Evaluation of analytical performance and comparison of clinical results of the new generation method AccuTnI + 3 for the measurement of cardiac troponin I using both patients and quality control plasma samples

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ABSTRACT

The study aims are to evaluate the analytical performance and the clinical results of the chemiluminescent Access AccuTnI + 3 immunoassay for the determination of cardiac troponin I (cTnI) with DxI 800 and Access2 platforms and to compare the clinical results obtained with this method with those of three cTnI immunoassays, recently introduced in the European market. The limits of blank (LoB), detection (LoD), and quantitation (LoQ) at 20% CV and 10% CV were 4.5 ng/L and 10.9 ng/L, 17.1 and 30.4 ng/L, respectively. The results of STAT Architect high Sensitive TnI (Abbott Diagnostics), ADVIA Centaur Troponin I Ultra (Siemens Healthcare Diagnostics), ST AIA-Pack cTnI third generation (Tosoh Bioscience), and Access AccuTnI + 3 (Beckman Coulter Diagnostics) showed very close correlations (R ranging from 0.901 to 0.994) in 122 samples of patients admitted to the emergency department. However, on average there was a difference up to 2.4-fold between the method measuring the highest (ADVIA method) and lowest cTnI values (AccuTnI + 3 method). The consensus mean values between methods ranged from 6.2% to 29.6% in 18 quality control samples distributed in an external quality control study (cTnI concentrations ranging from 29.3 ng/L to 1557.5 ng/L). In conclusion, the results of our analytical evaluation concerning the AccuTnI + 3 method, using the DxI platform, are well in agreement with those suggested by the manufacturer as well as those reported by some recent studies using the Access2 platform. Our results confirm that the AccuTnI + 3 method for the Access2 and DxI 800 platforms is a clinically usable method for cTnI measurement.

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1. Introduction

Cardiac troponins I (cTnI) and T (cTnT) are currently considered the most sensitive and specific biochemical markers of myocardial damage [1–11]. Since 2000, all international guidelines from the year 2000 recommend that an increased concentration of cardiac troponin should be defined as a value exceeding the 99th percentile upper reference limit (99th URL) [1–5]. Moreover, an assay imprecision ≤10%, estimated by coefficient of variation (CV), was also recommended for the values corresponding to the 99th URL [1–5]. Unfortunately, none of the immunoassay methods, commercially available at the time of publication of the first guidelines [1], was able to full-fill these quality specifications. Only in the last 10 years, a new generation of the cTnI and cTnT immunoassays has been set up by manufacturers in order to improve the analytical performance in accordance with international guidelines and quality specifications [9,10].

The aim of this study is to evaluate the analytical performance and the clinical results of the Access AccuTnI + 3 method, which is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cTnI levels using the DxI 800 and Access2 platforms. We also compare the cTnI values measured with this new method to those obtained in our laboratory by other three recent cTnI immunoassays in plasma samples of patients admitted to the Emergency Department (ED), as well as to results reported by the laboratories taking part in an external quality control (EQC) study in Italy.

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2. Materials and methods

2.1. Assay methods

The Access AccuTnI + 3 assay is a two-site immunometric assay (Beckman Coulter, Inc. Brea, CA 92821 USA). Beckman Coulter distributes two different kits specific for the DxI 800 (code A98264) and Access2 (code A98143) platforms, respectively. The assays were performed in our laboratory according to the manufacturer's instructions. Instrumentation aspirates 55 μL of sample for the assay, but only 50 μL is needed for the measurement. Monoclonal anti-cTnI antibody conjugated to alkaline phosphatase, binding to an epitope corresponding to the amino acids 24–40 of the peptide chain, is added to a reaction vessel along with a surfactant-containing buffer and sample (50 μL). After a short incubation (36 s), paramagnetic particles coated with monoclonal anti-cTnI antibody, binding to an epitope corresponding to the amino acids 41–49 of the peptide chain, are also added. The human cTnI binds to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody–alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. After another short incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent reagent Lumi-Phos 530 is added at 37 °C to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of cTnI in the sample. The cTnI amount in the sample is determined from a stored, multi-point calibration curve. The relationship between RLU value (Y axis) and the cTnI concentrations (X axis) very closely approximates a second-degree polynomial equation. For this study, several lots of reagents (code 337132, 426619, 434885 and 431544) and calibrators (424474, 429710 e 433808) were used.

