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A New Generation of Biomarkers Tests of Myocardial Necrosis: The Real Quality a Physician can get from the Laboratory

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Data Interpretation D
Manuscript Preparation E
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Background: Recent guidelines recommended by ESC, ACC, AHA, and WHF concerning biomarkers of myocardial necrosis also apply to the work of clinical laboratories. Methodological modification for tests used in determining cardiac biomarkers reduced the time of the analytical procedure to 9 min (STAT version of the tests). We decided to determine and compare analytical quality of the tests in standard and STAT versions for determining serum level: troponin T, MB isoenzyme of creatine kinase, and myoglobin, as well as to verify whether the TnThs STAT test meets the following requirements: CV <10% at the level close to diagnostic, equal to the 99th percentile of reference population, and turnaround time <60 min.

Material/Methods: We evaluated real precision and accuracy for both standard and STAT versions of tests as well as the correlation of results of physiological and pathological levels. Additionally, observations of turnaround time were made.

Results: Calculated values of total errors did not exceed the recommended acceptable total error (<20%). Comparable precision of the 2 measurement methods (CV=3.07%) was obtained. A strong correlation (R>0.99) between both variants of tests for all the parameters was confirmed. Thanks to the application of new reagent kit, the percentage of results with turnaround time <60 min increased from 40% to 75% (n=115; p=0.000008).

Conclusions: The new generation of STAT cardiac biomarkers has high analytical quality and meets international precision requirements. It guarantees high analytical and clinical reliability of results. Use of the STAT version of biomarkers contributes to a significant decrease in turnaround time and allows obtaining a good result of an analysis.

MeSH Keywords: Biological Markers • Myocardial Infarction • Troponin T

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Background

A rapid development of medical sciences in all fields of laboratory diagnostics entails a need to improve the analytical process, which now must meet increasingly strict requirements of scientific societies that set forth new standards in diagnostics and treatment. The most recent guidelines recommended by ESC, ACC, AHA, and WHF [1] concerning biomarkers of myocardial necrosis also apply to the work of clinical laboratories. Both good analytical quality and the time of the analysis play a decisive role in assays of these biomarkers. These 2 closely connected elements allow for obtaining a reliable result of the analysis as quickly as possible, which makes it possible for a physician to promptly perform a medical intervention. It is particularly important in acute coronary syndrome (ACS) [2,3], especially with persistent ST-segment elevation, which might indicate coronary artery occlusion.

In urgent analyses this period of time is called *turnaround time* (TAT), measured from the moment the analysis is ordered to when a result is obtained. This period of time consists of: taking the material (blood), most often from peripheral venous vessels; transporting it to a laboratory; clotting and centrifugation (if it is required by the methodology of the assay); the analytical procedure itself; and authorization and presenting the result to a physician [4]. ESC, ACC, AHA, and WHF guidelines state that TAT should not be longer than 60 min [1] for assays of cardiac biomarkers: cardiac isoforms of troponins T and I (cTnT and cTnI), MBmass isoenzyme of creatine kinase (CK-MBmass), and myoglobin (MYO).

However, it is quite difficult to achieve this TAT for assays of laboratory parameters, which just include assays of concentrations of cardiac biomarkers, with use of immunochemical methods [5]. These assays, unlike traditional chemical assays, have a relatively long pre-analytical phase (longer clotting time so as to obtain serum) and a longer analytical procedure (usually lasting 20–40 min).

A way of determining troponin concentration with the high sensitivity method (hsTn) has been a standard method in Western European countries for more than a year. Thanks to this test, new possibilities have open up for cardiologists, especially in the treatment of ACS in patients with no persistent ST- segment elevation [6] and in patients with coronary disease, as a predictive test [7]. Methodological modification for tests used in determining cardiac biomarkers has been in use for more than 1 year now. It reduced the time of the analytical procedure from 18 min (the standard version of the test) to 9 min (the Short Turn-Around Time version of the test).

We should answer the question: Is it possible to determine the markers of acute coronary syndrome easily, promptly, and accurately and receive reliable results?

Having analyzed these observations, we decided to determine and compare the analytical quality of the tests in the standard and STAT versions for determining serum level: cardiac isoform of troponin T with high sensitivity method (TnThs), CKMBmass, and myoglobin, as well as to verify whether the TnThs STAT test meets requirements for use in patients with ACS [1,8]. These requirements are the following: coefficient of variation <±10% at the concentration level close to diagnostic TnThs, equal to the 99th percentile of reference population; and TAT <60 min for TnThs assays, with the use of the standard and STAT versions.

