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Clinica Chimica Acta 346 (2004) 211–219

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Evaluation of a point-of-care assay for cardiac markers for patients suspected of acute myocardial infarction

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Received 9 February 2004; received in revised form 20 March 2004; accepted 26 March 2004

Abstract

Background: Creatine kinase MB (CK-MB), and cardiac troponin I (cTnI) are important biomarkers for the diagnosis and rule-out of acute myocardial infarction (AMI) of patients who presented to the emergency department (ED) with chest pain. With new rapid ED assessment protocols, there is increasing pressure to produce results with a short turnaround time (TAT), and point-of-care (POC) testing is one alternative for providing fast results. *Methods*: In a multicenter study, we evaluated the analytical precision, sensitivity and specificity of the RAMP® (Response Biomedical) CK-MB and cTnI POC assays and compared results against the Triage (Biosite) POC and the Dimension RxL (Dade Behring) central-laboratory assays on 365 subjects, including 185 patients suspected of AMI, and determined the normal range on 180 healthy individuals. At one site, the clinical sensitivity and specificity were estimated in 121 patients and healthy subjects with AMI using the European Society of Cardiology (ESC)/American College of Cardiology (ACC) definition of AMI. Results from healthy individuals and those with ST elevation and non-ST elevation AMI were included in a receiver operating characteristic (ROC) curve analysis. *Results*: Intra- and total imprecision ranged from 7.2% to 11.4% for cTnI at 0.22, 1 and 5 ng/ml and 4.8% to 8.6% for CK-MB at 7, 14 and 25 ng/ml. The upper limit of linearity was 32 ng/ml with an average recovery of 105% for cTnI and 80 ng/ml with a 106% recovery for CK-MB. The lower limit of detection was 0.03 ng/ml (10% coefficient of variance [CV] = 0.21 ng/ml) for cTnI and 0.32 ng/ml for CK-MB. The upper reference limit (normal range) was <0.03 ng/ml for cTnI and 0–3.7 ng/ml for CK-MB. Analytical correlation against Dimension RxL were RAMP=(0.456 × RxL) + 0.11 ($r = 0.988$, $n = 364$) for cTnI and RAMP=(0.966 × RxL) + 0.60 ($r = 0.986$, $n = 363$) for CK-MB and against Triage, RAMP=(0.626 × Triage) + 0.164 ($r = 0.969$, $n = 364$) for cTnI and RAMP=(0.845 × RxL) − 0.495 ($r = 0.952$, $n = 363$) for CK-MB. On 39 AMI and 67 non-AMI patients, the clinical sensitivity, specificity and diagnostic efficiency of the cTnI and CK-MB RAMP assays were not significantly different from predicate assays. *Conclusions*: The RAMP cardiac marker assays are alternatives to other FDA-cleared central laboratory and POC testing devices.

Keywords: Acute myocardial infarction; Point-of-care testing; Clinical sensitivity and specificity

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doi:10.1016/j.cccn.2004.03.036

1. Introduction

Clinical guidelines written by laboratory medicine [1], emergency medicine [2] and cardiology [3] have established the important role of cardiac markers, especially cardiac troponin, in the diagnosis and rule-out of acute myocardial infarction (AMI). The European Society of Cardiology (ESC)/American College of Cardiology (ACC) have redefined AMI predicated on a clinical presentation of ischemia and an increased concentration of cardiac markers. Although cardiac troponin I (cTnI) and T (cTnT) are emerging as the biomarker of choice, these guidelines and many clinical laboratories continue to use creatine kinase MB (CK-MB). With the development of accelerated protocols for the rule-out of acute coronary syndromes (ACS) in patients who present to the emergency department (ED) with chest pain [4], there is increasing need for clinical laboratories to reduce the turnaround time (TAT) for cardiac marker results. Recommendations for the optimum TAT for cardiac markers, defined as blood collection to the electronic availability of results [5], vary from 30 to 60 min [1,3]. This TAT is a challenge for most central laboratories due to the time needed for the delivery of blood, the time for full clot retraction if serum is used, centrifugation to obtain serum or plasma and the 10–20-min assay time required for most automated immunoassay analyzers. The emergence of quantitative point-of-care (POC) assays offer an attractive alternative because of the potential for bedside analysis, obviating the need to deliver the sample to the lab, shorter assay times and the use of whole blood, thereby eliminating the time necessary for full clot retraction, and the centrifugation step [6,7].