The limits of blank (LoB) and detection (LoD) were calculated following the CLSI EP17-A protocol [12], using the DxI 800 platform. The 0 calibrator of the AccuTnI + 3 method, which does not contain cTnI, was considered as the blank of the method and it was measured in 57 different runs, using two lots of reagents. We also estimated the 0 point of the standard calibration curve by taking into account 244 cTnI values in the range of concentration between 0 and 90 ng/L. The LoD value was calculated following the formula: $LoD = LoB + 1.645$ SD [12], where SD was estimated by the distribution of cTnI values measured in a sample with a plasma concentration of 10 ng/L. The reproducibility of the AccuTnI + 3 using the DxI 800 platform was evaluated according to the CLSI EP5-A2 protocol [13], using two heparinized plasma samples. The imprecision profile was estimated by repeatedly measuring some heparinized plasma pools collected from healthy subjects and patients with cardiovascular diseases. These pools were repeatedly measured (from 32 to 44 different runs) using two lots of reagents. To calculate the limit of quantification (LoQ), the relationship between the error of the measurement (expressed as % CV values, Y axis) and cTnI concentrations (X axis) was interpolated by means of a nonlinear regression power curve.

Beckman Coulter reports in the instruction bulletin that samples can be accurately measured within the analytical range of the assay (i.e., from 10 to 100,000 ng/L) with the AccuTnI + 3 method, suggesting not to dilute patient samples. We verified whether it was possible to dilute 5 patient samples with cTnI concentration from 55,000 to 400,000 ng/L up to 256-fold. We obtained linear correlation coefficient R^2 values ranging between 0.997 and 0.999 and CV values always <10% with both the DxI 800 and Access2 platforms.

For between-methods comparisons, other 3 immunoassay methods were also tested in this study: the STAT Architect high Sensitive TnI using the Architect i1000SR platform (Abbott Diagnostics, Ref. B3P250), the ADVIA Centaur Troponin I Ultra (Siemens Healthcare Diagnostics, Ref. 02790309), and the ST AIA-Pack cTnI third generation method for AIA 2000LA platform (Tosoh Bioscience, Ref. 0025215). The analytical characteristics, as evaluated by some recent studies

Table 1
Limit of detection (LoD), limit of quantification (LoQ) at 10% and 20% CV, and 99th upper limit of reference population of cTnI immunoassay methods tested in this study, according to the data reported by previous peer review studies [2,11,14–18].

Methods	LoD (ng/L)	LoQ 10% CV (ng/L)	LoQ 20% CV (ng/L)	99th percentile (ng/L)	References
cTnI ADVIA	6	30–64	–	13–87	[2,11,14]
cTnI DxI	8	20	9	25	[15,16]
cTnI AIA	8.7	100	30	33	[17]
cTnI Architect	1.1–1.9	5.6	2.2	19.3	[18]

[2,11,14–18], of the four cTnI immunoassay methods tested in this study are reported in Table 1.

2.2. Experimental samples

For the evaluation of analytical performance of the AccuTnI + 3 method, cTnI concentration was measured in blood samples of patients with cardiac disease admitted to the Heart Hospital of the Fondazione CNR Regione Toscana G. Monasterio (Massa, Italy). In order to reduce the volume of collected blood, cTnI was measured in the plasma remaining after the routine clinical analyses. Samples were collected in polypropylene tubes with lithium heparin (heparinized plasma). Plasma was obtained shortly after venipuncture by centrifugation for 10 min at room temperature (about 22 °C) and then the samples, if not immediately assayed, were frozen and stored at −20 °C in 0.5-mL aliquots in polypropylene tubes until assay with the DxI 800 platform. The reproducibility of the AccuTnI + 3 method was evaluated using two heparinized plasma samples with a mean cTnI of 26.5 ng/L (sample A) and 69.1 ng/L (sample B) around the cutoff value of the method (i.e., 40 ng/L). The imprecision profile was estimated by repeatedly measuring 8 heparinized plasma pools with mean cTnI concentrations ranging from 13.5 ng/L to 69.1 ng/L, collected from healthy subjects and patients with cardiovascular diseases, also including the two plasma pools used for the evaluation of the reproducibility. The dilution tests were performed using 3 heparinized samples of patients with myocardial infarction with cTnI concentrations ranging from 55,000 to 400,000 ng/L with both the DxI 800 and Access2 platforms. Two samples were diluted and measured with both the DxI 800 (measured cTnI concentrations 335,420 ng/L and 412,660 ng/L) and Access2 (measured cTnI concentrations 354,660 ng/L and 406,020 ng/L) platforms, while the third sample was diluted and measured only with the DxI 800 platform (measured cTnI concentration 55,000 ng/L).

