Research Article

Validation of a Novel Point-of-Care Testing Device Designed for Assessment of NT-pro BNP

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Abstract

Aim: Our main objective was to compare Point-Of-Care Technology (POCT) to central laboratory immunochemistry testing, to assess N-terminal pro B-type Natriuretic Peptide (NT-proBNP) in ambulatory patients. A second objective was to use POCT to analyze NT-proBNP in a cohort of healthy blood donors to define reference values. **Methods:** Blood samples were obtained from 102 outpatients and 133 blood donors, respectively. Samples analyzed using a point-of-care instrument [NT-proBNPLumiraDx (LumiraDx, Solna, Sweden)] were compared to a commercial electrochemiluminescence immunoassay method [(NT-proBNPRoche) on the Cobas Pro analyzer (Roche Diagnostics, Mannheim, Germany)]. The study was ethically approved (01–367) and complied with the Declaration of Helsinki. Values are given as Median and Interquartile Range (IQR). **Results:** There was a distinct correlation between the two assays for assessing the circulating levels of NT-proBNP in outpatients (R^2 = 0.9546). NT-proBNPLumiraDx ranged between 50–3966 ng/L [Median: 276 (IQR: 679)] whereas NT-proBNPRoche ranged between 50–3820 ng/L; (Median: 268 (IQR: 628)]. NT-proBNPLumiraDx was 3% higher than NT-proBNPRoche ($p<0.05$). NT-proBNPLumiraDx levels were not affected by age in our cohort of blood donors. **Conclusion:** In cases where short turn-around-times for assessment of NT-proBNP are desirable, the LumiraDx instrument can safely be used as an analytical option.

Introduction

The main source of N-terminal pro B-type natriuretic peptide (NT-proBNP) are cardiac myocytes [1] and its secretion is stimulated by cardiac wall stress [2]. NT-proBNP is considered the gold standard biomarker in Heart Failure (HF) [3-5]. NT-proBNP belongs to a family of hormones with pleiotropic effects that, among other cardioprotective effects, provide natriuresis, diuresis and vasodilation [6]. Increased levels of NT-proBNP are seen in persons with HF, whereas low levels of this peptide rule out HF [7]. There is an increasing awareness of the possibility of Point-Of-Care Testing (POCT) and its helpfulness for patients' self-management in health controlling [8]. Several various POCT devices, suitable for management of a variety of diseases, e.g., diabetes mellitus, hypertension, congestive heart failure, and anticoagulation. POCT may provide rapid laboratory diagnostic results and hereby improve disease management as well as a reduction of health care costs. POCT available for home use, focusing on monitoring of chronic diseases may allow patients to easily share important health information with health care providers using modern communication technology [9].

The LumiraDx POCT device, used in this study, offers several advantages compared to conventional analyzers. The most obvious advantage would probably be the short time (12 minutes) from blood sampling to test result. Also, 20 μL of whole blood is sufficient for this analysis, which is considerably less than the amount of plasma/serum, needed by conventional analyzers. This implies that blood sampling via a direct finger stick is satisfactory. Furthermore, storage can be at room temperature and the same method can be used for whole venous blood, capillary blood and plasma, which means that it is possible to use varying sample materials.

The primary aim of this study was to assess the performance of a new quantitative LumiraDx POCT instrument, developed for evaluation of NT-proBNP, when compared to a commercial electrochemiluminescence immunoassay method, considered to be gold standard in NT-proBNP immunoassay test i.e. the Cobas Pro analyzer (Roche Diagnostics, Mannheim, Germany) [10], in an unselected cohort of primary care patients. A second aim was to assess the LumiraDx instrument in healthy blood donors to define normal values for the method.

Patients and Methods

Study population

In 102 patients, living in the county of Uppsala, Sweden, scheduled for primary care visits during February and March 2023, NT-proBNP was analyzed when considered clinically relevant. Blood samples were collected in vacutainer test tubes (LH PST II tube 366567, Becton Dickinson, Franklin Lakes, NJ, USA), coated with Lithium-Heparin as anticoagulant. Analyses of NT-proBNP were performed both by a commercial sandwich electrochemiluminescence immunoassay, using the Cobas Pro e411 analyzer (Roche Diagnostics, Mannheim, Germany) and by point-of-care technology, utilizing a LumiraDx instrument (Solna, Sweden). NT-proBNP in blood samples from 133 healthy blood donors (aged: 19–72 years; 65 females) were evaluated by the LumiraDx instrument. One obvious outlier had already been excluded from this study. All analyses were performed at the Department of Clinical Chemistry, Uppsala University Hospital, Uppsala, Sweden. The Roche Cobas Pro instrument had a total Coefficient of Variation (CV) of 4% at 120 ng/L and 4% at 1900 ng/L. NT-proBNP values below 50 ng/L were replaced by 50 ng/L. All analyses were performed according to the recommendations of the respective manufacturer. Values are given as Median and interquartile range [3rd quartile minus 1st quartile equals Interquartile Range (IQR)].

