



# Impact of N-terminal pro-B-type natriuretic peptide response on long-term prognosis after transcatheter aortic valve implantation for severe aortic stenosis and heart failure

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## Abstract

N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels prior to transcatheter aortic valve implantation (TAVI) are known to be associated with outcomes of patients undergoing TAVI. However, little has been known about the NT-proBNP response after TAVI. Therefore, we aimed to clarify the role of the NT-proBNP response and identify the determinants of the NT-proBNP nonresponse among patients with severe aortic stenosis (AS) and heart failure (HF) undergoing TAVI. We examined 717 patients with severe AS and HF undergoing TAVI. NT-proBNP nonresponders were defined as patients whose NT-proBNP levels decreased by  $\leq 30\%$ . Mean NT-proBNP levels decreased from  $7698 \pm 7853$  pg/mL (baseline) to  $4523 \pm 5173$  pg/mL (post-TAVI); 269 patients (38%) were nonresponders. Female gender and prevalence of diabetes mellitus (DM), chronic kidney disease (CKD), atrial fibrillation (AF), and history of coronary artery revascularization were more common for NT-proBNP nonresponders. Permanent pacemaker implantation rate was higher for NT-proBNP nonresponders. In addition to the baseline NT-proBNP level  $> 7500$  pg/mL (hazard ratio [HR], 1.8;  $p=0.03$ ), NT-proBNP nonresponse (HR 2.3;  $p=0.001$ ) was associated with lower survival rates. Baseline NT-proBNP level  $\leq 7500$  pg/mL (OR 3.2;  $p<0.001$ ), female gender (odds ratio [OR], 1.5;  $p=0.049$ ), DM (OR 1.6;  $p=0.016$ ), CKD (OR 1.8;  $p=0.001$ ), AF (OR 2.4;  $p<0.001$ ), history of coronary revascularization (OR 1.7;  $p=0.003$ ), and permanent pacemaker implantation after TAVI (OR 1.7;  $p=0.034$ ) were independent determinants of NT-proBNP nonresponse. In “conclusion”, NT-proBNP response is important for long-term survival after TAVI. We should consider the aforementioned determinants, particularly permanent pacemaker implantation, as risk factors for NT-proBNP nonresponse.

**Keywords** Transcatheter aortic valve implantation · N-terminal pro-B-type natriuretic peptide · Heart failure · Pacemaker implantation

## Introduction

Transcatheter aortic valve implantation (TAVI) is a novel and reliable therapeutic option for high-risk or inoperable patients with severe symptomatic aortic stenosis (AS) [1–4]. Heart failure (HF) is complicated for most candidates for TAVI [2,5,6]. Natriuretic peptide (NP) is a cardiac hormone

mainly produced by cardiac myocytes in response to pressure and volume overload, and serum NP levels are useful for the diagnosis and management of patients with HF [7–10]. Previous studies reported that elevated NP levels at baseline were associated with outcomes of patients with AS undergoing not only surgical aortic valve replacement [11,12] but also TAVI [13–15]. In association with the improvement in acute phase outcomes of TAVI (because of the evolution of device and technique), chronic phase outcomes after TAVI have attracted clinical interests. Because TAVI leads to the resolution of pressure overload of the left ventricle, NP levels can decrease after the procedure, and the NP response after TAVI may affect the long-term prognosis of patients undergoing TAVI. However, little is known about the response of NP levels after TAVI; therefore, determinants

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of the NP response after the procedure remain unclear. We sought to clarify the role of the NP response after TAVI and to identify the determinants of the NP nonresponse among patients with severe AS and HF undergoing TAVI.

## Patients and methods

### Study population

We examined 1497 patients who underwent transfemoral TAVI at the Heart Center Brandenburg between July 2008 and May 2017. AS was diagnosed based on the mean transvalvular pressure gradient and aortic valve area calculated using the continuity equation. Left ventricular ejection fraction (LVEF) was measured using Simpson's method. We excluded 43 patients who died during hospitalization, 187 patients whose serum NT-proBNP levels were not available, 541 patients due to low baseline NT-proBNP levels according to rule-in cutoff values for heart failure [16] (450 pg/mL for those younger than 50 years, 900 pg/mL for those aged 50–75 years, and 1800 pg/mL for those older than 75 years), and 9 patients requiring hemodialysis. We examined the remaining 717 patients in this study (Fig. 1).