For the between methods comparison, we used heparinized plasma samples collected from 36 patients with thoracic pain (27 patients) or supraventricular tachyarrhythmias (9 patients) admitted to the emergency department (ED) of the City Hospital of Alessandria between June and November 2014. The measurement of cTnI was performed in 122 heparinized plasma samples, collected from these patients at the admission to ED and then 3, 6, 12 and 24 h after. In 17 (of 27) patients admitted with thoracic pain to ED, the clinical diagnosis was acute myocardial infarction (10 STEMI and 7 NSTEMI).

For the EQC study, 18 study samples with different cTnI concentrations were prepared according to the ILAC G13 guidelines, and measured by all participant laboratories (on average 110 laboratories for each annual cycle) for a total of 941 determinations for the 18 control samples distributed in the annual 2014 and 2015 cycles (Table 2). Some of these samples were repeatedly assayed by all laboratories to test the within-laboratory variability, too. Sample pools were prepared using residuals from heparinized plasma samples collected from patients with cardiac diseases. For the preparation of study samples, several heparinized plasma specimens, containing different cTnI

Table 2
cTnI concentrations measured with the four immunoassay methods by laboratories taking part to the EQC study organized by QualiMedLab in the 2014 and 2015 cycles.

Samples	DxI (ng/L)	ADVIA (ng/L)	AIA (ng/L)	Architect (ng/L)	Mean (ng/L)	CV (%)
1	24	25	35	33	29.3	19.0
2	31	32	28	32	30.8	6.2
3	48	56	56	71	57.8	16.6
4	58	50	72	88	67.0	24.9
5	59	56	73	94	70.5	24.6
6	89	98	116	148	112.8	23.1
7	96	84	119	151	112.5	26.2
8	99	96	143	160	124.5	23.7
9	113	92	133	147	121.3	19.8
10	106	178	210	197	172.8	26.9
11	126	154	202	232	178.5	26.6
12	125	163	222	236	186.5	27.8
13	126	167	227	235	188.8	27.4
14	142	162	222	242	192.0	24.8
15	420	585	585	615	551.3	16.1
16	495	787	1068	883	808.3	29.6
17	1097	1016	1432	1682	1306.8	23.6
18	1252	1469	1494	2015	1557.5	20.8
Results	331	241	200	179	951	
(% of total)	(34.8%)	(25.3%)	(21.0%)	(18.8%)	(100%)	

Table 3
Analytical sensitivity parameters of the AccuTnI + 3 method for cTnI assay, as evaluated in the present study using the DxI 800 platform, compared to those reported by the manufacturer and a previous study [19].

LoB, ng/L	LoD, ng/L	LoQ 20 CV%	LoQ 10 CV%	
4.5	10.9	17.1	30.4	Present study*
–	<10	20	–	Manufacturer
5	8	20	–	Previous study**

 * Two lots of calibrators (433808 and 429710) and reagents (431544 and 434885) were used on the DxI 800 platform for the calculation of analytical performance.
 ** In the multicenter study by Greene et al. [15] the analytical performance was evaluated using 42 different Access2 platforms.

4. Results

4.1. Evaluation of the analytical performance of the AccuTnI + 3 method

In Table 3, we reported the LoQ, LoD and LoQ values assessed in the present study, using the DxI 800 platform according to the CLSI EP17-A protocol [12], and, for comparison, those reported by the manufacturer and in two peer review articles [15,16]. The data reported in this table indicate that estimated values found in the present study are similar to those reported by the manufacturer, as well as by two peer review articles, in which the Access2 platform was used instead of the DxI 800 platform [15,16]. It is noteworthy that the LoQ value at 10 CV% was not reported by both manufacturer and previous studies [15,16]. The results of reproducibility evaluation for the AccuTnI + 3 using the DxI 800 platform according to the CLSI EP5-A2 protocol [13] are reported in Table 4.