Ethical considerations

This is a cohort study with no intervention for the participants, where original data are securely stored in an online database. All samples analyzed at our central laboratory were recorded in the laboratory information system and only test reports with a valid quantitative result were included in further analyses.

The study was approved by the ethics committee of the Faculty of Medicine, Uppsala University, Sweden (01–367) and performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [11], which are consistent with ICH/Good Clinical Practice (GCP) E6 (R2), EU Clinical Trials Directive, and applicable local regulatory requirements. The ethical permit limits the sample information to gender and age. Since the present study consists of de-identified data without any new collection of clinical information; patient consent was not required. Hence, renewed ethical permission was not necessary [12]. Blood samples were collected from blood donors after obtaining written informed consent. Age and gender were noted. These samples were only analyzed with the LumiraDx instrument.

Statistical analysis

The coefficient of variations and figures were prepared using Excel (Microsoft, Seattle, WA, USA). Deming correlations were calculated using Method Validator version 1.1 (Metz, France). Calculations of reference intervals and 90% confidence intervals were performed by bootstrap estimation utilizing RefVal 4.0 (Department of Clinical Chemistry, Rikshospitalet, N-0027 Oslo, Norway) [13,14]. The determination and evaluation of equality of the reference intervals were performed according to Clinical Laboratory Standards Institute guidelines EP28-A3C [15], and used by Lahti et al. [16] in order to test whether there were differences between genders. Descriptive statistics are presented as medians and interquartile ranges, respectively [IQR (3rd quartile-1st quartile)] for continuous variables. The two-tailed Wilcoxon Signed-Rank test was used to assess possible differences in NT-proBNP, when blood samples were evaluated by the two instruments.

Results

When NT-proBNP was analyzed by the LumiraDx instrument the range was 50–3966 ng/L [Median: 276 (IQR: 679)] whereas the plasma levels of this peptide were lower (p<0.05), when determined by the Roche instrument [range: 50–3820; (Median: 268 (IQR: 628)]. However, as seen in Figure 1, there was a high degree of consistency between the two analytical options as shown by the strong correlation coefficient ($R^2 = 0.9546$) between the two methods.
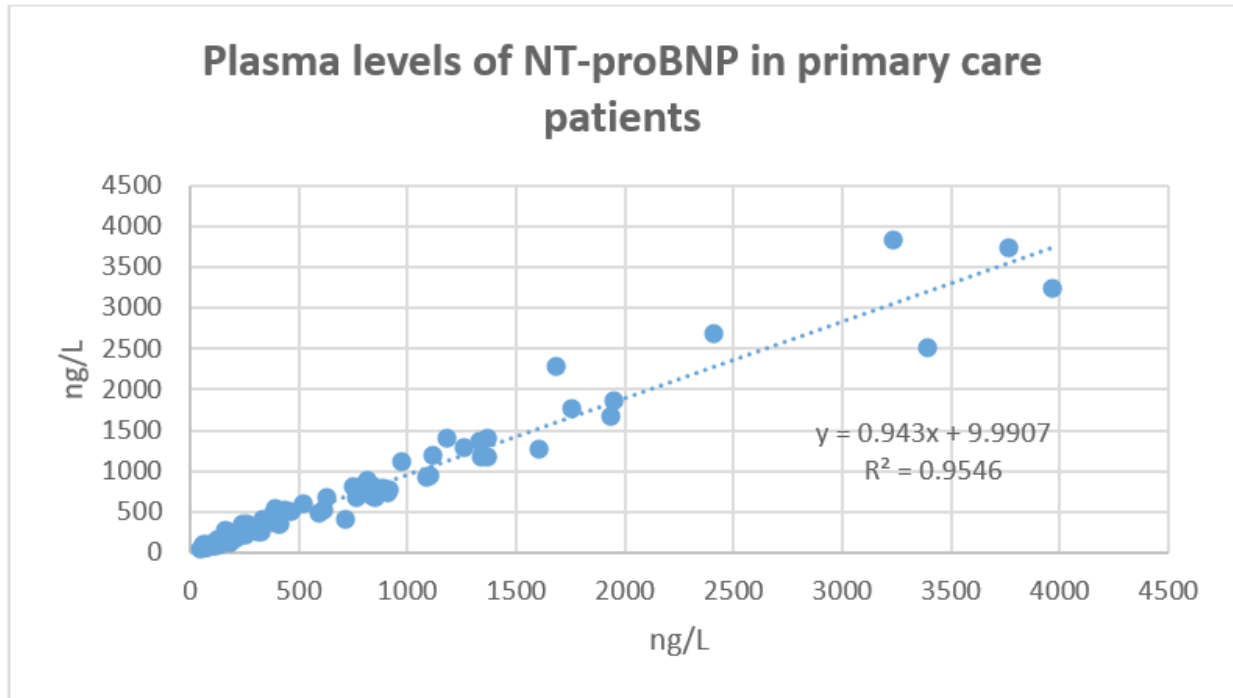
Figure 1: Plasma levels of NT-proBNP (ng/L) values determined by the LumiraDx instrument (abscissa) and the Roche instrument (ordinate), respectively. The directional coefficient is $y = 0.943x + 9.9907$ and the correlation coefficient (R^2) is 0.9546.

