

Conversion formula from B-type natriuretic peptide to N-terminal proBNP values in patients with cardiovascular diseases☆

Shintaro Kasahara^a, Yasuhiko Sakata^{a,b,*}, Kotaro Nochioka^a, Masanobu Miura^a, Ruri Abe^a, Masayuki Sato^a, Hajime Aoyanagi^a, Takahide Fujihashi^a, Shinsuke Yamanaka^a, Takashi Shiroto^a, Koichiro Sugimura^a, Jun Takahashi^a, Satoshi Miyata^c, Hiroaki Shimokawa^{a,b,c}

^a Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan

^b The Big Data Medicine Center, Tohoku University, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan

^c Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan

ARTICLE INFO

Article history:

Received 26 September 2018

Received in revised form 7 December 2018

Accepted 24 December 2018

Available online 7 January 2019

Keywords:

Conversion formula

BNP

NT-proBNP

Heart failure

Cardiovascular disease

ABSTRACT

Background: Although B-type natriuretic peptide (BNP) and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) are released in equimolar proportions, their values differ depending on clinical conditions. A useful conversion formula between BNP and NT-proBNP remains to be developed for the clinical use.

Aim: To develop a conversion formula from BNP to NT-proBNP.

Methods: In the derivation cohort, 923 patients with chronic heart failure, in whom both BNP and NT-proBNP values were available, were enrolled from our SUPPORT (Supplemental Benefit of ARB in Hypertensive Patients with Stable Heart Failure using Olmesartan) trial. The validation cohort included 1154 consecutive patients with or at risk of cardiovascular diseases, in whom both BNP and NT-proBNP values were measured simultaneously at Tohoku University Hospital. We regressed \log_{10} NT-proBNP onto \log_{10} BNP and factors influencing BNP and NT-proBNP values.

Results: We adopted the model with the smallest Akaike information criterion consisting of \log_{10} BNP, age, sex, BMI, creatinine clearance (CCr), hemoglobin, and atrial fibrillation (AF). As compared with the previously reported conversion formulas, the present conversion formula utilized non-linear transformation by spline function, and exhibited the strongest correlation between actual and calculated values of NT-proBNP ($r = 0.928$). The root mean squared error (RMSE) of the present conversion formula was smallest compared with the previously reported conversion formulas, indicating that this formula most effectively converts BNP values to NT-proBNP values.

Conclusions: We have developed a useful conversion formula from BNP to NT-proBNP values, using age, sex, BMI, CCr, hemoglobin, and AF, which could be widely used in daily clinical practice.

© 2018 Published by Elsevier B.V.

1. Introduction

Clinical guidelines recommend measurement of B-type natriuretic peptide (BNP) and/or N-terminal prohormone B-type natriuretic peptide (NT-proBNP) for diagnosis of heart failure (HF) and prognostic evaluation of patients with chronic HF (CHF) [1–3]. Moreover, BNP values have been shown to predict mortality in apparently healthy subjects and patients without HF [4–6]. BNP is synthesized as a prohormone of proBNP, with 108 amino acids [7]. When released into the circulation,

it is cleaved into the biologically active 32 amino acid BNP in equimolar proportion, which represents the C-terminal fragment, and the biologically inactive 76 amino acid N-terminal fragment (NT-proBNP) [7]. However, their actual molar values in the blood differ primarily depending on a difference in their clearance pathways; BNP is cleared from the plasma by binding to the natriuretic peptide receptor type C and through proteolysis by neutral endopeptidases, while NT-proBNP is mainly cleared by renal excretion, resulting in a difference in the half-life time between BNP and NT-proBNP (20 and 120 min, respectively) [7]. Moreover, several conditions, including age, sex, obesity, renal function, anemia, and atrial fibrillation (AF), have been shown to influence both BNP and NT-proBNP values regardless of the severity of HF [1,8]. However, few conversion formulas between BNP and NT-proBNP [9–16] have been previously developed with these factors, and a useful conversion formula between BNP and NT-proBNP remains to be developed for clinical use. In the present study, we thus aimed to develop a

☆ Acknowledgement of grant support: This study was supported in part by the Grants-in Aid from the Japanese Ministry of Health, Labour and Welfare and the Japanese Ministry of Education, Culture, Sports, Science and Technology, Tokyo, Japan.

* Corresponding author at: Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan.

E-mail address: sakatayk@cardio.med.tohoku.ac.jp (Y. Sakata).

useful conversion formula from BNP to NT-proBNP with those factors in cardiovascular diseases (CVD) patients.

2. Methods

2.1. Subjects

The present study was approved by the ethics board of Tohoku University Graduate School of Medicine (2016-1-488) and registered in the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN000032258). Informed consent was obtained in the form of opt-out on the web site. The study cohorts consisted of a derivation cohort from our previous trial, named Supplemental Benefit of ARB in Hypertensive Patients with Stable Heart Failure using Olmesartan (SUPPORT) trial (NCT00417222) [17,18] (Table S1) and a validation cohort recruited at Tohoku University Hospital, Sendai, Japan. The SUPPORT trial has been previously described in detail [17,18]. Briefly, the SUPPORT trial examined whether an additive treatment with olmesartan, an angiotensin II receptor blocker (ARB), reduces the mortality and morbidity in hypertensive CHF patients who had been treated with evidence-based medications. Inclusion criteria of the SUPPORT trial were the followings; New York Heart Association (NYHA) functional class II or over, history of hypertension or treated with anti-hypertensive medications, aged 20 or older and 80 years or younger at the entry, clinically stable with angiotensin-converting enzyme inhibitors and/or β -blockers, and no prior treatment with ARBs. Main exclusion criteria included patients who had renal dysfunction (serum creatinine ≥ 3.0 mg/dl) or severe liver dysfunction, or those who were under chronic hemodialysis. In the present study, we enrolled 923 out of 1147 CHF patients whose BNP and NT-proBNP values at enrollment were available from the SUPPORT trial. The validation cohort included consecutive patients with or at risk of CVD in whom both BNP and NT-proBNP values were measured simultaneously at the Department of Cardiovascular Medicine, Tohoku University Hospital, Sendai, Japan, between April 2017 and October 2017 (Table S1). BNP and NT-proBNP values were measured in 1381 patients. If the measurements were repeated in the same patient, values of the first measurement were used. Finally, after excluding patients aged <20 years, estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m², hemoglobin (Hb) values >20 g/dl, or incomplete data of height, body weight, creatinine, Hb, and/or AF, we enrolled 1154 CVD patients in the validation cohort.