4.2. Between methods comparison

In Table 5 (part A), we reported the correlation matrix between the cTnI values measured with the four cTnI methods tested in the 122 plasma samples collected from 36 patients. Very close correlations were obtained between the results of different methods with correlation coefficient R ranging from 0.937 to 0.994. When we added to these data the results obtained in the 18 control samples distributed in the EQC study, the correlation coefficients did not significantly vary (Table 5 part B).

However, significant systematic differences between the cTnI methods were observed when the 122 samples of patients were taken into account (Fig. 1). In particular, on average, there was a difference up to 2.4-fold between the method measuring the highest cTnI values (ADVIA method using Centaur platform, mean cTnI 8310 ng/L) and that measuring the lowest values (AccuTnI + 3 method using the DxI platform, mean cTnI 3535 ng/L) (Fig. 1). As far as only the results of 18 quality control samples were considered, the differences between methods were less significant: in particular, there were no significant differences between the results observed with the AIA and Architect platforms and also between the ADVIA method using the Centaur platform and AccuTnI + 3 method (Fig. 2). Moreover, the varability of the consensus mean values between methods ranged from 6.2% to 29.6% (mean ± SD = 22.7 ± 5.6%), without a significant variation throughout all the range of cTnI concentrations from 29.3 ng/L to 1557.5 ng/L (Table 2).

concentrations, were pooled together (about 30–50 patients for each pool) to obtain sample pools with a final volume of about 100 mL. After the preparation, the pools were immediately stored at −20 °C. All samples were tested for the absence of HBsAg, antiHCV, and antiHIV. Patients gave the informed consensus for the use of their residual blood samples in the study. Information concerning the 18 study samples was reported in Table 2.

Control study samples were sent by mail as lyophilized materials. Lyophilization procedure was performed by Polymed (Sambuca, Firenze, Italy) within two weeks after preparation of sample pools. Stored sample pools, were thawed, then distributed in approximately 150 vials (each containing a plasma/serum volume of 0.5 mL), and finally lyophilized, as previously reported [19]. The lyophilized materials were reconstituted with 0.5 mL of distilled water by participant laboratories before the assay.

3. Statistical analysis

For the evaluation and comparison of the analytical performance of tested cTnI immunoassay methods, standard statistical analyses were carried on using the Stat-View 5.0.1 program (1992–98, SAS Institute Inc., SAS Campus Drive, Cary, NC, USA). Because cTnI circulating levels are not normally distributed, both non-parametric tests and parametric tests after logarithmic transformation of data were used for statistical analysis. Statistical analyses of the collected results were computed by the reference laboratory (i.e., Department of Laboratory Medicine, Fondazione Regione Toscana G. Monasterio, Pisa).

For the EQC study, periodic and cumulative reports were prepared and sent by mail to each participant laboratory by the QualiMedLab, spin-off of the CNR Institute of Clinical Physiology (Pisa, Italy), as previously described in detail [19]. It was also possible for the participant laboratories to find their individual results and the periodic and cumulative reports in a specific web site using a personal password (http://www.ifc.cnr.it/eqas/). Total variability was estimated by averaging the CVs computed from the results of each study sample [19]. This variability includes both systematic between-methods differences and differences introduced by the laboratories. The imprecision of the methods was estimated by averaging the CVs of the results produced by participants (using the same method) for the same study sample.

Table 4
Evaluation of reproducibility of AccuTnI + 3 method using the DxI 800 platform according to the CLSI EP5-A2 protocol [13].

Sample	N	Mean cTnI concentration (ng/L)	Within-run CV (%)	Total CV (%)
A	20	26.5	10.5	13.0
B	20	69.1	2.7	3.4

Table 5
Correlation matrix between cTnI values measured with the four methods tested in the study.

A. Correlation matrix obtained considering the 122 samples collected from 36 patients with thoracic pain or supraventricular tachyarrhythmias admitted to the ED.				
Methods	ADVIA	DxI	AIA	Architect
ADVIA	1.000	0.987	0.992	0.937
DxI	0.987	1.000	0.994	0.948
AIA	0.992	0.994	1.000	0.943
Architect	0.937	0.948	0.943	1.000
B. Correlation matrix obtained considering the 122 samples collected from patients and also the 18 quality control sample distributed in the EQC study (n = 140)				
Methods	ADVIA	DxI	AIA	Architect
ADVIA	1.000	0.987	0.992	0.938
DxI	0.987	1.000	0.995	0.948
AIA	0.992	0.995	1.000	0.943
Architect	0.938	0.948	0.943	1.000