An important issue for any cardiac troponin assay is the assay's lower limit of detection and total precision. This is especially critical for POC testing for cardiac markers as these attributes may be sacrificed for assay convenience [8]. The ESC/ACC have recommended cardiac troponin cutoffs at the 99th percentile of a reference population with a total assay imprecision of $\leq 10\%$ [9]. The International Federation of Clinical Chemistry (IFCC) Committee on the Standardization of Markers of Cardiac Damage (C-SMCD) has shown that no cardiac troponin assay currently meets this criteria [10]. An approach that minimizes false positive results due to assay imprecision is to use a higher cardiac troponin cutoff concentration set at the 10% coefficient of variance (CV) [11,12]. The purpose of the current multicenter study was to evaluate the analytical and clinical performance of the RAMP cTnI and CK-MB point-of-care assays.

2. Materials and methods

2.1. Device description and clinical trial sites

The RAMP cTnI and CK-MB assays are separate quantitative whole-blood immunochromatographic assays. The cTnI assay contains a monoclonal detection antibody and a polyclonal capture antibody, both directed to the stable (central) part of the molecule (between amino acid residues 30 and 110) [13]. The CK-MB makes use of CK-MM capture antibody, which is immobilized and anti-CK-MB detection antibody [14]. Diluted whole blood is applied to the sample well. The red blood cells are retained in the sample pad, and the separated plasma migrates along the strip. Fluorescent-dyed latex particles bind to the analyte and are immobilized at the detection zone. Additional particles are immobilized at the internal control zone. The fluorescence of the detection and internal control zones are measured on the RAMP Clinical Reader®, and the ratio between these values is calculated. This ratio is used to determine the analyte concentration by interpolation from a lot-specific standard curve supplied by the manufacturer in each test kit. The on-instrument turnaround time for the RAMP assays is about 12 min for CK-MB and about 10 min for cTnI. The RAMP assay procedure is similar to the Triage assay, except that the RAMP assay requires a dilution step with buffer prior to insertion of the device into the reader. Only whole blood collected in EDTA can be used for the RAMP assay, while both whole blood and plasma collected in heparin can be used for Triage. Either serum of heparinized plasma can be used for the Dimension RxL. The upper limit of linearity for the RAMP cTnI and CK-MB assays is 32 and 80 ng/ml, respectively, according to the manufacturer. For Triage, the sensitivity and upper limit of linearity are 0.75 and 125 ng/ml for CK-MB

and 0.19 and 50 ng/ml for cTnI, respectively. For RxL, the corresponding values are 0.5 and 300 ng/ml for CK-MB and 0.04 and 40 ng/ml for cTnI, respectively.

This study was conducted at three sites using laboratory personnel who received training from the manufacturer of the RAMP device: Hartford Hospital, Hartford, CT, Hennepin County Medical Center, Minneapolis, MN, and University of Maryland, Baltimore, MD. The protocol was reviewed and approved by the Institutional Review Boards at each site. Each site performed testing on the RAMP and Triage. Samples were frozen and sent to Hennepin County Medical Center for retrospective testing on the RxL.