2.2. BNP and NT-proBNP analysis

In the derivation cohort, blood samples were centrifuged within 30 min at 4 °C, and were stored at -20 °C until assay. BNP values were measured with the MIO2 Shionogi BNP (Shionogi, measurement range, 4–2000 pg/ml). In the validation cohort, BNP values were measured with the ARCHITECT BNP-JP (Abbott Japan, measurement range, 5.8–14,510 pg/ml). NT-proBNP values were measured with the Elecsys NT-proBNP II (Roche Diagnostics, measurement range, 5–35,000 pg/ml) in both the derivation and validation cohorts. In order to ensure the reliability of the measurement values, we excluded out-of-range values of BNP and NT-proBNP.

2.3. Statistical analysis

All continuous variables are reported as mean \pm SD or median with interquartile range (IQR) and all categorical variables are reported as frequency (%). To compare the clinical backgrounds between the derivation and the validation cohorts, we performed Welch's *t*-test for continuous variables and Fisher's exact test for categorical variables. In addition to BNP and NT-proBNP values, we used data of age, sex, height, body weight, creatinine values, Hb values, and AF. AF was defined as chronic AF, consisting of both permanent and persistent AF, which had been diagnosed before blood sampling for BNP and NT-proBNP measurements in the derivation cohort. We used the Minnesota code (8-3) [19] for electrocardiography (ECG) to diagnose AF in the validation cohort. Body mass index (BMI) was defined as the body weight divided by the square of the height. Creatinine clearance (CCr) was calculated by the Cockcroft-Gault formula [20]. To develop the conversion formula, we regressed \log_{10} NT-proBNP onto covariates, where all possible combinations of covariates were considered among \log_{10} BNP, age, sex, BMI, CCr, Hb and AF. In these regression models, we applied either linear or non-linear functions for continuous variables, \log_{10} BNP, age, BMI, CCr, and Hb. Non-linear functions for \log_{10} BNP, age, BMI, CCr, and Hb were obtained by the cubic spline models and expressed as $s(\log_{10}$ BNP), $s(\text{age})$, $s(\text{BMI})$, $s(\text{CCr})$, and $s(\text{Hb})$. Finally, we developed the conversion formula by selecting the set of the covariates with the smallest Akaike information criterion (AIC) in the derivation cohort. We calculated each NT-proBNP value using the present conversion formula or other previously reported conversion formulas [9–14]. We calculated correlation coefficients between \log_{10} (measured NT-proBNP) and \log_{10} (calculated NT-proBNP) in the derivation cohort and the validation cohort overall. Moreover, we performed subgroup analysis for age, renal function, and status of CVD in the validation cohort. We divided the patients into 4 subgroups by age (<60 years, $N = 312$; 60–70 years, $N = 324$; 70–75 years, $N = 194$; ≥ 75 years, $N = 324$), 4 subgroups by eGFR (<50 ml/min/1.73 m², $N = 312$; 50–70 ml/min/1.73 m², $N = 330$; 70–90 ml/min/1.73 m², $N = 258$; and ≥ 90 ml/min/1.73 m², $N = 254$), and 3 subgroups by CVD status (patients hospitalized to the Department of Cardiovascular Medicine, Tohoku University Hospital within the past 1 year of the measurement time of BNP and NT-proBNP owing to worsening HF ($N = 128$), those owing to CVD but not for worsening HF ($N = 450$), and those without hospitalization within the past 1 year ($N = 576$)). Then, we compared the predictive accuracy of the conversion formula in the present study with those of the

previously reported formulas based on their values of the root mean squared error (RMSE) [21] in the validation cohort; $\text{RMSE} = \sqrt{(1/n) \sum_{i=1}^n (y_i - \hat{f}(x_{1i}, \dots, x_{ki}))^2}$, where y_i is the i -th observation of NT-proBNP and \hat{f} is its calculated value with the covariates from x_{1i} to x_{ki} . P value <0.05 was considered to be statistically significant. All statistical analyses were performed with the open-source statistics computing software R version 3.4.3. [22].

3. Results

3.1. Baseline characteristics

Table 1 shows baseline characteristics of the derivation and the validation cohorts. Age was comparable between the 2 cohorts. In the derivation cohort as compared with the validation cohort, proportion of women was smaller, BMI was slightly lower, while CCr and Hb values were higher. BNP and NT-proBNP values were higher in the derivation cohort than in the validation cohort; median BNP and NT-proBNP values were 77 pg/ml and 361 pg/ml, respectively, in the derivation cohort, while they were 51 pg/ml and 253 pg/ml, respectively, in the validation cohort (Table 1).

