with high specificity for cardiac injury [see comments]. Circulation 1993; 88:101-6.

26. Apple FS, Anderson FP, Collinson P et al. Clinical evaluation of the first medical whole blood, point-of-care testing device for detection of myocardial infarction. Clin Chem 2000; 46:1604-9.

27. Collinson PO, Gerhardt W, Katus HA et al. Multicentre evaluation of an immunological rapid test for the detection of troponin T in whole blood samples. Eur J Clin Chem Clin Biochem 1996; 34:591-8.

28. Heeschen C, Goldmann BU, Langenbrink L, Matschuck G, Hamm CW. Evaluation of a rapid whole blood ELISA for quantification of troponin I in patients with acute chest pain. Clin Chem 1999; 45:1789-96.

29. Apple FS, Murakami MM, Christenson RH et al. Analytical performance of the i-STAT cardiac troponin I assay. Clin Chim Acta 2004; 345:123-7.

30. Wu AH, Smith A, Christenson RH, Murakami MM, Apple FS. Evaluation of a point-of-care assay for cardiac markers for patients suspected of acute myocardial infarction. Clin Chim Acta 2004; 346:211-9.

31. Greiser A, Winter T, Mahfoud H et al. The 99th percentile and imprecision of point-of-care cardiac troponin I in comparison to central laboratory tests in a large reference population. Clin Biochem 2017; 50:1198-202.

32. Kemper DW, Semjonow V, de TF et al. Analytical evaluation of a new point of care system for measuring cardiac Troponin I. Clin Biochem 2017; 50:174-80.

33. Christenson RH, Mullins K, Duh SH. Validation of high-sensitivity performance for a United States Food and Drug Administration cleared cardiac troponin I assay. Clin Biochem 2018; 56:4-10.

34. Braga F, Aloisio E, Panzeri A, Nakagawa T, Panteghini M. Analytical validation of a highly sensitive point-of-care system for cardiac troponin I determination. Clin Chem Lab Med 2019; 58:138-45.

35. Wieczorek SJ, Wu AH, Christenson R et al. A rapid B-type natriuretic peptide assay accurately diagnoses left ventricular dysfunction and heart failure: a multicenter evaluation. Am Heart J 2002; 144:834-9.

36. Maisel AS, Krishnaswamy P, Nowak RM et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161-7.

37. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. BMJ 2002; 324:1498-503.

38. Zugck C, Nelles M, Katus HA et al. Multicentre evaluation of a new point-of-care test for the determination of NT-proBNP in whole blood. Clin Chem Lab Med 2006; 44:1269-77.

39. Franzini M, Masotti S, Prontera C et al. Systematic differences between BNP immunoassays: comparison of methods using standard protocols and quality control materials. Clin Chim Acta 2013; 424:287-91.

40. Yeo KT, Wu AH, Apple FS et al. Multicenter evaluation of the Roche NT-proBNP assay and comparison to the Biosite Triage BNP assay. Clin Chim Acta 2003; 338:107-15.

41. Lee-Lewandrowski E, Januzzi JL, Green SM et al. Multi-center validation of the Response Biomedical Corporation RAMP NT-proBNP assay with comparison to the Roche Diagnostics GmbH Elecsys proBNP assay. Clin Chim Acta 2007; 386:20-4.

42. Zaninotto M, Mion MM, Di SF, Caputo M, Ottomano C, Plebani M. PATHFAST NT-proBNP (N-terminal-pro B type natriuretic peptide): a multicenter evaluation of a new point-of-care assay. Clin Chem Lab Med 2010; 48:1029-34.

43. Reenen AV, Berger M, Moreau E et al. Analytical performance of a single epitope B-type natriuretic peptide sandwich immunoassay on the Minicare platform for point-of-care diagnostics. Pract Lab Med 2019; 15:e00119.

44. Al MM, Morris N, McDowell G, Body R. The interobserver reliability of a novel qualitative point of care assay for heart-type fatty acid binding protein. Clin Biochem 2016; 49:1199-201.

45. Loewenstein D, Stake C, Cichon M. Assessment of using fingerstick blood sample with i-STAT point-of-care device for cardiac troponin I assay. Am J Emerg Med 2013; 31:1236-9.

46. Hammerer-Lercher A, Collinson P, Dieijen-Visser MP et al. Do laboratories follow heart failure recommendations and guidelines and did we improve? The CARdiac MArker Guideline Uptake in Europe (CARMAGUE). Clin Chem Lab Med 2013;1-6.