2.2. Analytical evaluations

The intra-assay and total imprecison of the RAMP assays were determined by one operator assaying duplicates of quality control materials and pooled human plasma twice each day for 10 days. The linearity was checked by preparing a cTnI and CK-MB antigen concentrations of 27.5 and 60 ng/ml, respectively, in normal donor EDTA blood, then serial diluting these samples using the same baseline EDTA blood to concentrations of 0.86, 1.7, 3.4, 6.9, 13.7 and 27.5 ng/ml for cTnI and 2.5, 5.0, 10.0, 20.0 and 40.0 for CK-MB. Linear regression analysis of measured value were plotted against the expected cardiac marker concentrations. The percent recovery was determined by assaying five replicates of each dilution and the baseline sample. Potentially interfering substances were tested by spiking different concentrations of hemoglobin (500–2000 mg/dl), triglyceride (750–3000 mg/dl), bilirubin (40–80 mg/dl) cholesterol (100–500 mg/dl) and heparin (16–104 IU/ml). The cTnI assay was tested against skeletal troponin I (500–1000 ng/ml), cardiac troponin T (500–1000 ng/ml) and cardiac troponin C (500–1000 ng/ml), and the CK-MB assay was tested against CK-MM (5000–50,000 ng/ml) and CM-BB (250–1000 ng/ml). Commercially available patient plasma samples previously identified as containing human anti-mouse, human anti-goat, human anti-rabbit antibodies, or rheumatoid factor (Scantibodies Laboratory, Santee, CA) were tested with and without a buffer that contains an additive included specifically to reduce potential interference by these factors. The high-dose hook effect was examined at concentrations of 125, 250 and 500 ng/ml for cTnI and 500 and 1000 ng/ml for CK-MB.

The lower limit of detection was determined by assaying 20 replicates of the zero standard and five replicates of the lowest nonzero calibrator (0.5 and 1.25 ng/ml for cTnI and CK-MB, respectively). The mean plus 2 S.D. of the zero standard were used to calculated the lower limit of detection. For cTnI, the low-end precision of the RAMP assay was determined by one operator assaying 10 replicates of 5 spiked cTnI samples in human plasma. From these data, the 10% and 20% CVs were determined by interpolation of the CV vs. cTnI concentration curve. The 20% CV is often referred to as the ‘‘functional sensitivity’’ [15].

2.3. Clinical evaluations

All samples were collected into vacutainers containing EDTA or heparin. There were 180 blood samples collected from healthy individuals without a reported or known history of heart disease (84 males and 96 females, 60 from each site). The health status of each participant was determined by interview. We did not attempt to match the age of healthy individuals to those of enrolled with myocardial infarction. The normal range was determined nonparametrically by computing the central 95th and 99th percentile of this population for cTnI and CK-MB. We also determined if there was a difference in normal range concentrations by gender. There were 185 samples collected on patients suspected of AMI based on the individual hospital criteria (115 males and 70 females, 61 from Hennepin County Medical Center, 60 from the University of Maryland and 64 from Hartford Hospital). Results of the RAMP assay were compared to the Dimension RxL Immunoassay Analyzer (Dade Behring Diagnostics, Deerfield, IL) [16] and the Triage Cardiac Panel (first-generation assay, Biosite, San Diego, CA) [6]. Samples from normal subjects and those with suspected AMI were used in this comparison.

For the 61 patients collected at the Hartford site, a medical records review was conducted at discharge. An AMI was diagnosed in 42 cases using the ESC/ACC criteria using clinical history, 12-lead electro-

cardiogram and results of cardiac troponin T (Roche Diagnostics, Indianapolis, IN, cutoff ≥ 0.03 ng/ml). Subsequently, the results from four AMI patients were excluded because blood was collected at presentation before results were increased (cTnT < 0.03 ng/ml). Later samples from these patients (not used in this trial) produced abnormal cTnT and CK-MB results. There was one case of an acute cardiac arrest and cardiogenic shock that was included as true cardiac damage, and the total number of AMI cases used in the calculations was 39. The non-AMI cases composed of the remaining 18 cases where an AMI was ruled out and 60 healthy subjects for a total of 78. The 99th percentile value was used for cTnI [12], and the manufacturer's recommendation of 95th percentile cutoffs was used for CK-MB: 0.12 and 5.0 ng/ml for the RAMP cTnI and CK-MB assays, respectively, 0.40 and 4.3 ng/ml for the Triage and 0.14 and 3.6 ng/ml, respectively, for the Dimension RxL. We did not use gender-specific reference intervals for calculation of clinical sensitivity, specificity and efficiency, because comparative male and female cutoffs were not available for the two predicate assays.