3.2. The conversion formula

Table S2 shows the top 5 combinations which have the smallest AIC values for \log_{10} NT-proBNP among those of each variable either in the linear regression model or cubic regression spline model. Among them, we employed the model with the smallest AIC consisting of \log_{10} BNP, age, sex, BMI, $s(\text{CCr})$, Hb, and AF (Table S2), and developed the conversion formula as follows; $\text{NT-proBNP} = 10^{[2.05 + 0.907 * \log_{10} \text{BNP} - 0.00522 * \text{Age} + 0.00283 * \text{BMI} - 0.00866 * \text{Hb} + s(\text{CCr}) + 0.0164 (\text{if women}) + 0.194 (\text{if with AF})]}$. In the present model, $s(\text{CCr})$ was expressed by $[-0.0422 * \text{CCr} + 0.000530 * \text{CCr}^2 - 0.00000214 * \text{CCr}^3 - 0.00000278 * \max\{0, (\text{CCr} - \text{CCr}_{q1})\}^3 + 0.00000621 * \max\{0, (\text{CCr} - \text{CCr}_{q2})\}^3 - 0.00000133 * \max\{0, (\text{CCr} - \text{CCr}_{q3})\}^3]$ for the truncated power basis representation in the cubic spline function [23] with knot sequence set of (CCr_{q1} , CCr_{q2} , CCr_{q3}) the 25th, 50th, and 75th percentiles CCr in the derivation cohort, respectively. Finally, we developed the conversion formula as $\text{NT-proBNP} = 10^{[2.05 + 0.907 * \log_{10} \text{BNP} - 0.00522 * \text{Age} + 0.00283 * \text{BMI} - 0.00866 * \text{Hb} - 0.0422 * \text{CCr} + 0.000530 * \text{CCr}^2 - 0.00000214 * \text{CCr}^3 - 0.00000278 * \max\{0, (\text{CCr} - 56.5)\}^3 + 0.00000621 * \max\{0, (\text{CCr} - 72.4)\}^3 - 0.00000133 * \max\{0, (\text{CCr} - 93.7)\}^3 + 0.0164 (\text{if women}) + 0.194 (\text{if with AF})]}$. In order to automatically calculate NT-proBNP value, we developed the auto-calculation tool (Fig. S1) (<https://www.cardio.med.tohoku.ac.jp/calc/nt-probnp.html>).

Table 1
Baseline patient characteristics.

	Derivation cohort ($N = 923$)	Validation cohort ($N = 1154$)	P value
Age (years)	65.9 \pm 10.0	65.9 \pm 14.1	0.900
Women (N, %)	239 (26)	473 (41)	<0.001
BMI (kg/m ²)	24.4 \pm 3.8	24.8 \pm 4.3	0.025
CCr (ml/min)	77.1 \pm 29.7	71.4 \pm 31.6	<0.001
Hb (g/dl)	13.8 \pm 1.7	13.3 \pm 1.9	<0.001
AF	274 (30)	166 (14)	<0.001
\log_{10} BNP (pg/ml)	1.9 \pm 0.5	1.7 \pm 0.5	<0.001
\log_{10} NT-proBNP (pg/ml)	2.5 \pm 0.5	2.4 \pm 0.6	<0.001
BNP (pg/ml)	77 (36, 169)	51 (21, 125)	0.453
NT-proBNP (pg/ml)	361 (143, 847)	253 (87, 786)	0.036

Results are expressed as mean \pm SD, IQR, or frequency (%).

AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; CCr, creatinine clearance; Hb, hemoglobin; NT-proBNP, N-terminal proBNP.

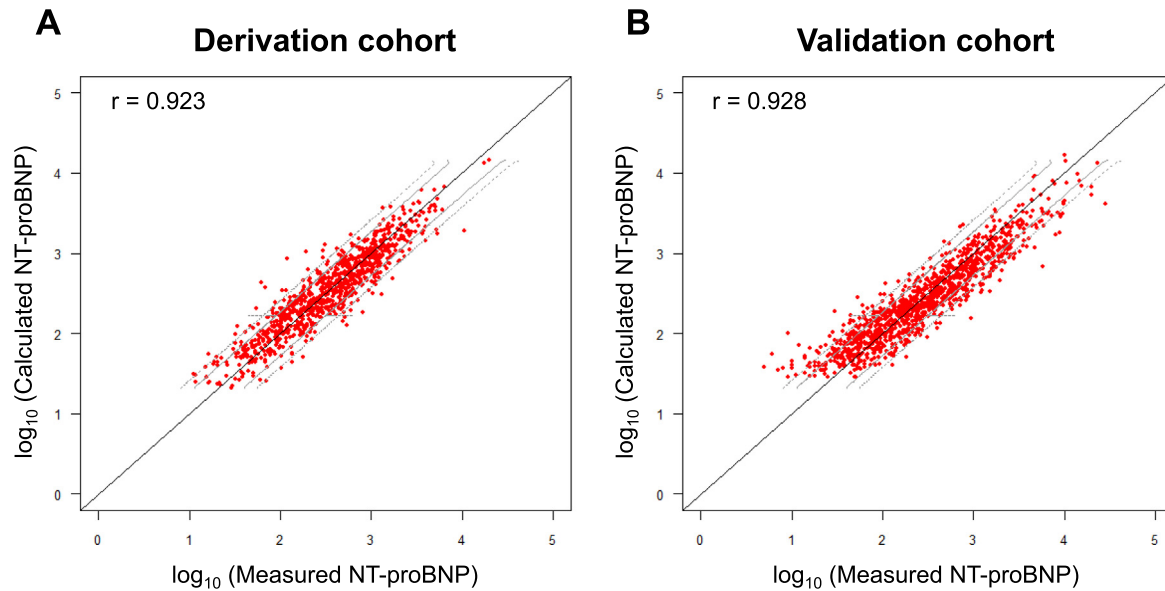


Fig. 1. Correlations between measured and calculated values of NT-proBNP in the derivation cohort (A) and in the validation cohort (B). The grey solid lines and dotted lines indicate 80% and 95% prediction intervals, respectively.