The range of NT-proBNP evaluated by the LumiraDx instrument in the total cohort of healthy blood donors was 50–181 ng/L. Fig. 2 shows no significant correlation between age and plasma levels on NT-proBNP when assessed by the LumiraDx instrument in this cohort.
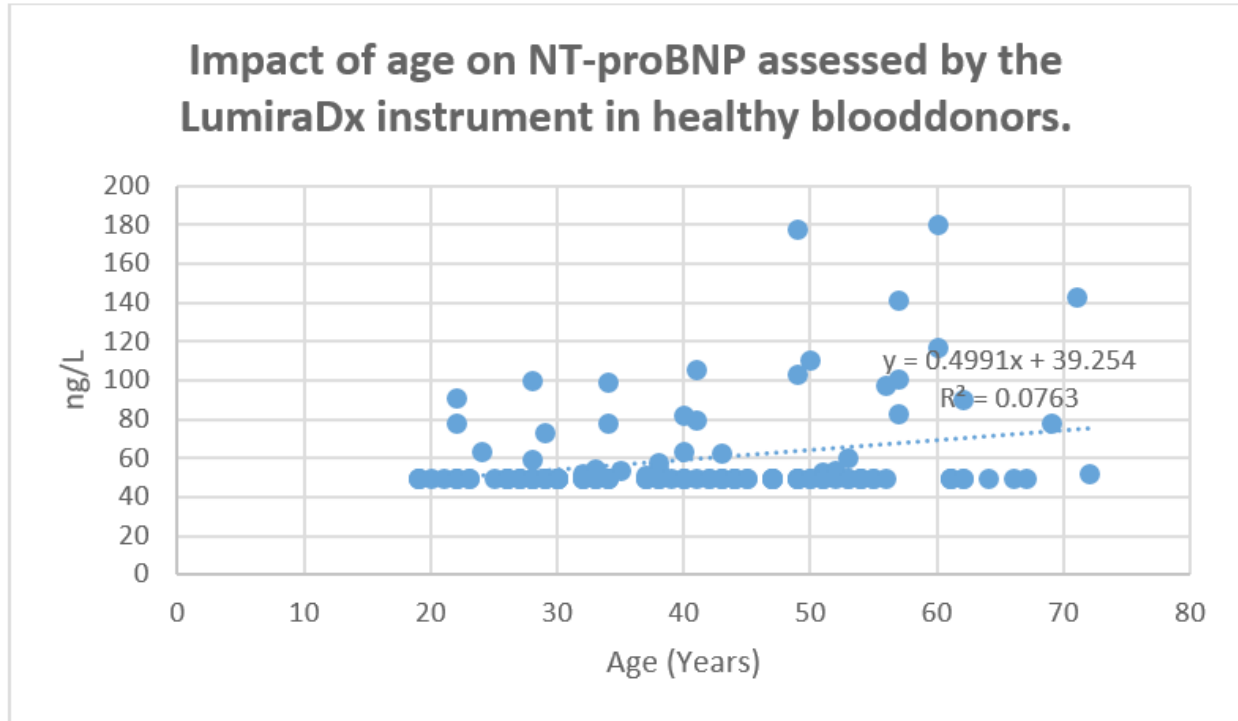

Figure 2: Plasma levels of NT-proBNP (ng/L) in healthy blood donors, determined by the LumiraDx instrument. Age is on the abscissa and concentrations of peptide is on the ordinate. The directional coefficient is y = 0.4991x + 39.254. The correlation coefficient (R^2) is 0.0763.

Upper reference interval limits, 90% confidence intervals, calculated according to the bootstrap estimation, median, IQR and age among blood donors are shown in Table 1. According to Lahti et al. [16], the upper reference interval limit for females or males were not significantly different from the upper reference interval limit for both females and males.