The estimation of clinical sensitivity and specificity performed in this are not necessarily representative of the true clinical performance expected in real patients because of the limitations imposed on this analytical study. For example, data from healthy individuals are not normally included in the ROC analysis. In addition, we have not excluded patients with ST elevation AMI, a diagnosis that is usually made with electrocardiographic recordings. These patients were included to increase the sample size for the data analysis. Estimates of clinical sensitivity and specificity were made to compare results across assay platforms as a means for evaluating analytical performance using samples from a clinical setting. This data cannot be used to determine assay performance in a group of patients with non-ST elevation AMI vs. non-cardiac patients who present with acute chest pain.

2.4. Statistical analysis

Receiver operating characteristic (ROC) curve analysis and the area under the ROC curve was conducted using Analyse-it+ (ver. 1.68, Clinical Laboratory Software, UK). The 95% confidence intervals for the clinical sensitivity, specificity and efficiency were calculated as proportions using a standard formula.

3. Results

The within-run and total imprecision of the RAMP cTnI ranged from 7.2% to 8.7% and 8.3% to 11.4%, respectively (Table 1). The imprecision was slightly better for CK-MB, range 4.8–7.8% and 6.9–8.6%, respectively. The linear regression equations of measured vs. expected cTnI and CK-MB concentrations were measured=(1.019 × expected) + 0.279 ($r = 0.997$) and measured=(1.050 × expected) + 0.098 ($r = 0.999$), respectively. The percent recovery for the spiked linearity samples ranged from 95% to 115% (mean 105%) for cTnI and 99–111% (mean 106%) for CK-MB. There was minimal interference with hemoglobin, triglyceride, bilirubin, cholesterol, or heparin (% recovery ranged 79.3–115.8% for cTnI and 89.7–113.4% for CK-MB). There was no cross-reactivity towards skeletal troponin I, cTnT, or cTnC for the RAMP cTnI assay and CK-MM and CK-BB for the RAMP CK-MB assay ($< 0.06\%$ for all). Table 2 shows the results of the heterophile antibody

Table 1
Imprecision of cTnT and CK-MB assays[a]

Assay	Concentration	Intra-assay (%)	Total (%)
RAMP cTnI	0.22	7.2	11.4
	1.05	8.7	10.0
	5.01	8.3	8.3
Triage cTnI	0.35	19.5	19.4
	2.03	11.7	12.1
	20.8	9.1	9.1
RxL cTnI	0.16	4.0	9.2
	1.44	2.6	5.2
	27.7	1.9	3.6
Ramp CK-MB	7.2	7.7	8.6
	14.3	7.8	8.5
	25.1	4.8	6.9
Triage CK-MB	5.31	12.2	12.0
	23.2	10.0	9.4
	64.4	9.5	10.2
RxL CK-MB	3.58	8.7	9.7
	16.7	2.6	6.8
	46.0	1.4	4.0

[a] All results in nanograms per milliliter.

Table 2
Interference from heterophile antibodies for the RAMP cTnI and CK-MB assays[a]

Sample number	HAMA (ng/ml)	RF (ng/ml)	Heterophilic specificity[b]			cTnI		CK-MB	
			HAMA	HAGA	HARA	No buffer	Buffer	No buffer	Buffer
1	<3	997	4	4	4	0.41	0.09	58.6	20.8
2	ND	ND	2	3	3	0.00	0.01	3.7	1.0
3	<3	322	4	4	4	2.09	0.00	25.5	3.7
4	100	1080	4	2	2	0.00	0.03	3.2	2.0
5	<3	25	3	4	1	0.30	0.22	0.42	0.46
6	<3	<20	4	4	3	0.00	0.00	0.00	0.00
7	<3	119	4	4	2	8.10	0.00	18.9	0.50
8	<3	1165	4	4	4	>32	0.37	>80	5.7
9	585	178	3	4	1	0.00	0.00	5.4	2.7
10	<40	1645	4	4	4	0.00	0.00	10.9	1.6