3.3. Correlation between calculated and measured NT-proBNP values

Fig. 1 shows scatter plots for the correlations between calculated NT-proBNP values (calculated from BNP values with the conversion formula) and actual measured NT-proBNP values for the derivation and the validation cohorts. Correlation coefficients between calculated NT-proBNP and measured NT-proBNP values were excellent in both the derivation and the validation cohorts (0.923 and 0.928, respectively). In the subgroup analyses, correlation coefficients were 0.920, 0.934, 0.915, and 0.932 for patients with age <60, 60–70, 70–75, and >75 years, respectively (Fig. S2), 0.925, 0.923, 0.934, and 0.879 for those with eGFR <50, 50–70, 70–90, and >90 ml/min/1.73 m², respectively (Fig. S3) and 0.930, 0.918, and 0.918 for those hospitalized owing to worsening HF, those hospitalized owing to CVD except worsening HF, and those who had not been hospitalized, respectively (Fig. S4).

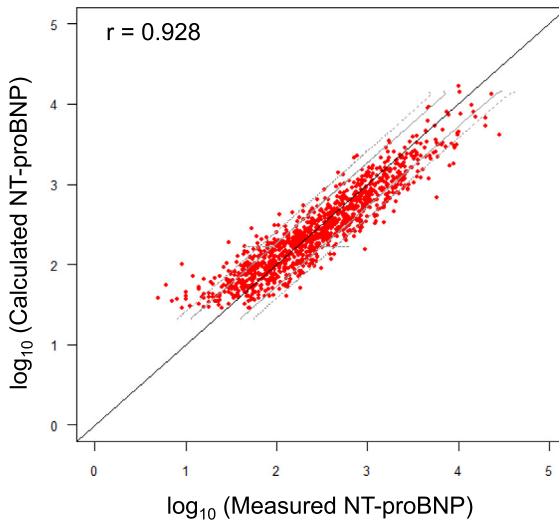
3.4. Comparison with previous formulas

Fig. 2A and B show scatter plots depicting correlations between calculated and measured NT-proBNP values based on the previously reported conversion formulas and the present one in the derivation and the validation cohort, respectively. As compared with the conversion formulas, the present conversion formula exhibited the strongest correlation between calculated and actually measured NT-proBNP values. Table 2 shows RMSE of each conversion formula in the validation cohort. RMSE of the present conversion formula was 0.251, which was the smallest among those of the present and previously reported conversion formulas, indicating that this formula could most excellently convert BNP to NT-proBNP values.

4. Discussion

In the present study, we have developed a useful and reliable conversion formula from BNP to NT-proBNP values in CVD patients. Non-linear multiple analysis based on large-scale data enable us to develop an accurate conversion formula and to confirm the accuracy of external validation.

B Validation cohort



4.1. The conversion formula available in both HF and non-HF cohorts

Previous conversion formulas were derived from study subjects with various types of diseases and symptoms, including patients with dyspnea, suspected HF and suspected acute coronary syndrome (Table 2), and had no validation cohorts. In the present study, we have developed the conversion formula from the cohort of our SUPPORT trial, consisting of stable CHF patients with hypertension, and validated its accuracy in patients with various severity of CVD, including those with and without HF, all of whom visited outpatient clinic or were hospitalized at the Department of Cardiovascular Medicine, Tohoku University Hospital. As a result, we confirmed an excellent estimation from BNP to NT-proBNP with the conversion formula in the validation cohort, with the smallest RMSE, as compared with the previous formulas (Table 2) [9–16]. Thus, we may conclude that the present formula is useful in various CVD patients to calculate NT-proBNP values from the BNP values.

4.2. Subgroup analyses

Subgroup analyses in the validation cohort showed comparable accuracy of the present calculated conversion formula among patients divided by age, renal function, or CVD status, indicating that our conversion formula is useful in a broad range of patients. However, further validation studies are warranted to confirm the accuracy among HF patients, since BNP/NT-proBNP ratio may differ depending on the severity of HF, possibly due to impaired conversion from proBNP to BNP and NT-proBNP by specific proteases [24–26].

4.3. Accuracy of the present conversion formula

In the present study, we have developed the new conversion formula, which could be useful in daily practice particularly when a physician needs to calculate a NT-proBNP value from the previously or currently measured BNP value. As compared with the previously reported formulas, the present formula has strength in accuracy to calculate NT-proBNP values, for the following reasons. First, the present formula has been derived from the SUPPORT trial with the largest sample size compared with the previous formula derivation cohorts. Second, the formula includes factors that could affect the values of BNP