Material and Methods

The study was performed with the use of Roche assay kits (TnThs STAT catalogue no. 0509278190, CKMBmass STAT catalogue no. 11731432122, and Myoglobin STAT catalogue no. 11820788122) as well as reference material for the following reagents (TnThs catalogue no. 5092744190; CKMBmass catalogue no. 11821598322, and Myoglobin catalogue no. 12178214122). All assays were performed with a Cobas e411 Hitachi immunochemical analyzer, with the use of calibrators and control materials produced by Roche [9].

According to statistical metrology, the analytical method is exact when it is precise and accurate. We evaluated analytical quality by using comparative analysis of exactness (precision and accuracy) of measurement methods of all assay kits, as well as analyzing the correlation of the obtained results using 2 tests: the standard and STAT versions.

In the first module of the studies, we used standardized materials made by Roche – the PreciControl Cardiac II and PreciControl Troponin. We determined *lege artis* concentration levels of the analyzed parameters on 2 levels: diagnostic low and pathological high (Table 1) in test-to-test repeatability.

In the second module of the studies, we evaluated the precision of a series of 21 assays of concentration level of troponin T at a level close to diagnostic level (99th percentile of reference population) in native serum in within-test repeatability. The sample of serum was taken from randomly selected patients from the Interventional Cardiology Unit.

While performing quantitative definition, we used a relative measurement of imprecision (I%), which, according to metrological terminology, is coefficient of variation (CV) and contains information about random error (standard deviation, SD) and mean value of measurements (x).

$$I\% = \left({}^{SD}/_{\bar{x}}\right) \times 100\%$$

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Table 1. Results of precision and accuracy analysis of tested reagent kits and recommended values of total errors acceptable.

Biomarker (µg/L)	Control serum: diagnostic level value					BVDs			CQCLD
	Nominal	Obtained	I%	B%	TE%	I%	B%	TEA%	TEA%
TnT hs	0.026±0.007	0.026±0.003	3.58	1.15	7.1	7	16	28	20
TnT hs STAT	0.026±0.007	0.027±0006	7.13	–3.85	15.6				
CK MBmass	5.13±1.53	5.13±0.46	3.83	0.00	6.3	9	16	30	20
CK MBmass STAT	5.14±1.53	5.28±0.88	5.55	–2.72	11.9				
MYO	86±21	83±8	3.06	3.11	8.2	7	8	20	20
MYO STAT	86±21	85±6	2.33	0.85	4.7				
Biomarker (µg/L)	**control serum: pathological level value**					**BVDs**			**CQCLD**
	Nominal	**Obtained**	**I%**	**B%**	**TE%**	**I%**	**B%**	**TEA%**	**TEA%**
TnT hs	2.170±0.327	2.103±0.065	1.04	3.09	4.8	7	16	28	20
TnT hs STAT	1.820±0.273	1.870±0.141	2.55	–2.75	7.0				
CK MBmass	51.06±15.03	45.73±5.39	3.93	10.44	16.9	9	16	30	20
CK MBmass STAT	49.40±14.82	46.52±9.11	6.53	5.83	16.6				
MYO	1050±315	1036±72	2.23	1.37	5.0	7	8	20	20
MYO STAT	1050±315	1023±100	3.25	2.54	7.9				

BVDs – Biological Variation Database and quality specifications, Ricos et al.; CQCLD – The Centre of Quality Control for Laboratory Diagnostics in Lodz, I% – imprecision; B% – bias; TE% – total error; TEA% – total error acceptable.

The evaluation of accuracy was performed with regard to reference values of concentration levels (Xr) in the control material. The difference between these values and mean values obtained from the series of measurements, presenting systematic error, was expressed as bias deviation (B%).

$$B\% = \left(\bar{x} - X_r / X_r \right) \times 100\%$$

Using experimentally determined quantitative information on precision and accuracy, we evaluated exactness of measurement methods and expressed it as the total error value (TE%). Then the result was compared with the expected quality of measurements – acceptable total error (TE_A%) obtained from the Centre of Quality Control for Laboratory Diagnostics in Łódź, as well as with biological variation database and quality specifications, which Ricos et al. obtained [10] (Table 1).

