Implementation of the N - terminal proB-type Natriuretic Peptide Test in National Guidelines for Diagnosis of Heart Failure in Croatia

Rinea Barbir[1], Matea Zoric[1]. Sonja Perkov[1]. Darko Pocanic[2], Tomo Svagusa[2], Ingrid Prkacin[2]

[1] Department of Medical Biochemistry and Laboratory Medicine, Merkur University Hospital, Zagreb, Croatia

[2] Department of Internal Medicine, Merkur University Hospital, Zagreb, Croatia

Corresponding author: Rinea Barbir - rineabarbir@gmail.com

Abstract

Aim: Our aim was to implement N - terminal proB-type natriuretic peptide (NT-proBNP) testing at the Department of Medical Biochemistry and Laboratory Medicine (DMBLM), accredited according to the HRN EN ISO 15189 standard, for clinical use at the Emergency Unit of the Internal Medicine Department in Merkur University Hospital.

Methods: Electro-chemiluminescence immunoassay (ECLIA) is a sandwich principle test with two monoclonal NT-proBNP-specific antibodies. PreciControl Cardiac II level 1 and level 2 were analyzed using the ECLIA on Roche Cobas e411, in triplicate, for five consecutive days, for the purpose of calculating within-laboratory precision, according to the Clinical and Laboratory Standards Institute (CLSI) protocol. We prospectively studied 87 Emergency Department (ED) patients with symptoms of decompensated heart failure (HF) during one month, measuring their NT-proBNP levels.

Results: According to the CLSI protocol, we calculated standard deviation and coefficient of variation for repeatability, intermediate precision and within-laboratory precision from control results. Calculated coefficient of variation for the overall laboratory precision for level 1 and level 2 was within the desirable biological criteria for precision, and within the manufacturer's criteria for overall laboratory precision. We assessed the association between the new NT-proBNP method and the outcome in HF patients during one month, and showed the distribution of NT-proBNP values in our ED patients.

Conclusion: Results indicate that the NT-proBNP test met all the set criteria and it has been implemented at the DMBLM for clinical use in Merkur University Hospital, according to Croatian national guidelines for diagnosis of heart failure.

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Introduction

Croatian guidelines have been prepared in accordance with the new 2016 European Society of Cardiology (ESC) Guidelines (1) and they note the use of N - terminal proB-type natriuretic peptide (NT-proBNP) biomarker as the first line of diagnosis of heart failure (HF), which enables rapid diagnosis and proper cardiac monitoring. The Guidelines were launched on November 3, 2016, the first day of the 11th Congress of the Croatian Cardiac Society. The guidelines were accepted with great enthusiasm by the participants – both primary care physicians and cardiology specialists.

Our aim was to implement the NT-proBNP test at the Department of Medical Biochemistry and Laboratory Medicine (DMBLM), accredited according to the HRN EN ISO 15189 standard, for clinical use at the Emergency Unit of the Internal Medicine Department in Merkur University Hospital.

Materials and methods

ECLIA is a sandwich principle test with two monoclonal NT-proBNP-specific antibodies. In the first incubation antigen in the sample, a biotinylated monoclonal NT-proBNP-specific antibody and a monoclonal NT-proBNP-specific antibody, labeled with ruthenium complex, form a sandwich complex. After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. After addition, tripropylamine voltage is applied to the electrode, which induces chemiluminescent emission (2). Accreditation requirements include the need to verify the method performance prior to using it on patient samples (3). During verification, lyophilized control samples were stored at 2-8°C and stabilized at 20-25°C before measurement. PreciControl Cardiac II level 1 and level 2 with values of 150 ng/L and 4930 ng/L were analyzed by the ECLIA on Roche Cobas e411, in triplicate, for five consecutive days, in order to calculate within-laboratory precision, according to the Clinical and Laboratory Standards Institute (CLSI) protocol: User Verification of Performance for Precision and Trueness, EP15-A2 (4). According to the protocol, we calculated arithmetic mean and standard deviation for each day of measurement, from which we determined the repeatability for each day, as well as the standard deviation for intermediate precision for all five days. Standard deviation for within-laboratory precision was calculated from the square root of the sum of standard deviation for repeatability and intermediate precision.

We prospectively studied the Emergency Department (ED) patients with symptoms of decompensated heart failure (HF) during one month, and measured their NT-proBNP levels. We included 87 consecutive patients in whom HF was determined based on clinical symptoms and congestive HF symptoms were determined based on admission chest X-Ray. Patients without decompensated heart failure were excluded. Patients' characteristics were: females/males = 41/47 (45%/55%), age: females 77 (range 52 – 92 years) and males: 65 (range 44 – 86 years).

The study was approved by the local Ethics Committee and written informed consents to participate were obtained.