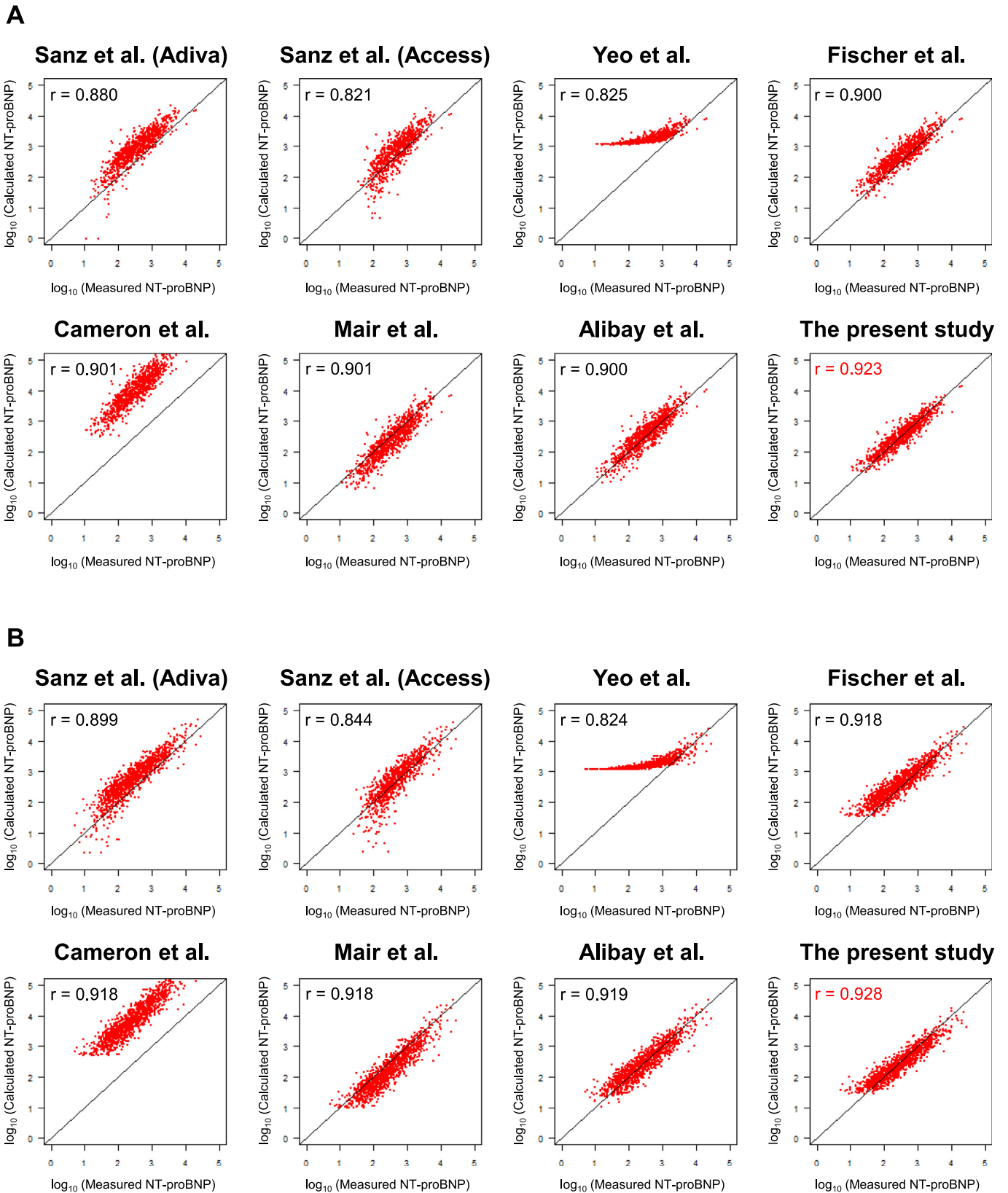


Fig. 2. Comparisons between the previous formulas and the present formula in the derivation cohort (A) and in the validation cohort (B).

and/or NT-proBNP. As shown in Table S3, several factors, such as age [27,28], sex [27,28], obesity [29–32], renal function [33,34], anemia [34,35] and AF [36,37] have been reported to influence BNP and/or NT-proBNP values, and some of them differently affect BNP and NT-

proBNP values [38–42]. However, the previous formulas did not include those factors except that by Alibay et al. that only included renal function. In addition, to further improve the accuracy, we examined all possible combinations of linear and non-linear terms of the candidate

Table 2
Comparisons with the previous conversion formulas.

Year	Author	Derivation cohort (N)	Variables in model	Validation cohort (N)	RMSE in the present validation cohort
2006	Sanz MP et al. [9] (Adiva BNP assay)	Patients with acute dyspnea and a control group (100)	BNP	None	0.417
2006	Sanz MP et al. [9] (Access BNP assay)	Patients with acute dyspnea and a control group (100)	BNP	None	0.359
2003	Yeo KT et al. [10]	Not reported (327)	BNP	None	0.925
2001	Fischer Y et al. [11]	Patients with underlying cardiac disease and suspected HF (95)	BNP	None	0.295
2005	Cameron SJ et al. [12]	Patients with suspected acute coronary syndromes (420)	log ₁₀ BNP	None	1.464
2008	Mair J et al. [13]	Consecutive samples for routine NT-proBNP determination (458)	log ₁₀ BNP	None	0.352
2005	Alibay Y et al. [14]	Patients with acute dyspnea (160)	log ₁₀ BNP, CCr	None	0.253
2003	Lainchbury JG et al. [15]	Patients with acute dyspnea (205)	Not reported	None	Not available
2013	Curciati MN et al. [16]	Consecutive samples (138)	Not reported	None	Not available
	The present study	HF patients (923)	log ₁₀ BNP, Age, Sex, BMI, s(CCr), Hb, AF	HF and non-HF patients (N = 1154)	0.251

AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; CCr, creatinine clearance; Hb, hemoglobin; HF, heart failure; NT-proBNP, N-terminal proBNP; RMSE, root mean squared error.

covariates for the conversion formula. Moreover, since BNP and NT-proBNP data usually follow a lognormal distribution [43], we used log transformation of BNP and NT-proBNP values, which was not necessarily employed in the previous formulas. These attempts, including derivation from a large-scale cohort, multiple variable approach, consideration of non-linear regression, and employment of log₁₀ transformation of BNP and NT-proBNP values, enabled us to provide a more reliable formula. Of note, the present formula also showed the smallest RMSE in the validation cohort, indicating the most excellent estimation accuracy among others.

