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ORIGINAL SCIENTIFIC PAPER

Performances of a novel chemiluninescence ABEI-based NT-proBNP immunoassay

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ABSTRACT

Natriuretic peptides are widely used in clinical practice as cardiac markers for early diagnosis, prognosis and for the monitoring of treatment efficiency of heart Failure (HF). According to the clinical relevance of natriuretic peptides testing, it is important to assess the performances of novel platform for testing. Our study showed the overall good performances of a new NT-proBNP ABEI-based automated immunoassay.

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1. Introduction

B-type Natriuretic Peptide (BNP) belongs to the natriuretic peptide family together with other structurally similar peptides: Atrial Natriuretic Peptide (ANP), C-type Natriuretic Peptide (CNP), and urodilatin [1,2]. BNP is synthesised as a pre-hormone (proBNP) comprising 108 amino acids. Upon release into the circulation, it is cleaved into the biologically active 32 amino acid BNP, which represents the C-terminal fragment, and the biologically inactive 76 amino acid N-Terminal fragment (NT-proBNP) [1,3,4]. The major source of synthesis and secretion of BNP is the ventricular myocardium, in response to increased wall pressure and stretching of myocardial fibres [1,2].

Testing for natriuretic peptides is recommended in European and International guidelines for the diagnosis and management of heart failure (HF) and to distinguish HF from other causes of dyspnoea [3–5]. NT-proBNP is also a valuable prognostic biomarker in HF patients but also in patients with other cardiac disorders such as myocardial infarction, valvular heart disease, atrial fibrillation or pulmonary embolism [6–9]

Even if BNP, NT-proBNP and MR-proANP have comparable diagnostic and prognostic accuracy, NT-proBNP is reported as more reliable to estimate treatment efficacy, especially when using pharmacological agents such as angiotensin receptor neprilysin inhibitor (ARNI) inhibiting the degradation of natriuretic peptides [1,2,8,10].

According to the clinical value of NT-proBNP testing, it is important to determine the performances of novel assays before their use in clinical practices. The aim of our study was therefore to evaluate the performances of a novel chemiluminescent ABEI-based NT-proBNP automated immunoassay.

2. Methods and materials

We evaluated the performances of the Maglumi® 800 (Snibe diagnostics, Shenzhen, China) NT-proBNP chemiluminescent immunoassay that applies ABEI labels. ABEI, *N*-(4-Aminobutyl)-*N*-ethylisoluminol, is a non-enzyme small molecule with a special molecular formula that enhances stability in acid and alkaline solutions. The chemical reaction process of ABEI using sodium hydroxide (NaOH) and hyperoxide (H2O2) finishes in 3 s.

The imprecision of the Maglumi NT-proBNP was assessed by repeatedly measuring two different levels of Internal Quality Control (IQC). IQC at low concentration (level 1, range 140–260 pg/ml) and IQC at high concentration (level 2, range 529–983 pg/ml) were tested 3 times a day for 5 consecutive days according

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to the EP 15-A3:2014 protocol from CLSI guidelines. A method comparison was performed with Cobas® 8000 NT-proBNP electrochemiluminescent immunoassay (Roche Diagnostics, Mannheim, Germany) by measuring 68 patients' blood samples (53 men and 15 women) aged between 35 and 88 years (mean age 68 years). Both methods were performed according to the manufacturer's specifications. Blood was taken by venipuncture in the antecubital vein and collected into dry serum tubes (S Monovette® 7.0 mL tubes, Sarstedt, Nümbrecht, Germany). After centrifugation (1500 g, 10 min, 4 °C), within 1 h, serum was carefully separated and stored at −80 °C before testing in Cobas® 8000 and subsequently in Maglumi® 800. Each patient gave informed consent and the local institutional review board approved the protocol. We also assessed the correlation with the peptide precursor of BNP and NT-proBNP, $proBNP_{1\text{-}108}$ (proBNP), determined with a specific automated immunoassay (Bioplex®, Biorad) [9]. Relationships with two biomarkers of adverse cardiovascular remodelling, fibroblast growth factor 23 (FGF-23) and Galectin-3, were also investigated with immunoassays.

Data were analysed with the Medcalc 7.2.1.0 package (Medcalc Software, Belgium) and the Analyse-it Software. Passing and Bablock regression analysis were performed for method comparison and Pearson's coefficient of correlation were calculated. Bland and Altman plots were used to calculate the mean bias between methods. The non-parametric Spearman rank correlation coefficients were used to assess the relationships between age, left ventricular ejection fraction (EF) and biomarkers.