[a] HAMA, HAGA, and HARA: human antimouse, antigoat, and antirabbit antibodies; all results are expressed as nanograms per milliliter.
[b] False positive results in a commercially available assay caused by cross-bridging assay of the antibodies listed. Presence of interferents are expressed in relative values: (1) >cutoff but <2 cutoff; (2) between 2× and 5× cutoff; (3) between 5× and 10× cutoff; (4) >10× cutoff. Data are from Scantibodies Laboratory.

and rheumatoid factor study. There were two samples (5 and 8) for cTnI and two samples (1 and 8) for CK-MB that had reduced cardiac marker concentrations in the presence of the heterophile antibody inhibiting buffer. Thus, interferences from heterophile antibodies may be possible in these assays on rare occasions.

There was no high-dose hook effect at the concentrations tested; samples with high cTnI and CK-MB concentrations produced values that all exceeded the upper limit of linearity. The lower limit of detection was 0.03 ng/ml for cTnI and 0.32 ng/ml for CK-MB. The within-day imprecision profile for RAMP cTnI is shown in Fig. 1. cTnI concentrations producing a 20% and 10% CV (coefficient of variance) were 0.10 and 0.21 ng/ml, respectively. The upper limit of normal was 0.03 ng/ml for cTnI at the central 95th percentile and 0.12 ng/ml at the 99th percentile. There was no difference between males and females. The upper limit of normal was 5.0 ng/ml for CK-MB at the central 95th percentile and 8.5 ng/ml at the 99th percentile. There was a significant ($p < 0.05$) gender bias for CK-MB at the 95th percentile (3.0 ng/ml for females and 8.0 ng/ml for males) and 99th percentile (3.8 ng/ml for females and 9.6 ng/ml for males).

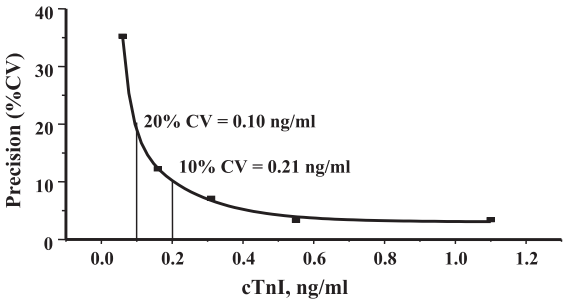

Fig. 1. Low-end total (between-day) precision profile for the RAMP cTnI assay. The 10% CV value was 0.21 ng/ml.

Fig. 2 shows the correlation of results for RAMP vs. Dimension RxL and Triage for cTnI and CK-MB. Table 3 lists the regression equation for all combinations of tests, including the subset of biomarker concentrations at the low end. When all data points were used, the correlation coefficient was >0.95. A higher degree of scatter was observed when low concentrations were plotted. The slope and *y*-intercept for the CK-MB assay was near unity exhibiting no standardization bias. Reported concentrations for the RAMP cTnI assay were consistently lower than either the Dimension RxL and Triage assays.

Using data from one clinical site, the estimated clinical sensitivity and specificity for the diagnosis of AMI using the ESC/ACC criteria for the three assays are shown in Table 4. For cTnI, the clinical sensitivity was the highest for the Dimension RxL, followed by the RAMP and then Triage. However, the cTnI clinical specificity for the Triage assay was the highest of the three assays. Given that there is an

