ORIGINAL RESEARCH

Periprocedural Changes of NT-proBNP Are Associated With Survival After Transcatheter Aortic Valve Implantation

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***Background*—**Cardiovascular biomarkers constitute promising tools for improved risk stratification and prediction of outcome in patients undergoing transcatheter aortic valve implantation. We examined the association of periprocedural changes of NT-proBNP (N-terminal pro–B-type natriuretic peptide) with survival after transcatheter aortic valve implantation.

***Methods and Results*—**NT-proBNP levels were measured in 704 patients before transcatheter aortic valve implantation and at discharge. Patients were grouped as *responders* and *nonresponders* depending on an NT-proBNP–based ratio (postprocedural NT-proBNP at discharge/preprocedural NT-proBNP). Overall, 376 of 704 patients showed a postprocedural decrease in NT-proBNP levels (NT-proBNP ratio <1). Responders and nonresponders differed significantly regarding median preprocedural (2822 versus 1187 pg/mL, $P<0.001$) and postprocedural (1258 versus 3009 pg/mL, $P<0.001$) NT-proBNP levels. Patients in the nonresponder group showed higher prevalence of atrial fibrillation (47.0% versus 39.4%, $P=0.042$), arterial hypertension (94.2% versus 87.5%, $P=0.002$), renal impairment (77.4% versus 69.1%, $P=0.013$), and peripheral artery disease (24.4% versus 14.6%, $P=0.001$). In contrast, patients in the responder group had higher prevalence of moderately reduced left ventricular ejection fraction (17.3% versus 11.0%, $P=0.017$), lower calculated aortic valve area (0.7 versus 0.8 cm^2, $P<0.001$), and higher mean pressure gradient (41 versus 35 mm Hg, $P<0.001$). Median follow-up was 22.6 months. Kaplan–Meier analysis showed a highly significant survival benefit for the responder group compared with the nonresponder group (log-rank test, $P<0.001$).

***Conclusions*—**A ratio based on periprocedural changes of NT-proBNP is a simple tool for better risk stratification and is associated with survival in patients after transcatheter aortic valve implantation. **(*J Am Heart Assoc*. 2019;8:e010876. DOI: 10.1161/JAHA.118.010876)**

Key Words: aortic stenosis • biomarker • NT-proBNP • risk stratification • transcatheter aortic valve implantation

Aortic stenosis (AS) is the most frequent type of aortic valve disease in North America and Europe, with an age-dependent prevalence of ≈5% in the population aged >65 years.[1] In recent years, transcatheter aortic valve implantation (TAVI) has emerged as the standard treatment of AS in high-risk and selected intermediate-risk patients.[2] Especially in light of the expansion of TAVI toward a lower risk and younger patient population, tools for improved risk stratification and evaluation of treatment response are essential. Several biomarkers of cardiovascular disease have been studied in the context of AS in an attempt to reflect and investigate the complex processes involved in its pathophysiology.[3] In TAVI, mainly preprocedural measurements of biomarkers such as high-sensitive troponin T,[4] GDF15 (growth differentiation factor 15),[5] osteopontin,[6] and soluble ST2 (suppression of tumorigenicity 2)[7] have been shown to provide robust prognostic information.

Natriuretic peptides (NPs) including BNP (B-type NP) and its prohormone NT-proBNP (N-terminal pro-BNP) are established biomarkers, especially in the field of heart failure (HF).[8] NPs have also been correlated to AS severity as well as symptom onset[9] and are of predictive value in patients undergoing aortic valve replacement.[10,11] In TAVI patients, elevated NP levels at

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Clinical Perspective

What Is New?

- Periprocedural changes of NT-proBNP (N-terminal pro–B-type natriuretic peptide) are significantly associated with survival after transcatheter aortic valve implantation.

What Are the Clinical Implications?

- Implementing a ratio based on periprocedural changes of NT-proBNP might improve risk stratification of patients undergoing transcatheter aortic valve implantation.
- Patients without a postprocedural decrease of NT-proBNP after transcatheter aortic valve implantation should be carefully evaluated for optimized medical treatment and closer follow-up.

baseline and after TAVI have been identified as predictors of adverse outcome.[11–13] However, the impact of periprocedural changes in circulating NT-proBNP levels after TAVI regarding survival remains unclear. We examined the value of an NT-proBNP–based ratio (postprocedural NT-proBNP at discharge/preprocedural NT-proBNP) in a single-center study.

Methods

For data protection reasons, individual patient data will not be made available to other researchers. Nevertheless, we are convinced that the calculation of our proposed NT-proBNP ratio is easily reproducible, and we encourage scientists to validate our findings in other TAVI studies.