$$TE\% = 1.65\ I\% + |B\%|$$
$$TE\% \leq TE_A\%$$

In the third module of the study, to evaluate the correlation of results, we used 80 samples of native serum of physiological and pathological concentration levels comprising maximum linearity of particular measurement methods. The results were taken from standard assays of cardiac biomarkers concentration levels in patients in the Interventional Cardiology Unit of the Military Medical Academy – Veterans Central Hospital. The concentration levels were: 0.003 µg/L to 10.160 µg/L for troponin T, 1.66 µg/L to 377.40 µg/L for CKMBmass, and 21 µg/L to 1225 µg/L for myoglobin. We compared the accuracy of determining the STAT series of the analyzed assay kits and standard assay kits as reference assays, assuming that the correlation is strong for correlation coefficient R >0.95.

In the fourth module of the study, we made some observations of TAT with the use of the standard and STAT versions. The observations were made in a series of unselected studies in the patients from the Admission Room of the Military Medical Academy – Veterans Central Hospital, in whom all the 3 biomarkers were determined. We analyzed the course of the study ordered on duty in two 10-day periods. In the first study, we analyzed TAT for assays with the use of the standard version (analysis time: 18 min, n=60); in the second study a similar procedure was used with the use of STAT tests (analysis time: 9 min, n=57). TAT started when the sample of the study, ordered to be performed by the physician, was entered into the Laboratory Information System and finished when it was authorized and made available in the Hospital Information

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Table 2. Analysis of precision of TnThs assays in native serum at diagnostic low level.

TnT, diagnostic level (low value); µg/L		
Statistics	**TnT hs**	**TnT hs STAT**
Average	0.025	0.028
SD	0.0008	0.0009
CV <10%	3.07%	3.07%
Range	0.024–0.027	0.027–0.030

System. The obtained variables were analyzed with the Fisher test (evaluating the divergence of qualitative distribution and random distribution) or Mann-Whitney test (evaluating medians of continuous variables).

Statistical calculations were carried out with Microsoft Excel calculation sheet and MedCalc 11 (MedCalc Software bvba) statistical program.

Results

The exactness analysis of reagent kits made in the first module did not indicate a significant decrease in the measurement quality of STAT version reagents in comparison to the standard versions, despite numerical differences in the precision and accuracy. Calculated values of TE% did not exceed the recommended TE_A% [10]. Table 1 presents detailed results of the exactness of the reagent kits used.

Most significantly, still acceptable precision differences were observed with regard to reagents used in determining troponin T. They were particularly visible in the reference material concentration corresponding to diagnostic concentrations. This is because the method has high sensitivity and the values in the analyzed concentration range are low and remain close to the limit of analytical sensibility. The TE% of the STAT method with regard to TnThs on both the controlled levels is almost 2-fold higher (15.6% and 7%) in comparison to the comparative method (7.1% and 4.8%). Yet, it still remains 2-fold lower than the maximum acceptable by the Centre of Quality Control for Laboratory Diagnostics in Lodz (20%) and almost 3-fold lower than the one connected with biological variability troponin concentration in human serum according to biological variation database and quality specifications BVDs (28%).

The analysis of a series of 21 samples of TnThs concentration level in native serum (module 2) showed a comparable precision of the 2 measurement methods. Measurement imprecision was characterized with almost identical coefficient of variation (CV=3.07% for both of the 2 measurement methods – TnThs and TnThs STAT (Table 2). It also confirmed that the particular analytical method meets precision requirements at CV <10% for troponin, diagnostic in the clinical aspect (99th percentile of healthy population) [8,11].

The analysis of the results of assays in the patients' serum (module 3) confirmed a close correlation between all the parameters (Figure 1), especially when the reference material appears to show various values of reference concentrations