In Fig. 3, we reported the linear regressions between the cTnI concentrations obtained with the 4 methods using log-transformation of the original 140 values (i.e. 122 patient samples and 18 quality controls) in order to obtain a better definition throughout all range of cTnI concentration. These data suggest that the cTnI values measured in the quality control samples showed the same analytical behavior of patient samples. Moreover, the between-methods variations, expressed as the percentage difference compared to the mean concentration for the cTnI values, measured in the EQC study [(method A − method B) ∕ mean concentration × 100], show a linear relationship with the log-transformation of mean cTnI concentration (DxI vs ADVIA, R = 0.652, $p < 0.0001$; DxI vs Architect, R = 0.727, $p < 0.0001$; DxI vs AIA, R = 0.589, $p < 0.0001$).

Finally, a very close linear regression was found between the cTnI values measured with the DxI and Access2 platforms by the laboratories that joined to the EQC study in the 18 quality control samples (Fig. 4). Moreover, there were no significant differences ($p = 0.3206$ by paired

t test using log-transformed values) between the mean values ($\pm$SD) respectively measured with the DxI (250.3 $\pm$ 359.2 ng/L) and Access2 (260.9 $\pm$ 385.8 ng/L) platforms.

5. Discussion

The results of this study indicate that the AccuTnI + 3 method for cTnI assay exhibits a good reproducibility (Table 4) and a turnaround time of less than 30-min. A very recent multicenter study [16] reported that the 99th percentile of cTnI distribution values, measured with the Access2 platform in 1764 apparently healthy subjects (median age 47 years, range 18–89 years), is 25 ng/L (95% CL 22–33 ng/L), with a significant difference between men (31 ng/L, 95% CL 26–52 ng/L) and women (21 ng/L, 95% CL 19–25 ng/L). In the instruction document, the manufacturer reported that the 99th percentile of cTnI distribution value is 20 ng/L (95% CL 10–50 ng/L) in a reference population, including 527 apparently healthy subjects with age raging from 19 to 94 years. The data of the present study (Table 3) indicate that a cTnI value of about
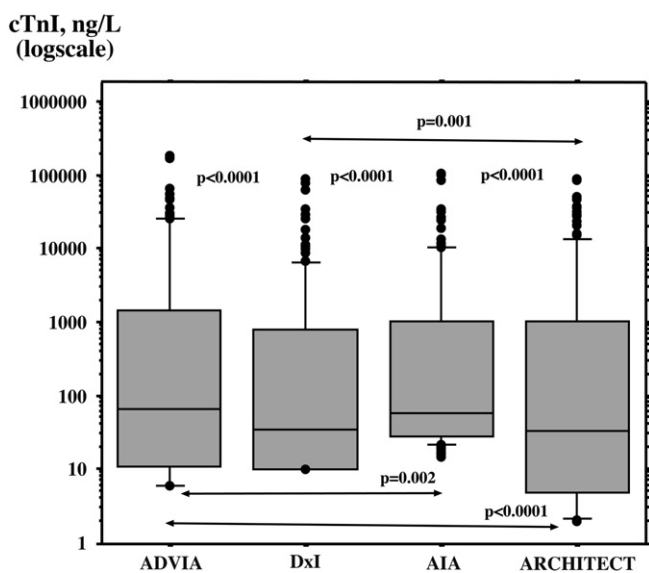