47. Burri E, Hochholzer K, Arenja N et al. B-type natriuretic peptide in the evaluation and management of dyspnoea in primary care. J Intern Med 2012; 272:504-13.

48. Stubbs P, Collinson P, Moseley D, Greenwood T, Noble M. Prospective study of the role of cardiac troponin T in patients admitted with unstable angina [see comments]. BMJ 1996; 313:262-4.

49. Galvani M, Ottani F, Ferrini D et al. Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina. Circulation 1997; 95:2053-9.

50. Wu AH, Apple FS, Gibler WB, Jesse RL, Warshaw MM, Valdes R, Jr. National Academy of Clinical Biochemistry Standards of Laboratory Practice: recommendations for the use of cardiac markers in coronary artery diseases. Clin Chem 1999; 45:1104-21.

51. Thygesen K, Alpert JS, White HD et al. Universal definition of myocardial infarction. Circulation 2007; 116:2634-53.

52. Collinson PO, Rao AC, Canepa-Anson R, Joseph S. Impact of European Society of Cardiology/American College of Cardiology guidelines on diagnostic classification of patients with suspected acute coronary syndromes. Ann Clin Biochem 2003; 40:156-60.

53. Apple FS, Collinson PO. Analytical Characteristics of High-Sensitivity Cardiac Troponin Assays. Clin Chem 2012; 58:54-61.

54. 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.

55. Shah AS, Anand A, Sandoval Y et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet 2015.

56. Roffi M, Patrono C, Collet JP et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016; 37:267-315.

57. Jaffe AS, Apple FS, Morrow DA, Lindahl B, Katus HA. Being rational about (im)precision: a statement from the Biochemistry Subcommittee of the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the definition of myocardial infarction. Clin Chem 2010; 56:941-3.

58. Evaluation of a bedside whole-blood rapid troponin T assay in the emergency department. Rapid Evaluation by Assay of Cardiac Troponin T (REACTT) Investigators Study Group. Acad Emerg Med 1997; 4:1018-24.

59. Ter AE, Visser A, Reitsma B, Breedveld R, Wolthuis A. Point-of-care troponin T is inferior to high-sensitivity troponin T for ruling out acute myocardial infarction in the emergency department. Eur J Emerg Med 2016; 23:95-101.

60. Mion MM, Bragato G, Casarotti A et al. Clinical performance of cardiac Troponin I: A comparison between the POCT AQT90 FLEX and the Dimension Vista analyzer in an emergency setting. Clin Biochem 2017; 50:763-7.

61. Venge P, van LL, Blaschke S et al. Equal clinical performance of a novel point-of-care cardiac troponin I (cTnI) assay with a commonly used high-sensitivity cTnI assay. Clin Chim Acta 2017; 469:119-25.

62. Peacock WF, Diercks D, Birkhahn R et al. Can a Point-of-Care Troponin I Assay be as Good as a Central Laboratory Assay? A MIDAS Investigation. Ann Lab Med 2016; 36:405-12.

63. Suh D, Keller DI, Hof D, von EA, Gawinecka J. Rule-out of non-ST elevation myocardial infarction by five point of care cardiac troponin assays according to the 0 h/3 h algorithm of the European Society of Cardiology. Clin Chem Lab Med 2018; 56:649-57.

64. Christ M, Geier F, Blaschke S et al. Clinical performance of a new point-of-care cardiac troponin I test. Clin Chem Lab Med 2018; 56:1336-44.

65. Chenevier-Gobeaux C, Deweerdt L, Cantero AV et al. Multi-centre evaluation of recent troponin assays for the diagnosis of NSTEMI. Pract Lab Med 2018; 11:23-32.

66. Sorensen NA, Neumann JT, Ojeda F et al. Diagnostic Evaluation of a High-Sensitivity Troponin I Point-of-Care Assay. Clin Chem 2019; 65:1592-601.

67. Boeddinghaus J, Nestelberger T, Koechlin L et al. Early Diagnosis of Myocardial Infarction With Point-of-Care High-Sensitivity Cardiac Troponin I. J Am Coll Cardiol 2020; 75:1111-24.

68. Collinson PO, John C, Lynch S et al. A prospective randomized controlled trial of point-of-care testing on the coronary care unit. Ann Clin Biochem 2004; 41:397-404.