### Ethics

We performed this study as a part of a retrospective analysis from a single-center TAVI registry according to the ethical

guidelines of our institution. All patients were informed about specific risks and alternative treatments and all of them provided informed consent regarding the use of general data for the scientific activity in future. This study was performed in accordance with the Declaration of Helsinki.

### Definition

The primary endpoint was all-cause death. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation:  $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 186 \times (\text{serum creatinine})^{-1.1544} \times (\text{age})^{-0.203} \times (0.742, \text{ if female})$  [17,18]. Chronic kidney disease (CKD) was defined as  $eGFR < 60 \text{ mL/min/1.73 m}^2$ . We determined the cutoff value of NT-proBNP at baseline as 7500 pg/mL based on its average value. We defined responders to NT-proBNP as patients whose NT-proBNP levels had decreased from baseline by  $> 30\%$  at the time of hospital discharge [19–21].

### Transfemoral TAVI

Indications for TAVI were decided by a discussion among members of our multidisciplinary heart team, including experienced cardiologists, cardiovascular surgeons, and anesthesiologists. If iliofemoral access was anatomically and technically possible, then patients underwent transfemoral TAVI. We performed transfemoral TAVI as previously described [22].

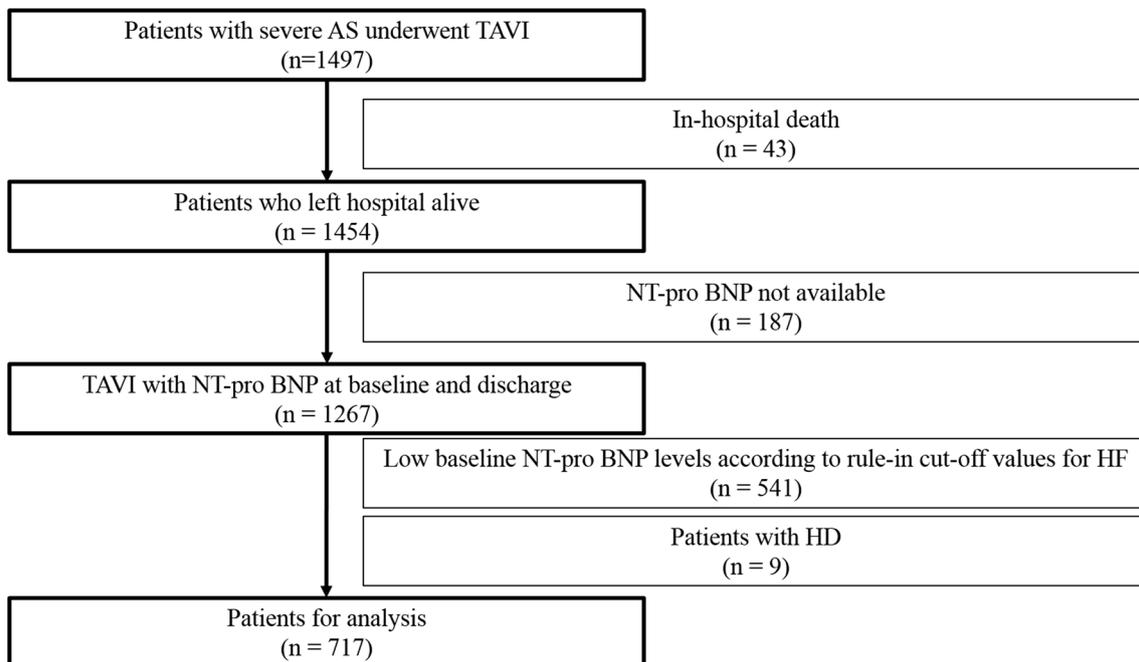


Fig. 1 Flowchart of study patients [16]