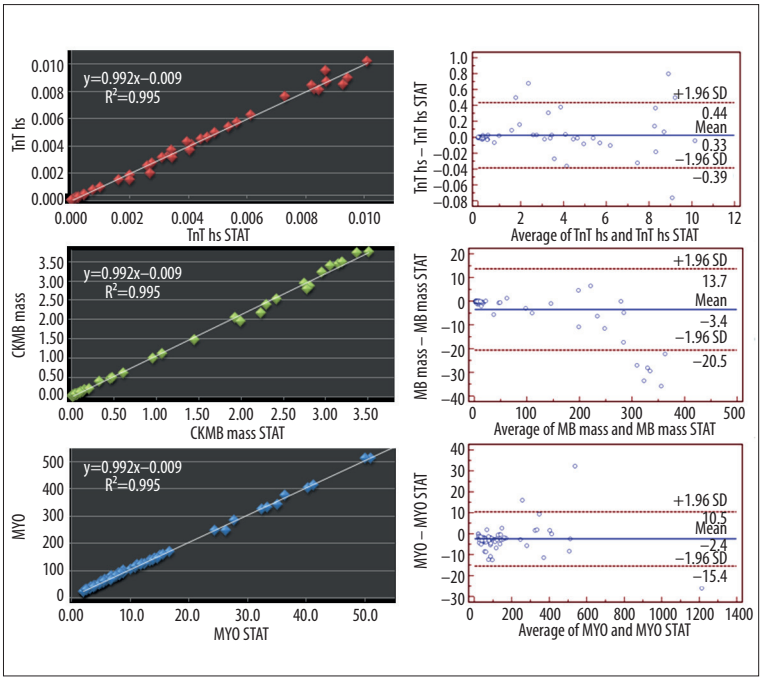

Figure 1. Correlation of results of biomarkers concentration assays with the use of particular reagents and the analysis of absolute differences according to Bland and Altman.

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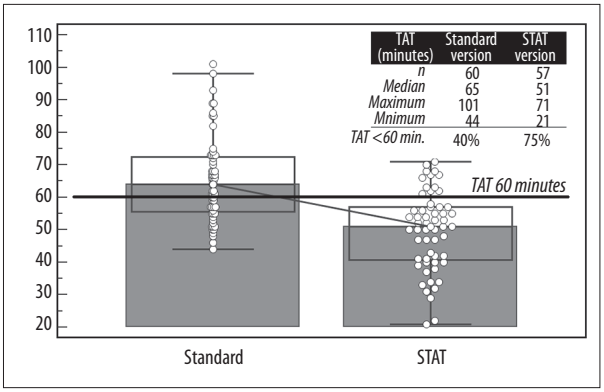

Figure 2. Comparative analysis of TAT obtained with the use of the standard and STAT methods.

of the same analyzed parameter referring to the corresponding measurement methods, which also occurred in this study.

We also analyzed real TAT in a series of unselected studies on the patients (module 4). In total, we analyzed 117 samples to simultaneously determine the 3 analyzed biomarkers: troponin T, CK-MBmass, and myoglobin. In the first stage of the observations, when the analysis was performed with the use of standard reagents, the mean TAT obtained for 60 samples was 65±13 min. In the second stage of the experiment, performed with the use of reagents having a shortened methodology time, the mean TAT obtained for 57 samples was 51±12 min ($p<0.001$) (Figure 2). Thanks to the application of a new reagent kit – the STAT version – it was possible to meet the criteria for obtaining TAT <60 min to determine troponin concentration. Thus, the percentage of results meeting the criteria for obtaining TAT<60 min increased from 40% to 75% ($p=0.000008$, Fisher's exact test).

Discussion

Bearing in mind in the criteria set forth by ESC, ACC, AHA, WHF, we asked a question in the introduction: Is it possible to determine markers of acute coronary syndrome easily, promptly, and accurately and receive reliable results? The obtained results allow us give a positive answer to the question.

The analytical quality of the tested cardiac biomarkers entirely meets all criteria applicable in Poland, both those referring to biological diversity and more restrictive ones recommended by the Centre of Quality Control for Laboratory Diagnostics in Lodz. In the new STAT kits, the analyzed methods do not significantly differ in terms of the analytical quality of the obtained results of the assays from corresponding standard methods; the evaluated precision of the methods meets all the criteria of the analytical quality. The correlation of results obtained with the use of the standard and STAT methods is very high; therefore, the results are analytically reliable and follow adopted standards [8]. The procedure of performing laboratory determination is equally easy with the use of the STAT method as well as the standard method.

The combination of the quality and speed of the analytical method helps to make a more clear decision – either rule out myocardial necrosis or diagnose it [12] and shorten the time the patient will have to spend in a Hospital Rescue Unit or Admission Room [2].