4.4. Perspectives of the present conversion formula

Recently, an angiotensin receptor neprilysin inhibitor (ARNI) LCZ696 has been developed as a new drug, which consists of the neprilysin inhibitor sacubitril (AHU377) and the ARB valsartan [2,44–46]. Since ARNI showed superiority to enalapril in reducing the risks of death and hospitalization for HF [45], the latest clinical guidelines in the US [46] and Europe [2] recommend the use of ARNI as a first choice for the treatment of CHF patients. However, since BNP is a substrate for neprilysin, BNP values are inaccurate for evaluating the cardiovascular protective effects of ARNI, which is not the case for NT-proBNP [47]. Since ARNI is yet available in Japan [48], patients treated with ARNI were not included in the derivation or validation cohorts in the present study. However, since the present formula may not convert BNP to NT-proBNP values accurately in patients treated with ARNI, the present formula should be used under recognition of the influence of this drug in daily practice.

4.5. Study limitations

Several limitations should be mentioned for the present study. First, in the present study, AF was defined as chronic AF consisting of both permanent and persistent AF in the derivation cohort, while the validation cohort had no data for prior or present history of AF, where 69% of the patients (N = 799) underwent both ECG and blood sampling for BNP and NT-proBNP measurements on the same day. Second, in the present study, the derivation cohort included Stage C/D CHF patients, and validation cohort patients with or at high risk of CVD in our hospital. Thus, it is unclear whether the present conversion formula could be useful for general population. Third, although elapsing time from blood collection to measurement affects the correlation between BNP and NT-proBNP, the present formula does not include it. Fourth, because it has been reported that BNP values differ among immunoassay methods up to 2-folds [49], the accuracy of the present formula may be weakened when using BNP assays except for the MIO2 Shionogi BNP and the ARCHITECT BNP-JP. Finally, since both the derivation and the validation

cohorts consist of Japanese patients alone, cautions should be taken when generalizing the present conversion formula to other racial populations [50].

4.6. Conclusions

We were able to develop a clinically useful conversion formula from BNP values to NT-proBNP values in CVD patients, considering the influences of age, sex, BMI, CCr, Hb, and AF. The present formula will help physicians to calculate NT-proBNP values from BNP values in daily clinical practice.

Acknowledgements

We thank all the members of the Tohoku Heart Failure Association, the SUPPORT Investigators, and the staff of the Departments of Cardiovascular Medicine and Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, for their contributions (Supplementary file), particularly Ikeno Y and Kato T for their significant contributions for developing and releasing the auto-calculation tool. We also thank the staff of the Department of Clinical Laboratory, Tohoku University Hospital, particularly Fujimaki S., Hiraizumi A, Sasaki K, Sato I, and Kashio K for their significant contributions.

Financial support and conflict of interest disclosure

The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by unrestricted research grants from Daiichi Sankyo (Tokyo, Japan), Bayer Yakuhin (Osaka, Japan), Kyowa Hakko Kirin (Tokyo, Japan), Novartis Pharma (Tokyo, Japan), Dainippon Sumitomo Pharma (Osaka, Japan), Astellas Pharma (Tokyo, Japan), AstraZeneca (Osaka, Japan), Chugai Pharmaceutical (Tokyo, Japan), GlaxoSmithKline (Tokyo, Japan), Kowa Pharmaceutical (Tokyo, Japan), Mitsubishi Tanabe Pharma (Osaka, Japan), Mochida Pharmaceutical (Tokyo, Japan), MSD (Tokyo, Japan), Nippon Boehringer Ingelheim (Tokyo, Japan), Otsuka Pharmaceutical (Tokyo, Japan), Shionogi (Osaka, Japan) and Takeda Pharmaceutical (Osaka, Japan). H.S. has received lecture fees from Bayer Yakuhin (Osaka, Japan), Daiichi Sankyo (Tokyo, Japan) and Novartis Pharma (Tokyo, Japan). NT-proBNP values in the derivation cohort were measured at Roche Diagnostics K.K. (Tokyo, Japan).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2018.12.069>.