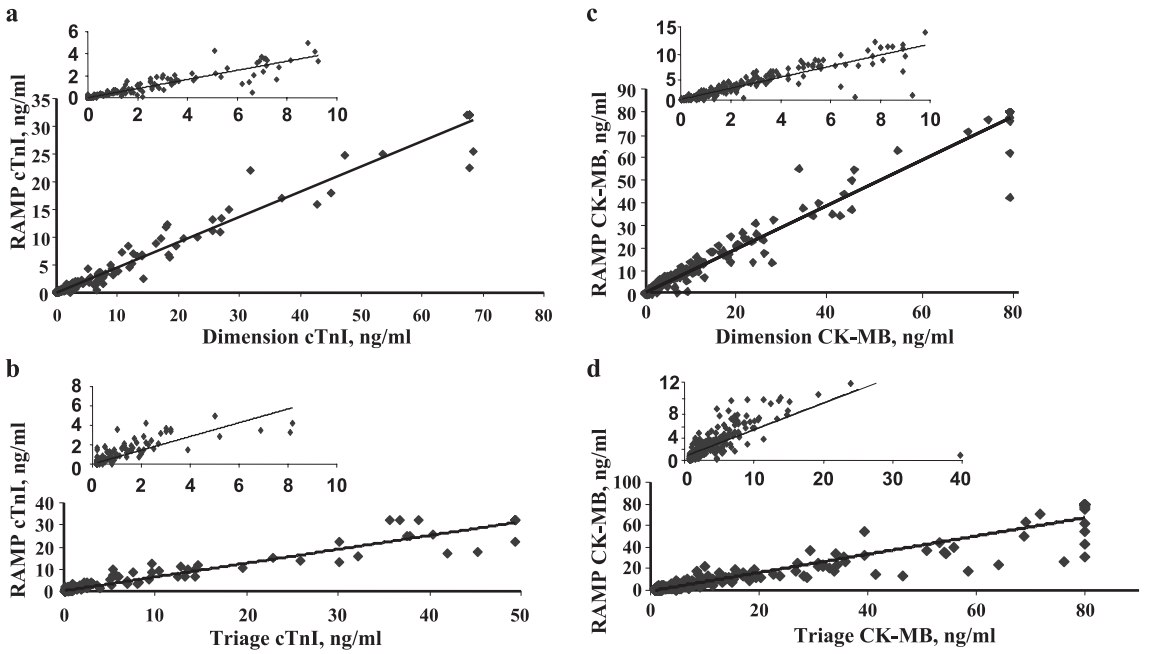

Fig. 2. Analytical correlation for (a) cTnI: RAMP vs. Dimension RxL; (b) cTnI RAMP vs. Triage; (c) CK-MB: RAMP vs. Dimension; (d) CK-MB RAMP vs. Triage.

inherent tradeoff between clinical sensitivity and specificity, lowering the Triage cutoff to 0.30 ng/ml improved clinical sensitivity of this data to 85% (95% CI: 73–96) while degrading the specificity to 91% (85–97%). The area under the ROC curve (Fig. 3) and the clinical efficiency (Table 4) shows that these three assays have essentially the same clinical performance.

The clinical sensitivity for the Triage CK-MB assay was slightly higher than for the other two assays (Table 4 and Fig. 3), but the clinical specificity was slightly lower than for the Dimension RxL or RAMP. Again, the ROC analysis and clinical efficiency shows that these assays are equivalent. On the basis of ROC analysis, these data show that cTnI as a cardiac marker (AUC ranging from 0.91 to 0.97) was overall superior to CK-MB (AUC range 0.85–0.86).

4. Discussion

This study has demonstrated that the RAMP whole-blood POC testing device had acceptable analytical characteristics and similar sensitivity and specificity for AMI detection to be an acceptable alternative to an automated central laboratory-based instruments (Dade Dimension RxL) and an established FDA-cleared POC testing device (Biosite Triage) for monitoring cardiac biomarkers at implementation of POC testing for cardiac markers can result in substantial reductions in assay turnaround times. In separate studies, Christenson [5] and Lee-Lewandrowski [17] showed a reduction in TAT relative to the central laboratory of 88% and 84.5%, respectively, when a qualitative bedside cTnI device was used (Spectral Diagnostics). Caragher et al. [18] showed a TAT 55% reduction vs. the central lab using a quantitative assay for cTnI, myoglobin and CK-MB.