3. Results

The imprecision of the Maglumi® NT-proBNP automated assay was estimated by calculating the Coefficient of Variation (CV) of the two IQC levels. For IQC level 1, with mean concentrations of 225 pg/mL (95% CI for the mean 220 to 227 pg/mL) the CV was 3.2% and for IQC level 2 with mean concentrations of 781 pg/ml (95% CI for the mean 770 to 790 pg/mL) the CV was 2.4%.

3.1. Comparison with the cobas NT-proBNP assay

The median concentration of NT-proBNP in patients' samples was 4536 pg/mL (range 190–35,000) with the Maglumi® assay and 3743 pg/mL (range 112–33,020) in the Cobas® assay. The method comparison between the two automated NT-proBNP assay showed a significant coefficient of correlation ($r = 0.97$, $p < 0.0001$). The Passing and Bablok regression analysis showed a slope 1.26 (95% CI: 1.13 to 1.38), an intercept of 83.69 (95% CI: −156.00 to 259.58) (95% CI: −42.6 to 19.4) and no significant deviation from linearity (Figure 1). The Bland and Altman Plots revealed a mean

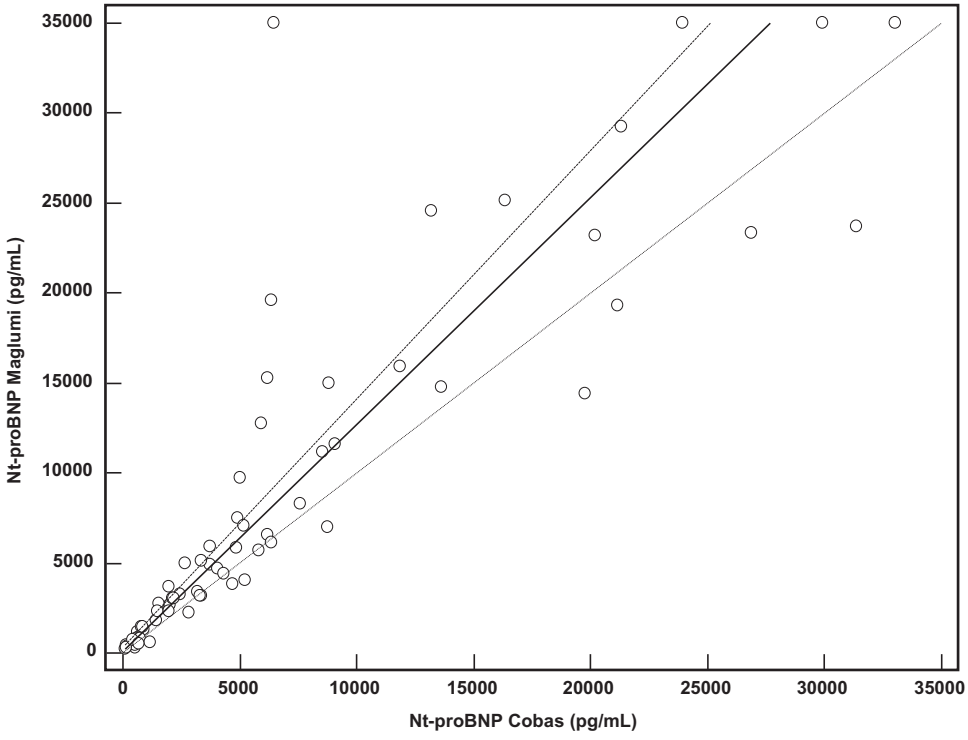

Figure 1. Passing and Bablok regression analysis between Maglumi® and Cobas® NT-proBNP automated immunoassays.