References

- [1] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey Jr., M.H. Drazner, et al., 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines, *J. Am. Coll. Cardiol.* 62 (2013) e147–e239.
- [2] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G.F. Cleland, A.J.S. Coats, et al., 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC, *Eur. Heart J.* 37 (2016) 2129–2200.
- [3] Group JCSJW, Guidelines for treatment of acute heart failure (JCS 2011), *Circ. J.* 77 (2013) 2157–2201.
- [4] T.J. Wang, M.G. Larson, D. Levy, E.J. Benjamin, E.P. Leip, T. Omland, et al., Plasma natriuretic peptide levels and the risk of cardiovascular events and death, *N. Engl. J. Med.* 350 (2004) 655–663.
- [5] M. Volpe, S. Rubattu, J. Burnett Jr., Natriuretic peptides in cardiovascular diseases: current use and perspectives, *Eur. Heart J.* 35 (2014) 419–425.
- [6] M.K. York, D.K. Gupta, C.F. Reynolds, E. Farber-Eger, Q.S. Wells, K.N. Bachmann, et al., B-type natriuretic peptide levels and mortality in patients with and without heart failure, *J. Am. Coll. Cardiol.* 71 (2018) 2079–2088.
- [7] M. Weber, C. Hamm, Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine, *Heart* 92 (2006) 843–849.
- [8] J. Steiner, M. Guglin, BNP or NTproBNP? A clinician's perspective, *Int. J. Cardiol.* 129 (2008) 5–14.
- [9] M.P. Sanz, L. Borque, A. Rus, B. Vicente, Y. Ramirez, L. Lasa, Comparison of BNP and NT-proBNP assays in the approach to the emergency diagnosis of acute dyspnea, *J. Clin. Lab. Anal.* 20 (2006) 227–232.
- [10] K.T. Yeo, A.H. Wu, F.S. Apple, M.H. Kroll, R.H. Christenson, K.B. Lewandowski, et al., Multicenter evaluation of the Roche NT-proBNP assay and comparison to the biosite triage BNP assay, *Clin. Chim. Acta* 338 (2003) 107–115.
- [11] Y. Fischer, K. Filzmaier, H. Stieglar, J. Graf, S. Fuhs, A. Franke, et al., Evaluation of a new, rapid bedside test for quantitative determination of B-type natriuretic peptide, *Clin. Chem.* 47 (2001) 591–594.
- [12] S.J. Cameron, G.B. Green, C.N. White, O.F. Laterza, W. Clarke, H. Kim, et al., Assessment of BNP and NT-proBNP in emergency department patients presenting with suspected acute coronary syndromes, *Clin. Biochem.* 39 (2006) 11–18.
- [13] J. Mair, F. Gerda, H. Renate, H. Ulmer, G. Andrea, O. Pachinger, Head-to-head comparison of B-type natriuretic peptide (BNP) and NT-proBNP in daily clinical practice, *Int. J. Cardiol.* 124 (2008) 244–246.
- [14] Y. Alibay, A. Beauchet, R. El Mahmoud, C. Schmitt, D. Brun-Ney, M.O. Benoit, et al., Plasma N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in assessment of acute dyspnea, *Biomed. Pharmacother.* 59 (2005) 20–24.
- [15] J.G. Lainchbury, E. Campbell, C.M. Frampton, T.G. Yandle, M.G. Nicholls, A.M. Richards, Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath, *J. Am. Coll. Cardiol.* 42 (2003) 728–735.
- [16] M.N. Curiati, O.M. Silvestre, L.J. Pires, S. Mangini, P.V. Pires, F.A. Gaiotto, et al., Agreement of BNP and NT-proBNP and the influence of clinical and laboratory variables, *Einstein (Sao Paulo)* 11 (2013) 273–277.
- [17] Y. Sakata, K. Nochioka, M. Miura, T. Takada, S. Tadaki, S. Miyata, et al., Supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial—rationale and design, *J. Cardiol.* 62 (2013) 31–36.
- [18] Y. Sakata, N. Shiba, J. Takahashi, S. Miyata, K. Nochioka, M. Miura, et al., SUPPORT Trial Investigators, Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial, *Eur. Heart J.* 36 (2015) 915–923.
- [19] R.J. Prineas, R.S. Crow, H.W. Blackburn, The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification, J. Wright, Boston, Mass, 1982.
- [20] D.W. Cockcroft, M.H. Gault, Prediction of creatinine clearance from serum creatinine, *Nephron* 16 (1976) 31–41.
- [21] T. Hastie, R. Tibshirani, J.H. Friedman, The Elements of Statistical Learning: Data Mining, Inference, and Prediction, 2nd ed Springer, New York, NY, 2009.
- [22] R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2017.
- [23] T. Hastie, R. Tibshirani, Generalized Additive Models, Chapman & Hall/CRC, Boca Raton, Fla., 1999.
- [24] A. Clerico, C. Passino, M. Franzini, M. Emdin, Cardiac biomarker testing in the clinical laboratory: where do we stand? General overview of the methodology with special emphasis on natriuretic peptides, *Clin. Chim. Acta* 443 (2015) 17–24.
- [25] A. Clerico, M. Zaninotto, C. Passino, M. Plebani, New issues on measurement of B-type natriuretic peptides, *Clin. Chem. Lab. Med.* 56 (2017) 32–39.
- [26] K. Kuwahara, Y. Nakagawa, T. Nishikimi, Cutting edge of brain natriuretic peptide (BNP) research—the diversity of BNP immunoreactivity and its clinical relevance, *Circ. J.* 82 (2018) 2455–2461.
- [27] M.M. Redfield, R.J. Rodeheffer, S.J. Jacobsen, D.W. Mahoney, K.R. Bailey, J.C. Burnett Jr., Plasma brain natriuretic peptide concentration: impact of age and gender, *J. Am. Coll. Cardiol.* 40 (2002) 976–982.
- [28] I. Raymond, B.A. Groenning, P.R. Hildebrandt, J.C. Nilsson, M. Baumann, J. Trawinski, et al., The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population, *Heart* 89 (2003) 745–751.