Results

We implemented the NT-proBNP test according to the CLSI protocol and calculated standard deviation (SD) and coefficient of variation (CV) for repeatability, intermediate precision and within-laboratory precision from the control results. CV calculated for within-laboratory precision was 4,48% for level 1 and 4,15% for level 2 (Table 1)..

Calculated coefficients of variation for within-laboratory precision for two control samples were compared with coefficients of variation for the two set criteria, desirable biological criteria for precision and manufacturer's criteria for within-laboratory precision (Table 2).

Table 1. *Calculated standard deviation (SD) and coefficient of variation (CV) for repeatability, intermediate precision and within-laboratory precision. (n – number of measurements per day, D – number of days)*

Control samples (n = 3, D = 5)	Repeatability		Intermediate precision		Within-laboratory precision	
Preci Control Cardiac II	SD (ng/L)	CV (%)	SD (ng/L)	CV (%)	SD (ng/L)	CV (%)
Level 1 (149 ng/L)	4,04	2,66	5,97	3,92	6,82	4,48
Level 2 (4920 ng/L)	83,96	1,77	189,98	3,89	197,27	4,15

Table 2. *Achieved coefficients of variation for within-laboratory precision and set criteria*

Preci Control Cardiac II	Manufacturers criteria for the overall laboratory precision	Achieved within-laboratory precision	Desirable biological criteria for precision
	CV (%)	CV (%)	Precision 0,5 CVintra (%)
Level 1 (149 ng/L)	5,00	4,48	5,00
Level 2 (4920 ng/L)	5,00	4,15	5,00

Figure 1. *Distribution of 105 NT-proBNP values (min. 8,29 ng/L-max. 70000 ng/L)*
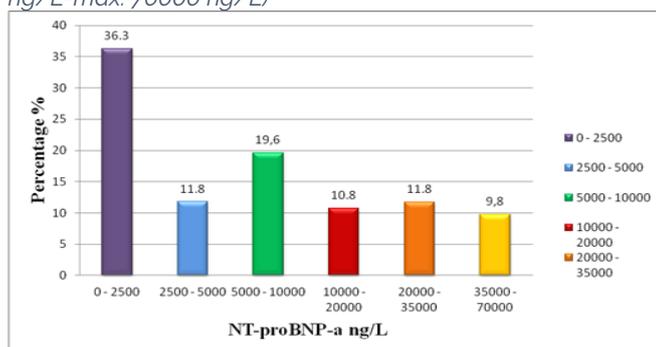
From January 5 to February 9, the concentration of NT-proBNP was measured in 87 patients, with repeated measurements for 18 patients. 20 – 30% increase in concentration was observed in three patients (3/87, 1F/2M) in the period of ten days after admission, with a fatal end (short-term mortality in 1 month). The highest NT-proBNP value was detected in a man with cardiac shock (>70000n/L). Results of the NT-proBNP levels are shown in Figure 1.

Discussion

Despite very good curative cardiology, Croatia is still among the countries with high cardiovascular risk and mortality. Therefore, Croatian Guidelines for HF Diagnosis were developed according to the ESC Guidelines. NT-pro BNP is a proven diagnostic and prognostic biomarker for acute and chronic HF. It is highly recommended by the ESC guidelines (1). Natriuretic peptides predict cardiovascular events in patients and are associated with prognosis in decompensated heart failure (5). Implementation of the NT-proBNP test was conducted according to the CLSI protocol – calculated CV for the within-laboratory precision was 4,48% for level 1 and 4,15% for level 2, which was compared with the set criteria. Desirable biological criteria for precision was 5,00%, according to Ricos C. and colleagues (6), and manufacturer's criteria for within-laboratory precision was also 5,00 %, which indicates that

the achieved results were within the set criteria, desirable biological criteria for precision and manufacturer's criteria for within-laboratory precision, respectively (7). Concentration of NT-proBNP in samples obtained from the ED patients indicate good negative predictive value of the test, whereas high values were correlated with a higher mortality risk (8). In our paper, elevated NT-proBNP values were strongly predictive of adverse outcomes and rising values identified a rising risk, but lowering of NT-proBNP denoted improved outcomes. Thus, the direction of change is important.

Very high NT-proBNP concentration is an independent predictor of adverse outcomes in patients (9). Serial NT-proBNP testing provides very important clinical information. Monitoring of HF with NT-proBNP serial testing provides more clinical information than single testing (1). Implementation of the NT-proBNP test could lower the number of repetitive referrals to ED, help improve the quality of service and reduce unnecessary waste of resources.

Conclusion

Results indicate that the NT-proBNP test met all the set criteria and it has been implemented at the DMBLM since January 5, 2017, for clinical use at the Emergency Unit of the Internal Medicine Department in Merkur University Hospital, in accordance with Croatian national guidelines for diagnosis of HF.

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