## Statistical analysis

Categorical and consecutive data regarding patient backgrounds are presented as percentage and mean values  $\pm$  standard deviation, respectively. The Chi-square test was used for comparisons between NT-proBNP responders and nonresponders, and the unpaired *t* test was used for comparison of consecutive variables. The paired *t* test was used for comparison between serum NT-proBNP levels at baseline and at hospital discharge. Long-term survival after hospital discharge was estimated using Kaplan–Meier curves and the log-rank test to assess the significance of differences between NT-pro BNP responders and nonresponders. We performed the multivariable Cox regression analysis to identify prognostic determinants after hospital discharge using factors potentially associated with patient survival, including NT-proBNP nonresponse, NT-proBNP > 7500 pg/mL at baseline, female gender, age  $\geq$  80 years, LVEF  $\leq$  40%, history of coronary artery revascularization, history of heart surgery, diabetes mellitus (DM), history of myocardial infarction, hypertension, dyslipidemia, atrial fibrillation (AF), chronic obstructive pulmonary disease, peripheral artery disease, history of stroke, and CKD. To identify the determinants of NT-proBNP nonresponse, we performed a multivariable logistic regression analysis using the following covariates selected from factors that were significantly different between NT-proBNP responders and nonresponders: NT-pro BNP  $\leq$  7500 pg/mL female gender, DM, CKD, AF, history of coronary revascularization, LVEF  $\leq$  40%, and permanent pacemaker implantation after TAVI. A *p* value of < 0.05 indicated a statistically significant difference. We conducted statistical analyzes using SPSS version 19.0 software (SPSS Inc, Chicago, IL, USA).

## Results

### NT-pro BNP response after TAVI

The paired *t* test demonstrated that the mean NT-proBNP levels significantly decreased from  $7698 \pm 7853$  pg/mL at baseline to  $4523 \pm 5173$  pg/mL at hospital discharge ( $p < 0.001$ ) (Fig. 2). Among a total of 717 patients, 448 patients (62%) were NT-proBNP responders and 269 patients (38%) were NT-proBNP nonresponders. NT-proBNP decreased from  $8853 \pm 8335$  pg/mL at baseline to  $3106 \pm 3149$  pg/mL at discharge in NT-proBNP responders, whereas NT-proBNP increased from  $5773 \pm 6552$  pg/mL at baseline to  $6884 \pm 6783$  pg/mL at discharge in NT-proBNPnonresponders.

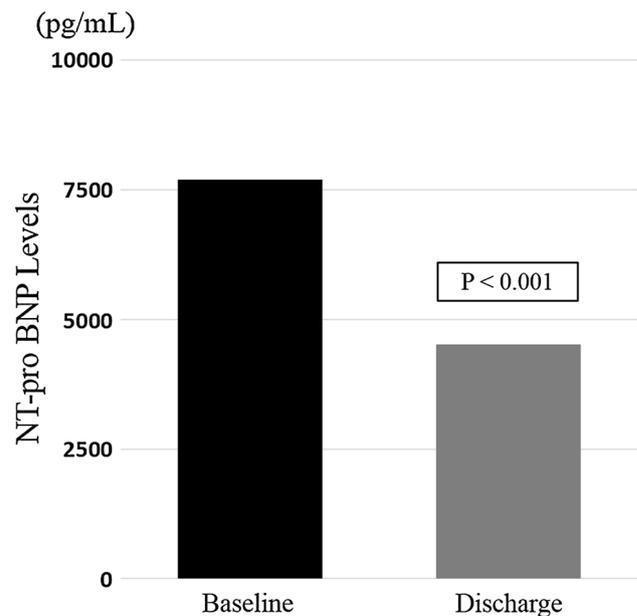


Fig. 2 Change in NT-pro BNP levels

### Characteristics and echocardiographic findings

Table 1 shows the characteristics and echocardiographic findings of study patients. NT-proBNP nonresponders were more likely to be female, and age was not significantly different between NT-proBNP responders and nonresponders. Serum NT-proBNP levels at baseline were higher for NT-proBNP responders. DM, CKD, and AF were more common for NT-proBNP nonresponders than for responders. History of coronary artery revascularization was more common for NT-proBNP nonresponders. Left ventricular (LV) diastolic dimension (Dd) was smaller and LVEF was higher for NT-proBNP nonresponders. The prevalence of moderate or higher grades of tricuspid regurgitation (TR) and tricuspid annular plane systolic excursion were not different between the two groups.