Unfortunately, established clinical practice guidelines with regards to TAT may not justify the additional reagent costs incurred with the use of POC testing for cardiac markers. Additional clinical advantages need to be demonstrated. From labor and reagent cost considerations, it may be difficult for laboratories to justify testing non-ED requests for cardiac markers monitored on a POC testing

Table 3
Analytical correlation between the cTnI and CK-MB assays

	cTnI	CK-MB
RAMP vs. Dimension RxL		
All data	RAM0P = (0.456 × RxL) + 0.011 $r = 0.988$, $n = 364$	RAMP = (0.966 × RxL) + 0.60 $r = 0.986$, $n = 363$
Low-end subset	RAMP=(0.414 × RxL) + 0.013 $r = 0.936$, $n = 323$	RAMP = (1.13 × RxL) + 0.189 $r = 0.914$, $n = 295$
RAMP vs. Triage		
All data	RAMP = (0.626 × Triage) + 0.164 $r = 0.969$, $n = 364$	RAMP = (0.845 × Triage) − 0.495 $r = 0.952$, $n = 363$
Low-end subset	RAMP = (0.707 × Triage) + 0.025 $r = 0.830$, $n = 323$	RAMP = (0.481 × Triage) + 0.715 $r = 0.726$, $n = 295$
Triage vs. Dimension RxL		
All data	Triage = (0.718 × RxL) − 0.138 $r = 0.974$, $n = 364$	Triage = (1.036 × RxL) + 2.20 $r = 0.981$, $n = 363$
Low-end subset	Triage = (0.420 × RxL) + 0.139 $r = 0.809$, $n = 323$	Triage =(1.28 × RxL) + 0.962 $r = 0.668$, $n = 295$

platform. Improved clinical outcomes may be the best justification for POC implementation. Clinical trials have shown that patients with non-ST elevation AMI benefit from early percutaneous coronary intervention [19] or glycoprotein IIb/IIIa inhibitors [20]. It may be possible that rapid cardiac marker testing could lead to earlier detection and enrollment of patients to these therapies. If aggressive early therapy is to be adopted, some recommendation for the TAT for cardiac markers results will need to be determined. A result produced within 20 min might not have any more impact compared to a result returned within 1–2 h. However, a reduction in the ED length of stay (LOS) of chest pain patients could justify use of POC testing. In the Massachusetts General Hospital study, implementation of POC testing in a satellite laboratory for cTnI reduced the LOS from 386 to 338 min, although the study was insufficiently powered to reach statistical significance [17].

The analytical correlation between cTnI results among the different testing platforms illustrates the urgent need for cTnI standardization [21]. Thus, when a patient presents with chest pain, it may be warranted to initially perform POC testing in the ED and then to use the central laboratory for follow-up testing should admission of this patient be warranted. Since the two POC testing devices for cTnI evaluated in this study are not standardized to a central-lab assay, one would have to perform repeat testing of the initial ED sample on a central lab platform or use POC device as a qualitative positive or negative result for triaging purposes.

Correlating the performance of these biomarkers as a function of time of blood collection relative to the onset of symptoms was beyond the scope of this study. Although there were a few cases of unstable angina defined as AMI under the existing ESC/ACC guidelines, this study did not focus on identifying patients with minor necrosis or the use of POC testing for risk stratification of patients for future adverse cardiovascular events. The relative clinical sensitivities and specificities between the two POC assays were equivalent to a robust central-laboratory assay.