Fig. 1. Box (distribution) plot of cTnI values measured by the 4 different methods tested in the study in 122 heparinized plasma samples collected from 36 patients with thoracic pain or supraventricular tachyarrhythmias admitted to the ED. The data are reported as boxes indicating the 10th, 25th, 50th (median), 75th and 90th percentiles of cTnI values measured; the values more than 90th percentile or below the 10th percentile were indicated as separated black circles. The concentrations (Y-axis) are reported as log-scale. The levels of statistical significance (p values calculated by Scheffé post hoc test after ANOVA) are also indicated in the figure. ADVIA: ADVIA method sing the Centaur platform (Siemens Health Diagnostics); DxI: AccuTnI + 3 method using the DxI platform (Beckman Coulter Diagnostics); AIA: ST AIA-Pack cTnI third generation method for AIA 2000LA platform (Tosoh Bioscience); ARCHI-TECT: STAT Architect high Sensitive TnI using the Architect i1000SR platform (Abbott Diagnostics).
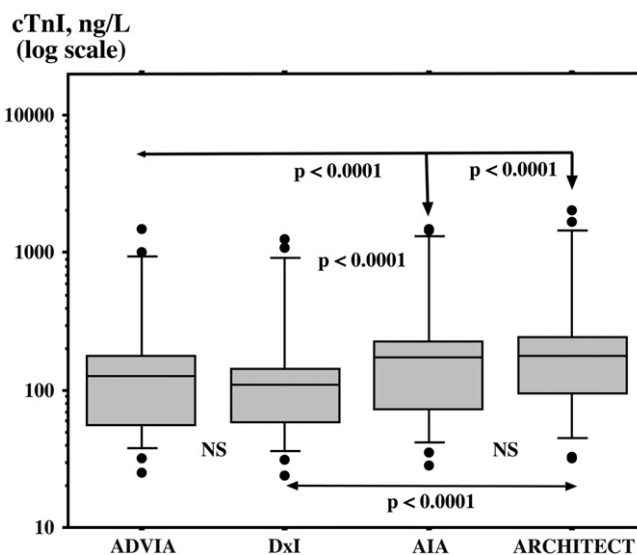
Fig. 2. Box (distribution) plot of cTnI values measured in 18 quality control samples by the 4 most popular methods of the EQC study. The data are reported as boxes indicating the 10th, 25th, 50th (median), 75th and 90th percentiles of cTnI values measured in the 18 study samples; the values more than 90th percentile or below the 10th percentile were indicated as separated black circles. The concentrations (Y-axis) are reported as log-scale. The levels of statistical significance (p values calculated by Scheffé post hoc test after ANOVA) are also indicated in the figure. ADVIA: ADVIA method sing the Centaur platform (Siemens Health Diagnostics); DxI: AccuTnI + 3 method using the DxI platform (Beckman Coulter Diagnostics); AIA: ST AIA-Pack cTnI third generation method for AIA 2000LA platform (Tosoh Bioscience); ARCHITECT: STAT Architect high Sensitive TnI using the Architect i1000SR platform (Abbott Diagnostics).
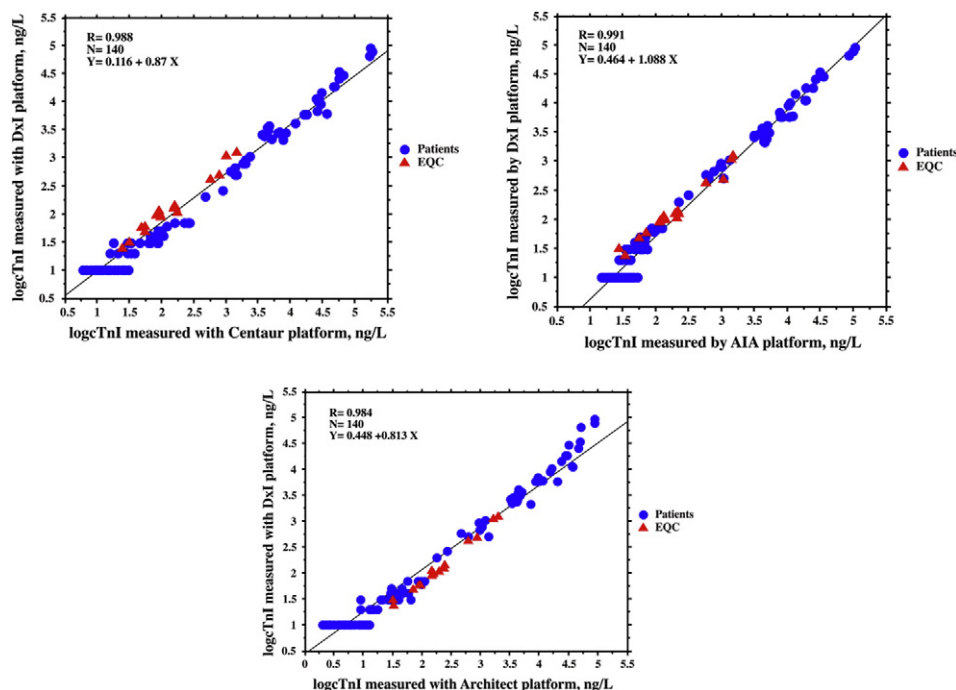
Fig. 3. The figure reports the linear regressions between the cTnI concentrations obtained by the 4 methods in 122 heparinized plasma samples collected from patients admitted to ED and 18 quality control samples distributed in the EQC study. The log-transformation of original values was used in order to obtain a better definition throughout all range of cTnI concentration measured.