### TAVI procedure and outcome

On average, peak and mean aortic valve pressure gradients decreased from  $71 \pm 28$  and  $47 \pm 19$  mmHg at baseline to  $20 \pm 9$  and  $12 \pm 8$  mmHg after the procedure, respectively (both  $p < 0.001$ ). The following devices were implanted in 717 patients: Sapien (Edwards Lifesciences, Irvine, CA) in 9 patients; Sapien XT (Edwards Lifesciences, Irvine, CA) in 96 patients; Sapien 3 (Edwards Lifesciences, Irvine, CA) in 383 patients; CoreValve (Medtronic, Inc., Minneapolis, MN) in 109 patients; CoreValve Evolut R (Medtronic, Inc., Minneapolis, MN) in 55 patients; Lotus (Boston Scientific, Marlborough, MA) in 10 patients; Boston Acurate neo (Boston Scientific, Marlborough, MA) in 8 patients; Portico (Abbott,

**Table 1** Characteristics of patients

	NT-pro BNP responder ( <i>n</i> = 448)	NT-pro BNP nonre- sponder ( <i>n</i> = 269)	<i>p</i> value
Male gender	50%	41%	0.027
Age (years)	80 ± 7	81 ± 7	0.16
Age ≥ 80 years	60%	65%	0.16
BMI (kg/m <sup>2</sup> )	27 ± 5	28 ± 6	0.16
Logistic euro SCORE (%)	20 ± 13	21 ± 12	0.19
NYHA IV	16%	16%	0.92
NT-proBNP (pg/mL) at baseline	8853 ± 8335	5773 ± 6552	< 0.001
NT-pro BNP ≤ 7500 pg/mL	61%	81%	< 0.001
Hypertension	69%	68%	0.77
Diabetes mellitus	36%	46%	0.016
eGFR (mL/min/1.73 m <sup>2</sup> )	58 ± 22	51 ± 19	< 0.001
Chronic kidney disease	51%	66%	< 0.001
Prior MI	12%	15%	0.28
Atrial fibrillation	47%	63%	< 0.001
Coronary artery revascularization	41%	51%	0.013
PCI	36%	46%	0.010
CABG	11%	13%	0.27
Peripheral artery disease	21%	21%	0.89
Pacemaker	12%	15%	0.20
Stroke/TIA	7%	7%	0.85
COPD	17%	16%	0.59
<i>Echocardiography</i>			
LVDd (mm)	49 ± 8	48 ± 8	0.015
LVEF (%)	45 ± 15	50 ± 13	0.001
LVEF ≤ 40%	35%	23%	0.001
TR grade ≥ moderate	20%	21%	0.73
TAPSE (mm)	19 ± 5	19 ± 5	0.68

*NT-proBNP* N-terminal pro-B-type natriuretic peptide, *BMI* body mass index, *NYHA* New York Heart Association, *eGFR* estimated glomerular filtration rate, *MI* myocardial infarction, *COPD* chronic obstructive pulmonary disease, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *TIA* transient ischemic attack, *LVDd* left ventricular diastolic dimension, *LVEF* left ventricular ejection fraction, *TR* tricuspid regurgitation, *TAPSE* tricuspid annular plane systolic excursion

Data are expressed as mean ± standard deviation, or percentage

Menlo Park, CA) in 20 patients, Direct Flow (Direct Flow Medical, Santa Rosa, CA) in 26 patients; and NVT Allegla (New Valve Technology, Hechingen, Germany) in 1 patient. Prevalence of moderate or higher grades of aortic regurgitation after TAVI was not different between NT-proBNP responders and nonresponders (3.5% vs. 3.3%; *p* = 0.864). Permanent pacemaker implantation rate was higher for NT-proBNP nonresponders than for responders (18% vs. 12%; *p* = 0.030).