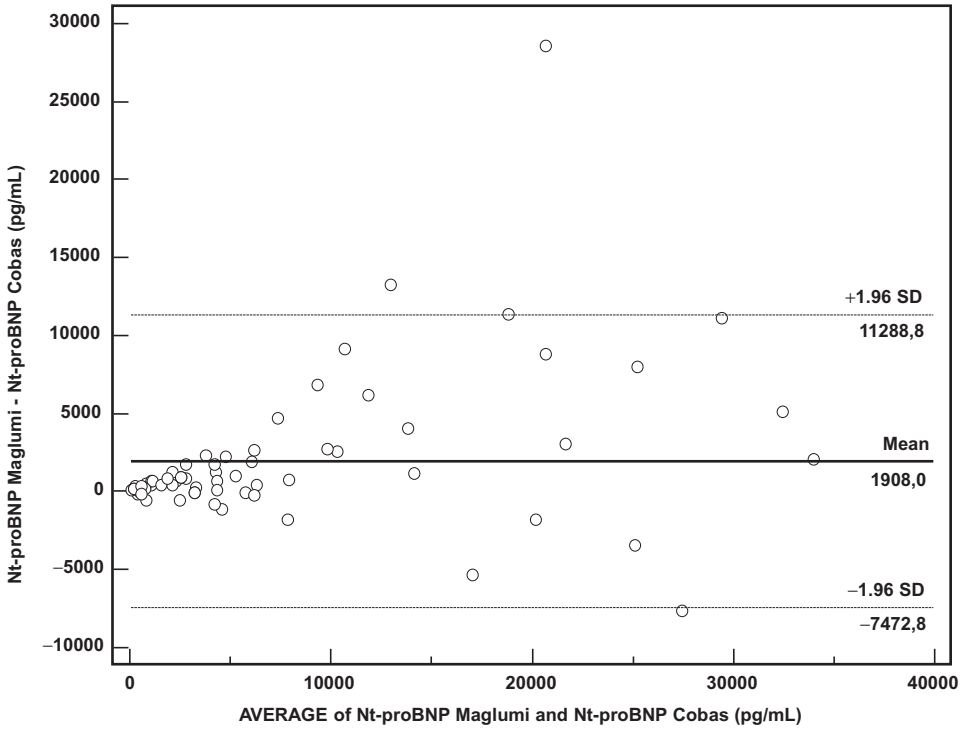

Figure 2. Bland Altman Plot between Maglumi® and Cobas® NT-proBNP automated immunoassays.

difference of 1908 pg/mL (95% CI: 11,289 to −7473) between the two NT-proBNP assays (Figure 2).

3.2. Relationship with proBNP and biomarkers of adverse outcomes

NT-proBNP concentrations measured with the Maglumi® assay were significantly correlated with the proBNP precursor ($\rho = 0.93$, $p < 0.0001$) and were also significantly and positively related to FGF-23 ($\rho = 0.73$, $p < 0.0001$) and Galectin-3 ($\rho = 0.58$, $p < 0.0001$).

4. Discussion

Our data showed overall good performances for the Maglumi® NT-proBNP ABEI-based automated immunoassay. Such automated assay could integrate routine laboratory automated workflows and therefore participate to a faster delivery of results to the physicians for diagnosis purpose or monitoring of treatment efficiency.

NT-proBNP is a first choice biomarker for the diagnosis and management of HF widely used in clinical laboratories [1,4]. NT-proBNP is also appears as a companion test to monitor treatment efficiency as recently illustrated in the PROVE-HF study [11]. It is therefore mandatory to determine the performances of novel assays. Analytical relevance of the Maglumi® ABEI based immunoassay was demonstrated through the imprecision assessment and through the method comparison. The imprecision evaluation showed the good precision of the ABEI based immunoassay with low CV. The method comparison showed a good agreement between Maglumi® and Cobas® assays. However, a significant bias was observed with the Bland and Altman analysis. This bias reflects the current lack of standardisation that still exists for NT-proBNP assays [12]. The difference could be related to the assay format as well as the detection method ABEI based assay in comparison to electrochemiluminecence for Cobas method. The difference between the two assays could also be related to the measurement of different circulating forms as the epitopes used by the Maglumi and the Cobas might differ [2,13].

It was also interesting in our study to demonstrate the significant relation with the proBNP, one of the most important circulating forms in HF patients [2,13]. This relationship highlights the reliability of the Maglumi® NT-proBNP according to the pathophysiology of HF as proBNP is related to disease severity [2,13]. Our data also showed that the NT-proBNP measured with the Maglumi assay was associated to the worsening of HF as it was significantly correlated to FGF-23 and Galectin-3, two biomarkers related to adverse cardiac remodelling and outcomes in HF patients [14,15].

5. Conclusion

Our study showed the overall good performances of the Maglumi® NT-proBNP ABEI-based automated immunoassay. This assay offers additional automated solution for the testing of NT-proBNP in the context of HF diagnosis and management.

Disclosure statement

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