Multi-centre studies conducted in the U.S. confirmed that of 159 U.S. hospitals, less than 25% of laboratories that made cTnT/cTnI and CKMBmass determinations obtained TAT <60 min [13]. The hospital that managed to obtain the shortest TAT median for troponin did so within 50 min and needed 48 min for CKMBmass. In more than 90% of the results, TAT exceeded 90 min. The data also indicate that mean TAT in U.S. hospitals increases with a growing number of patients simultaneously accepted by hospital rescue units [3]. When the number of patients staying in the hospital rescue unit, or those who are only waiting to be accepted (because the hospital is currently overcrowded), doubles, TAT for troponin assays increases by 12 and 33 min, respectively. With regard to the situation in Poland and elsewhere, the information might be meaningful in the case of large multi-profile and clinical hospitals. European data on TAT do not differ much from the U.S. data. Population studies conducted in Finland confirmed mean TAT for determining troponin at 69 min, on condition that the laboratory phase of the whole diagnostic procedure, which starts upon admitting the patient to the Admission Room, takes approximately half the time [14]. This closely corresponds to the laboratory experiment analyzed in this study, because shorter time of the analytical method directly results in reducing the laboratory component of TAT. What is interesting in our method is that reducing the analytical time to 9 min resulted in reducing TAT by up to 14 min. It should be pointed out that neither the staff in the Admission Room nor in the Laboratory knew about our experiment. We suspect a psychological component could play a role corresponding to laboratory phase of analyses, because laboratory diagnosticians were aware of the type of test kits they work with. However, we suggest more improvement might also be introduced in pre-laboratory procedures.

The application of new STAT methods led to a decrease in TAT by up to 14 min, which was then shorter than 60 min. It should be also emphasized that the reduction of time of the analytical procedure not only does not worsen the analytical quality of assays but also contributes to higher efficiency of the medical laboratory. The reduction of TAT for cardiac biomarkers plays a crucial role in strategic decision-making in hospital rescue units, admission rooms, and intensive cardiac supervision units [3,15].

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We assume that determining troponin concentration levels with the high-sensitivity method has already become, or if not, will soon become, common. Clinical specialists should thus take advantage of results obtained thanks to the high-sensitivity method rather than the ones obtained with the use of traditional methods, as the first gives more possibilities, but its interpretation is more difficult. The diagnostic specificity was reduced at the expense of a large increase in diagnostic sensitivity for diagnosing a myocardial infarction (MI) in the first hours following its onset. Difficulty in proper interpretation of troponin assays appeared shortly after they were introduced in 2010. Until now the saying was very accurate: *„When troponin was a lousy assay it was a great test, but now that it's becoming a great assay, it's getting to be a lousy test"* [16]. While interpreting the result of highly sensitive troponins assays, a physician should follow 10 strict clinical recommendations [15]. The first 2 refer to need for close cooperation with the laboratory conducting the analyses. This will facilitate understanding all analytical problems, which might considerably affect the interpretation of results. It is even recommended to avoid using the terms "troponin-positive" and "troponin-negative". Jaffe suggests that "detectable" levels will soon become the norm and that it should be differentiated from "elevated" levels [17]. The differential diagnosis is therefore becoming more difficult. Because highly sensitive troponins brought a decrease in diagnostic sensitivity of MI, the "delta cardiac troponin values strategy" appears to be adequate in clinical routine [18].

We would like to highlight the issues that physicians should be more aware of when cooperating with their laboratories, as those aspects (like the real imprecision of tests) are crucial in diagnostic and monitoring procedures, especially when we consider short periods of test repetition. This is especially true since information obtained from reagent sheets cannot be transferred directly to laboratory practice without checking and adjusting it to the real conditions in which the laboratory works (e.g., different analyzers, different procedures and laboratory equipment) – all these factors influence the quality of the results). Clinical judgment in interpreting changes in troponin levels is now even more essential [19]. Becoming familiar with analytical procedures and potential errors arising out of the procedures will definitely make it easier to interpret results of assays, especially in troponin and CKMBmass concentrations, close to cut-off values i.e., within the 99th percentile of the reference population [16]. We encourage physicians to cooperate closely with clinical laboratories.

Conclusions

1. The new generation of STAT cardiac markers has high analytical quality, guaranteeing high analytical and clinical reliability of results.
2. Application of myocardium necrosis biomarkers in the STAT version contributes to a significant decrease in TAT and allows for obtaining a good result of an analysis – recommended TAT <60 min.

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Conflict of interest

There is no conflict of interest to declare.

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