Clinical trials such as TACTICS II [22] have shown that non-ST elevation MI with troponin concentrations above the 99th percentile but below the 10% CV value are at increased risk for death and AMI. Thus, unless the POC assay has proven to

Table 4
Clinical sensitivity and specificity for the RAMP cTnI and CK-MB assays[a]

Parameter/assay	cTnI (95% CI) (%)	CK-MB (95% CI) (%)
Clinical sensitivity		
RAMP	90 (80–99)	59 (43–74)
Triage	74 (61–88)	77 (64–90)
Dimension RxL	95 (88–100)	64 (49–79)
Clinical specificity		
RAMP	86 (78–94)	90 (83–96)
Triage	96 (91–100)	60 (49–70)
Dimension RxL	87 (80–95)	89 (81–96)
Clinical efficiency[b]		
RAMP	87 (81–93)	80 (73–88)
Triage	88 (82–94)	81 (74–88)
Dimension RxL	90 (84–95)	80 (73–88)

[a] No significant difference between any testing platform for a given analyte (cTnI or CK-MB).

[b] Clinical efficiency is the sum of false positives and negatives divided by all data points.

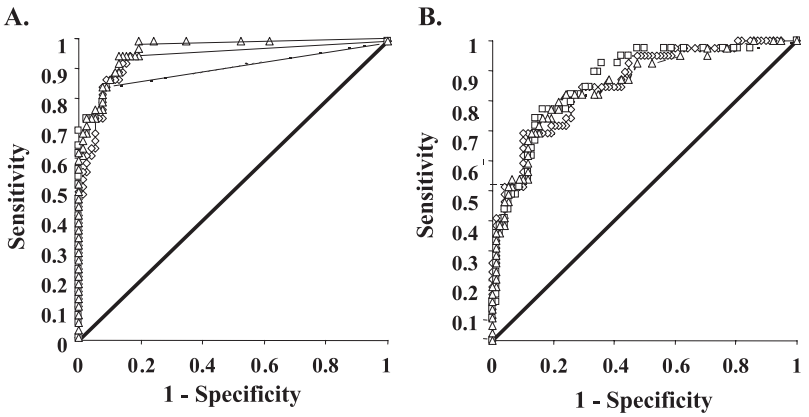

Fig. 3. Receiver operating characteristic curve analysis for the RAMP assay, Triage, and Dimension RxL assays. (A) cTnI. AUC: RAMP 0.94 (95%CI: 89–99), Triage 0.91 (0.84–0.98), Dimension RxL: 0.97 (0.94–0.99). (B) CK-MB. AUC: RAMP 0.86 (95%CI: 79–93), Triage 0.86 (0.79–0.93), Dimension RxL: 0.85 (0.78–0.93).

have high sensitivity for troponin or has demonstrated utility for risk stratification [23], it may be prudent to send these samples to a central laboratory for a high-sensitivity and precise troponin result rather than an assay that is designed for testing convenience and rapid assay turnaround times. Use of troponin assays that do not have high sensitivity may result in missed diagnoses [24].

In summary, the RAMP cTnI and CK-MB assays meets most of the quality specifications established by the IFCC C-SMCD [13]. The antibodies used in the assays are directed towards the stable part of the molecule. The assay does not react to non-cardiac troponins or other potentially interfering molecules and is minimally influenced by the presence of heterophile antibodies. The linearity, dilution recovery of the assays has been documented. The package insert specifies the only EDTA plasma is acceptable and that both cTnI or CK-MB are stable at ambient temperatures for up to 2 h, and 2–8 °C for 2 days. Given that the recommended sample to be tested is whole blood, there is no recommendation for freezer storage at −20 °C or lower. The cutoff concentrations have been established according to ESC/ACC guidelines. The assay is calibrated against a native troponin T-I-C complex purchased from Hytest (Turku, Finland). The concentration was determined by gel-scanning using enhanced laser densitometry. A nine-point calibration curve is prepared in plasma. As a limitation, we did not determine whether there is an equimolar response for the antibodies used when tested against different forms (i.e., free, binary and ternary complexes) of cardiac troponin. A second limitation was that this study was conducted by trained laboratory personnel. The intent of the assay is to be used at bedside or satellite laboratory by caregivers. It is possible that the performance could be reduced when testing is performed by the clinical staff, e.g., inaccuracy in the dilution step.

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