- [29] M.R. Mehra, P.A. Uber, M.H. Park, R.L. Scott, H.O. Ventura, B.C. Harris, et al., Obesity and suppressed B-type natriuretic peptide levels in heart failure, *J. Am. Coll. Cardiol.* 43 (2004) 1590–1595.
- [30] S.R. Das, M.H. Drazner, D.L. Dries, G.L. Vega, H.G. Stanek, S.M. Abdullah, et al., Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas heart study, *Circulation* 112 (2005) 2163–2168.
- [31] D.G. Krauser, D.M. Lloyd-Jones, C.U. Chae, R. Cameron, S. Anwaruddin, A.L. Baggish, et al., Effect of body mass index on natriuretic peptide levels in patients with acute congestive heart failure: a ProBNP investigation of dyspnea in the emergency department (PRIDE) substudy, *Am. Heart J.* 149 (2005) 744–750.
- [32] L.B. Daniels, P. Clopton, V. Bhalla, P. Krishnaswamy, R.M. Nowak, J. McCord, et al., How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the breathing not properly multinational study, *Am. Heart J.* 151 (2006) 999–1005.
- [33] I.A. Khan, J. Fink, C. Nass, H. Chen, R. Christenson, C.R. deFilippi, N-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide for identifying coronary artery disease and left ventricular hypertrophy in ambulatory chronic kidney disease patients, *Am. J. Cardiol.* 97 (2006) 1530–1534.
- [34] J. Hogenhuis, A.A. Voors, T. Jaarsma, A.W. Hoes, H.L. Hillege, J.A. Kragten, et al., Anaemia and renal dysfunction are independently associated with BNP and NT-proBNP levels in patients with heart failure, *Eur. J. Heart Fail.* 9 (2007) 787–794.
- [35] S. Ralli, T.B. Horwich, G.C. Fonarow, Relationship between anemia, cardiac troponin I, and B-type natriuretic peptide levels and mortality in patients with advanced heart failure, *Am. Heart J.* 150 (2005) 1220–1227.
- [36] Y. Ohta, T. Shimada, H. Yoshitomi, S. Inoue, Y. Murakami, H. Shimizu, et al., Drop in plasma brain natriuretic peptide levels after successful direct current cardioversion in chronic atrial fibrillation, *Can. J. Cardiol.* 17 (2001) 415–420.
- [37] R.J. Shelton, A.L. Clark, K. Goode, A.S. Rigby, J.G. Cleland, The diagnostic utility of N-terminal pro-B-type natriuretic peptide for the detection of major structural heart disease in patients with atrial fibrillation, *Eur. Heart J.* 27 (2006) 2353–2361.
- [38] J. Hogenhuis, A.A. Voors, T. Jaarsma, H.L. Hillege, F. Boomsma, D.J. van Veldhuisen, Influence of age on natriuretic peptides in patients with chronic heart failure: a comparison between ANP/NT-ANP and BNP/NT-proBNP, *Eur. J. Heart Fail.* 7 (2005) 81–86.
- [39] T.J. Wang, M.G. Larson, D. Levy, E.J. Benjamin, E.P. Leip, P.W. Wilson, et al., Impact of obesity on plasma natriuretic peptide levels, *Circulation* 109 (2004) 594–600.
- [40] L. Jafri, W. Kashif, J. Tai, I. Siddiqui, I. Azam, H. Shahzad, et al., B-type natriuretic peptide versus amino terminal pro-B type natriuretic peptide: selecting the optimal heart failure marker in patients with impaired kidney function, *BMC Nephrol.* 14 (2013) 117.
- [41] S. Vickery, C.P. Price, R.I. John, N.A. Abbas, M.C. Webb, M.E. Kempson, et al., B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy, *Am. J. Kidney Dis.* 46 (2005) 610–620.
- [42] J.P. Goetze, G. Jensen, S. Moller, F. Bendtsen, J.F. Rehfeld, J.H. Henriksen, BNP and N-terminal proBNP are both extracted in the normal kidney, *Eur. J. Clin. Invest.* 36 (2006) 8–15.
- [43] S. Kasahara, Y. Sakata, K. Nochioka, T. Yamauchi, T. Onose, K. Tsuji, et al., Comparable prognostic impact of BNP levels among HFpEF, borderline HFpEF and HFREF: a report from the CHART-2 study, *Heart Vessel.* 33 (2018) 997–1007.
- [44] J. Gu, A. Noe, P. Chandra, S. Al-Fayoumi, M. Ligueros-Saylan, R. Sarangapani, et al., Pharmacokinetics and pharmacodynamics of LCZ696, a novel dual-acting angiotensin receptor-neprilysin inhibitor (ARNi), *J. Clin. Pharmacol.* 50 (2010) 401–414.
- [45] J.J. McMurray, M. Packer, A.S. Desai, J. Gong, M.P. Leffkowitz, A.R. Rizkala, et al., Angiotensin-neprilysin inhibition versus enalapril in heart failure, *N. Engl. J. Med.* 371 (2014) 993–1004.
- [46] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey Jr., M.M. Colvin, et al., 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Failure Society of America, *J. Am. Coll. Cardiol.* 70 (2017) 776–803.
- [47] M. Packer, J.J. McMurray, A.S. Desai, J. Gong, M.P. Leffkowitz, A.R. Rizkala, et al., Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure, *Circulation* 131 (2015) 54–61.
- [48] H. Tsutsui, S.I. Momomura, Y. Saito, H. Ito, K. Yamamoto, T. Ohishi, et al., Angiotensin receptor neprilysin inhibitor in Japanese patients with heart failure and reduced ejection fraction—baseline characteristics and treatment of PARALLEL-HF trial, *Circ. J.* 82 (2018) 2575–2583.
- [49] A. Clerico, M. Zaninotto, C. Prontera, S. Giovannini, R. Ndreu, M. Franzini, et al., State of the art of BNP and NT-proBNP immunoassays: the CardioOrmoCheck study, *Clin. Chim. Acta* 414 (2012) 112–119.
- [50] N.S. Bajaj, O.M. Gutierrez, G. Arora, S.E. Judd, N. Patel, A. Bennett, et al., Racial differences in plasma levels of N-terminal pro-B-type natriuretic peptide and outcomes: the reasons for geographic and racial differences in stroke (REGARDS) study, *JAMA Cardiol.* 3 (2018) 11–17.