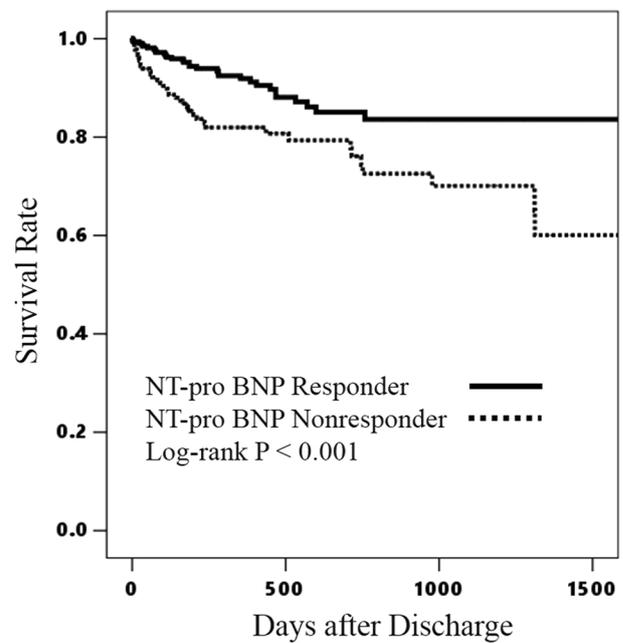
### Survival after TAVI

Kaplan–Meier curves showed that NT-proBNP nonresponders had lower survival rates after hospital discharge (log-rank *p* < 0.001) (Fig. 3). Multivariable Cox regression analysis revealed that NT-proBNP > 7500 pg/mL (hazard ratio

[HR], 1.8; *p* = 0.020; 95% confidence interval (CI) 1.1–3.1) and NT-proBNP nonresponse (HR 2.3; *p* = 0.001; 95% CI 1.4–3.9) were independently associated with higher mortality after hospital discharge (Table 2).

### Predictors of NT-pro BNP nonresponse

Multivariable logistic regression analysis revealed that baseline NT-pro BNP ≤ 7500 pg/mL (OR 3.2; *p* < 0.001), female gender (odds ratio [OR], 1.5; *p* = 0.049), DM (OR 1.6; *p* = 0.016), CKD (OR 1.8; *p* = 0.001), AF (OR 2.4; *p* < 0.001), history of coronary artery revascularization (OR 1.7; *p* = 0.003), and permanent pacemaker implantation after TAVI (OR 1.7; *p* = 0.034) were independent determinants of NT-proBNP nonresponse after TAVI (Table 3). LVEF ≤ 40% was not statically significant (*p* = 0.363).

**Fig. 3** Kaplan–Meier curves for survival after hospital discharge

Patients at risk

	0	30	100	365	730
NT-pro BNP Responder	448	321	302	149	65
NT-pro BNP Nonresponder	269	169	154	76	45

**Table 2** HRs for all-cause death after discharge

	<i>p</i> value	HR	95% CI
NT-pro BNP > 7500 pg/mL	0.030	1.8	1.1–3.1
NT-pro BNP nonresponse	0.001	2.3	1.4–3.9

HR hazard ratio, NT-pro BNP N-terminal pro-B-type natriuretic peptide, CI confidence interval

**Table 3** ORs for NT-pro BNP nonresponse

	<i>p</i> value	OR	95% CI
NT-pro BNP ≤ 7500 pg/mL	< 0.001	3.2	2.1–4.9
Female gender	0.049	1.5	1.0–2.1
Diabetes mellitus	0.016	1.6	1.1–2.2
Chronic kidney disease	0.001	1.8	1.3–2.6
Atrial fibrillation	< 0.001	2.4	1.7–3.4
Coronary artery revascularization	0.003	1.7	1.2–2.5
Permanent pacemaker implantation after TAVI	0.034	1.7	1.0–2.8