	All		Females		Males	
	Upper reference interval	**90% confidence intervals**	**Upper reference interval**	**90% confidence intervals**	**Upper reference interval**	**90% confidence intervals**
Reference intervals of NT-proBNP [ng/L (bootstrap estimation)]	145	105-188	165	135-196	103	103-119
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
NT-proBNP (ng/L)	50	2	50	14	50	0
Age (years)	40	20	37	24	41	18

Table 1: Characterization of the levels of NT-proBNP determined by the Lumira Dx instrument (Bootstrap estimation [16] and median/IQR) as well as age in a cohort of healthy blood donors.

Discussion

Although the plasma levels of NT-proBNP were 3% higher when assessed by the LumiraDx instrument as compared to the Roche Cobas Pro ($p < 0.05$), we postulate that this minor difference is clinically insignificant. However, the disparity between the two instruments increased both in relative and absolute numbers in a few subjects, when the highest levels of NT-proBNP were noted. Whether these inequalities tend to become more expressed in cases with extremely elevated levels of this peptide remains to be elucidated.

Commercial assays used for determination of NT-proBNP may underestimate the concentration of this peptide in blood, since both NT-proBNP and proBNP are O-glycosylated. Even minor variations in the extent of glycosylation of NT-proBNP cause deviations in the analytical estimations, since antibodies used in the assay adhere to glycosylated epitopes of the NT-proBNP molecule [17-20]. Such variances in the immunoassays used, may contribute to the observed differences between the two methods, although the accordance between the methods is remarkable.

Single determinations of natriuretic peptides aid to indicate risk stratifying in patients without HF and may thus, be of value in ambulatory patients with co-existing diseases contributing to increased risk of HF. Also, the ELIXA trial showed that a single measurement of natriuretic peptides is highly predictive without an absolute necessity of serial sampling [21]. Similar findings were reported from the ALTITUDE trial [22]. Put together, even a previous measurement of natriuretic peptides seems to be of long-term predictive value. In high-risk patients with an elevated baseline level of a natriuretic peptide, this would likely support close follow-ups and adjustments in medical therapy or other interventions. The most valuable natriuretic peptide measurement is the last one, which helps define the "in-the-moment" risk and inform direction for the more immediate plan of management. However, biomarkers of HF, whether serial or single point-in-time measurements, should be re-evaluated and compared to clinical examinations. This study focuses on determinations of NT-proBNP in ambulatory patients, which are seen in outpatient clinics, frequently without instant access to a central laboratory. POCT allows rapid turn-around-time of test results, which allows the treating doctor to inform the patient of test results at the time of the visit. Even in an emergency department, POCT provides significantly faster test results as transport and laboratory processing times are abolished. As samples are collected and analyzed at the time, or even immediately before, the patient is seen by a doctor, this process results in rapid feedback of test results to medical decision-makers [23,24].

Not only has POCT medical advantages, but it is also associated with patient satisfaction in a general practice setting, since patients reported significantly greater levels of trust in their medical care and a greater motivation to manage their own condition when POCT was used. Similar results were obtained in a randomized clinical trial, were self-reported medical adherence in patients undergoing long-term treatment [25,26].

Strengths and Limitations

Prospective sampling and analysis of identical samples is a strength of this study, as is the fact that the comparator (the Roche Cobas Pro instrument) is a most robust and reliable analyzer. Furthermore, analyses were performed in one single core laboratory, hereby avoiding different routines in the management of samples. A limitation is that sampling was merely performed in just one county, which opens up for the possibility of a local genetic variance [27], which could make our results less generalizable since genotype‑adjusted NT‑proBNP was not created [28]. However, the county of Uppsala has two universities and accommodates more than 400,000 inhabitants, many originating from regions, other than Swedish ones.

Conclusion

In blood samples obtained from 102 ambulatory patients, we noted a robust correlation ($R^2 = 0.9546$) in NT-proBNP levels, when assessed by a POCT device LumiraDx instrument (Solna, Sweden)], using the Cobas Pro analyzer (Roche Diagnostics, Mannheim, Germany) as comparator. In healthy blood donors, age did not influence the levels of NT-proBNP, when assessed by the LumiraDx instrument.

Hence, the LumiraDx instrument can safely be used for determination of NT-proBNP, when POCT analyses, i.e., short turn-around-times, are desirable.

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Author Contributions

A.O.L. and M.B.E. conceived the present study. A.O.L. analyzed the blood samples. M.B.E. drafted the first version of the manuscript. Both authors participated in the revisions of the manuscript, read, commented, and approved the final manuscript for publication.

Institutional Review Board Statement

This study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [11] and consistent with ICH/GCP E6 (R2) and relevant directives. The study was approved by the local ethical board (01–367).

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