69. Ryan RJ, Lindsell CJ, Hollander JE et al. A multicenter randomized controlled trial comparing central laboratory and point-of-care cardiac marker testing strategies: the Disposition Impacted by Serial Point of Care Markers in Acute Coronary Syndromes (DISPO-ACS) trial. Ann Emerg Med 2009; 53:321-8.

70. Renaud B, Maison P, Ngako A et al. Impact of point-of-care testing in the emergency department evaluation and treatment of patients with suspected acute coronary syndromes. Acad Emerg Med 2008; 15:216-24.

71. Straface AL, Myers JH, Kirchick HJ, Blick KE. A rapid point-of-care cardiac marker testing strategy facilitates the rapid diagnosis and management of chest pain patients in the emergency department. Am J Clin Pathol 2008; 129:788-95.

72. Loten C, Attia J, Hullick C, Marley J, McElduff P. Point of care troponin decreases time in the emergency department for patients with possible acute coronary syndrome: a randomised controlled trial. Emerg Med J 2010; 27:194-8.

73. Goodacre SW, Bradburn M, Cross E, Collinson P, Gray A, Hall AS. The Randomised Assessment of Treatment using Panel Assay of Cardiac Markers (RATPAC) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. Heart 2011; 97:190-6.

74. Goodacre S, Bradburn M, Fitzgerald P et al. The RATPAC (Randomised Assessment of Treatment using Panel Assay of Cardiac markers) trial: a randomised controlled trial of point-of-care cardiac markers in the emergency department. Health Technol Assess 2011; 15:iii-102.

75. Tomonaga Y, Gutzwiller F, Luscher TF et al. Diagnostic accuracy of point-of-care testing for acute coronary syndromes, heart failure and thromboembolic events in primary care: a cluster-randomised controlled trial. BMC Fam Pract 2011; 12:12.

76. Asha SE, Cooke A, Walter E, Weaver J. Three-month outcome of patients with suspected acute coronary syndrome using point-of-care cardiac troponin-T testing compared with laboratory-based cardiac troponin-T testing: a randomised trial. Emerg Med J 2015; 32:601-7.

77. Florkowski C, Don-Wauchope A, Gimenez N, Rodriguez-Capote K, Wils J, Zemlin A. Point-of-care testing (POCT) and evidence-based laboratory medicine (EBLM) - does it leverage any advantage in clinical decision making? Crit Rev Clin Lab Sci 2017; 54:471-94.

78. Bradburn M, Goodacre SW, Fitzgerald P et al. Interhospital variation in the RATPAC Trial (Randomised Assessment of Treatment using Panel Assay of Cardiac markers). Emerg Med J 2012; 29:233-8.

79. Tideman PA, Tirimacco R, Senior DP et al. Impact of a regionalised clinical cardiac support network on mortality among rural patients with myocardial infarction. Med J Aust 2014; 200:157-60.

80. Alghamdi A, Reynard C, Morris N et al. Diagnostic accuracy of the Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid with a point-of-care cardiac troponin assay. Emerg Med J 2020; 37:223-8.

81. Nilsson S, Andersson A, Janzon M, Karlsson JE, Levin LA. Cost consequences of point-of-care troponin T testing in a Swedish primary health care setting. Scand J Prim Health Care 2014; 32:241-7.

82. Tsui AKY, Lyon ME, van DS et al. Analytical Concordance of Diverse Point-of-Care and Central Laboratory Troponin I Assays. J Appl Lab Med 2019; 3:764-74.

83. Saenger AK. Pick a Number, Any Number...Choosing Your Troponin Cutoff Wisely. J Appl Lab Med 2019; 3:753-5.

84. Regan B, O'Kennedy R, Collins D. Point-of-Care Compatibility of Ultra-Sensitive Detection Techniques for the Cardiac Biomarker Troponin I-Challenges and Potential Value. Biosensors (Basel) 2018; 8.

85. Alawieh H, Chemaly TE, Alam S, Khraiche M. Towards Point-of-Care Heart Failure Diagnostic Platforms: BNP and NT-proBNP Biosensors. Sensors (Basel) 2019; 19.

86. McRae MP, Simmons G, Wong J, McDevitt JT. Programmable Bio-nanochip Platform: A Point-of-Care Biosensor System with the Capacity To Learn. Acc Chem Res 2016; 49:1359-68.

87. Tomonaga Y, Gutzwiller F, Luscher TF et al. Diagnostic accuracy of point-of-care testing for acute coronary syndromes, heart failure and thromboembolic events in primary care: a cluster-randomised controlled trial. BMC Fam Pract 2011; 12:12.