OR odds ratio, NT-pro BNP N-terminal pro-B-type natriuretic peptide, CI confidence interval

## Discussion

The key findings of the present study were as follows: mean NT-proBNP levels decreased from  $7698 \pm 7853$  pg/mL (baseline) at baseline to  $4523 \pm 5173$  pg/mL at discharge; 38% of study patients were nonresponders; baseline NT-proBNP level > 7500 pg/mL and NT-proBNP nonresponse were independently associated with lower survival rates after hospital discharge; and female gender, baseline NT-proBNP level > 7500 pg/mL, DM, CKD, AF, history of coronary artery revascularization, and permanent pacemaker implantation after TAVI were independent determinants of NT-proBNP nonresponse.

In accordance with previous studies [13–15], higher NT-proBNP levels at baseline were associated with worse survival rates of patients treated with TAVI. Interestingly, higher NT-proBNP levels negatively affected the outcomes of patients undergoing TAVI, even after hospital discharge. NP is mainly released by cardiac monocytes of the left ventricle in response to pressure and volume overload [9]. Therefore, it was shown that NT-proBNP levels were associated with AS severity and symptoms [23,24]. From this point of view, it is reasonable that NT-proBNP levels immediately decreased at hospital discharge after a rapid release of pressure overload by TAVI. Overall, NT-proBNP levels significantly decreased at hospital discharge. Nevertheless, nearly 40% of study patients were

categorized as nonresponders. Moreover, NT-proBNP nonresponders independently had worse survival rates after hospital discharge. This result is partially in line with the results of the study by Mizutani et al., which showed an association between BNP elevation at discharge and higher mortality after TAVI [25].

It should be noted that the NT-proBNP response was associated with outcomes of patients undergoing TAVI independent of baseline NT-proBNP levels. Accordingly, it is important to consider determinants of NT-proBNP nonresponse, including gender, DM, CKD, AF, history of coronary artery revascularization, and permanent pacemaker implantation. However, for most of these, intervention is not possible; therefore, permanent pacemaker implantation may have an essential role as a modifiable factor. Subsequent conduction disturbance requiring permanent pacemaker implantation is the most frequent adverse event [26] and could limit the clinical benefits of TAVI. This complication was associated with prolonged hospital stay and increased procedural costs [27]. Nazif et al. reported that permanent pacemaker implantation was associated with a longer duration of hospitalization and higher rates of repeat hospitalization and mortality or repeat hospitalization [28]. Those findings are in agreement with the results of the present study. Therefore, we need to focus attention on this complication to improve long-term outcomes of patients undergoing TAVI from the perspective of HF recovery.

### Study limitations

There were several limitations to this study. Because of the limited sample size, the statistical power may not be strong enough for any negative data to be conclusive. Furthermore, we did not have data regarding rehospitalization due to HF after TAVI. Paradoxically, NT-proBNP responses were more commonly observed in those with higher baseline NT-proBNP levels, suggesting that some degree of HF would remain even after TAVI. Therefore, the proportion of nonresponders defined by the degree of decline of NT-proBNP would be relatively higher for those with lower baseline NT-proBNP levels. The time interval between the TAVI procedure and timing of NT-pro BNP measurement before discharge is not assessed in this study. Periprocedural factors including volume overload and myocardial injury can influence the NT-proBNP response. Further study is required to clarify the association between these factors.

### Conclusion

NT-proBNP nonresponse is independently associated with lower long-term survival rates after TAVI. Female gender, DM, CKD, AF, history of coronary artery revascularization,

and permanent pacemaker implantation after TAVI were determinants of the NT-proBNP nonresponse. Therefore, we should consider these determinants, particularly permanent pacemaker implantation, as a modifiable target as risk factors for NT-proBNP nonresponse.

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### Compliance with ethical standards

**Conflict of interest** We have no conflict of interest for this study.

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