20 ng/L, such as the 99th percentile of cTnI distribution values in apparently healthy subjects [16], should be measured by the AccuTnI + 3 method with a CV <20%. Therefore, in accordance with some recent international guidelines and expert panel documents [2,6,9,11], the AccuTnI + 3 method for cTnI assay should be defined as a clinically acceptable contemporary sensitive assay, but not a high sensitive method.

The results of this study confirm that there are systematic differences between the cTnI immunoassays more frequently used in Italy (Figs. 1 and 2). In spite of these systematic differences, the cTnI methods tested in this study showed very close linear regressions throughout all the range of cTnI concentrations with R values ranging from 0.984 to

0.991 (Fig. 3). A very recent multicenter study [20] evaluated the clinical performance of the AccuTnI + 3 methods using the Access2 platform. In 1929 subjects with chest pain or equivalent ischemic symptoms suggestive of acute coronary syndromes at 14 medical centers the AccuTnI + 3 method provided 96.0% sensitivity and 89.4% specificity at 1–3 h after admission, and 94.9% sensitivity and 86.7% specificity at 3–6 h. The negative predictive value (NPV, rule-out for myocardial infarction) was 99.5% at 1–3 h, and 99.0% at 3–6. Moreover, NPV was 99.1% when TnI was <0.03 ng/mL and time of symptom onset was ≥8 h [20]. Another recent study from the same group [21] indicated that absolute delta variations of cTnI of 10 or 20 ng/L, measured with the AccuTnI + 3 methods using the Access2 platform, performed significantly better than relative delta variations (≥20% or 50%), as recommended by some international guidelines [3], for the diagnosis of myocardial infarction at all time intervals significantly.

This study may present some limitations. A relatively small number of clinical samples were used for method comparison. Indeed, samples from only 36 patients were used even if multiple samples were taken, and the latest sample was 24 h from admission. A previous study [22] reported different cTnI species present in sera collected at varying time points up to 48 h after acute myocardial infarction. There is therefore a theoretical risk that not all different forms of cTnI may be present in the samples of patients enrolled in this study. Another possible limitation is that the use of lyophilized control material, although prepared from patient pools, might potentially not mimic native plasma.

In conclusion, according to international guidelines [2,3], our results, together with those reported in other very recent studies [15,16,20,21], indicate that the cTnI AccuTnI + 3 immunoassay for the Access2 and DxI 800 platforms is a method that may be used in the clinical practice.
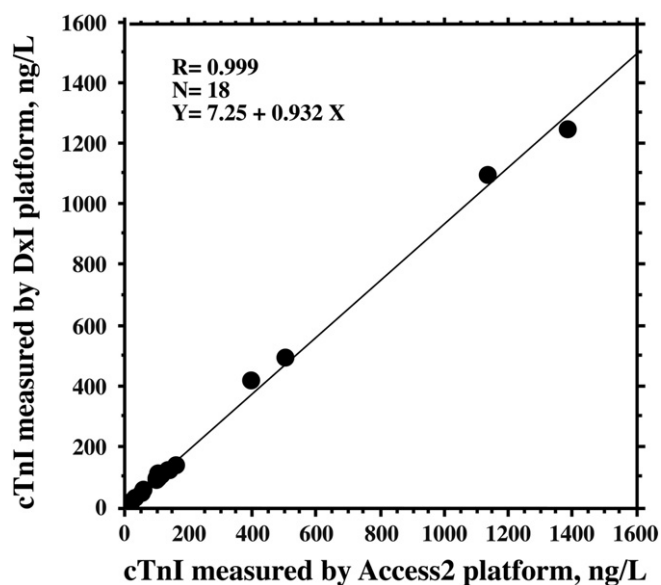

Fig. 4. The figure reports the linear regressions between the cTnI concentrations measured by DxI (Y-axis) and Access2 (X-axis) platforms using the AccuTnI + 3 method in the 18 quality control samples distributed in the EQC study.

Acknowledgments

Medical Solution Diagnostics Italia (Milan, Italy), and Tosoh Bioscence Srl (Rivoli, Turin, Italy).

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