Study Design

We conducted a retrospective analysis of 704 patients who underwent TAVI at our institution for symptomatic severe AS between January 2011 and March 2017. A ratio was calculated based on periprocedural changes of NT-proBNP (postprocedural NT-proBNP at discharge/preprocedural NT-proBNP).

Before TAVI, patients were discussed by our interdisciplinary heart team and precluded from surgical aortic valve replacement because of significantly elevated surgical risk. We used a few first-generation CoreValve valves (Medtronic) and mostly second-generation Sapien XT (Edwards Lifesciences, Irvine, California) and third-generation Sapien 3 and CoreValve Evolut R systems. The choice of the respective valve type was made at the discretion of the implanting physician. The default TAVI access route was transfemoral; otherwise, a transaortic or transapical approach was used. Procedures were typically performed under conscious sedation, with the exception of transaortic and transapical TAVI.

Data Collection

The data collection was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee at the University of Kiel. All patients provided informed consent to the procedure and the data acquisition.

Blood samples and patient data were usually collected 1 day before TAVI. Depending on the date of discharge, postprocedural blood samples were taken 3 to 7 days after TAVI. NT-proBNP was measured using a system obtained from Roche Diagnostics (proBNP II). In addition to biomarker levels, the following data were recorded: age, sex, body mass index, history of atrial fibrillation, presence of coronary artery disease, chronic obstructive pulmonary disease, diabetes mellitus, dyslipidemia, arterial hypertension, peripheral artery disease, pulmonary arterial hypertension, cerebrovascular disease, history of smoking, chronic kidney disease based on glomerular filtration rate, hemodynamic variables, logistic EuroSCORE, and TAVI procedural details. Patient outcomes were analyzed following the Valve Academic Research Consortium 2 (VARC-2) system.[14] The primary outcome of our study was survival. Follow-up after discharge usually included an in-person visit in our cardiology outpatient clinic 3 months after TAVI. Thereafter, a phone-call follow-up was obtained on an annual basis either by calling the patients or their general practitioner or cardiologist. This was done systematically for all patients who had given written consent to participate in our TAVI registry.

Statistical Analyses

Based on periprocedural changes in NT-proBNP levels, patients were stratified into 2 groups: those who had a decrease in NT-proBNP (NT-proBNP ratio <1) after TAVI were defined as *responders*, whereas patients who had postprocedurally increased or unchanged NT-proBNP levels (NT-proBNP ratio ≥ 1) were defined as *nonresponders*. Results are summarized using standard statistical evaluations. Continuous data are presented as median and interquartile range, and categorical data are expressed as counts (percentages). Variables were statistically tested for using the χ^2 test and the Mann–Whitney *U* test. Survival data were visualized by Kaplan–Meier plots and assessed using the log-rank test as well as Cox regression analysis. For the Cox regression model, all preprocedural factors significantly linked to mortality in the log-rank test were included. Backward selection was based on the likelihood ratio criteria. Cox regression results are presented as adjusted hazard ratios with 95% CIs. For each covariate, the proportional hazards assumption was approved by testing for interactions between Schoenefeld residuals and the log-transformed time (function "*cox.zph*()"). All statistical analyses were performed using the statistical software RStudio v1.1.453 (package "survival") and GraphPad PRISM v7.

Table 1. Baseline Characteristics of Patients Undergoing TAVI

	Total (n=704)	Responders (n=376)	Nonresponders (n=328)	*P* Value
Age, y	81.6 (77.6–86.0)	81.3 (77.5–85.7)	81.8 (78.0–86.3)	0.204
Female	386 (54.8)	200 (53.2)	186 (56.7)	0.350
BMI, kg/m^2	26.2 (23.6–29.4)	26.2 (23.7–29.0)	26.5 (23.5–30.0)	0.236
Atrial fibrillation	302 (42.9)	148 (39.4)	154 (47.0)	0.042
CAD	510 (72.4)	271 (72.1)	239 (72.9)	0.815
COPD	115 (16.3)	56 (14.9)	59 (18.0)	0.268
Diabetes mellitus	230 (32.7)	120 (31.9)	110 (33.5)	0.647
Dyslipidemia	358 (50.9)	188 (50.0)	170 (51.8)	0.628
Hypertension	638 (90.6)	329 (87.5)	309 (94.2)	0.002
PAD	135 (19.2)	55 (14.6)	80 (24.4)	0.001
CVD	133 (18.9)	62 (16.5)	71 (21.6)	0.081
PAH	132 (18.8)	85 (22.6)	47 (14.3)	0.005
LVEF				
<35%	67 (9.5)	41 (10.9)	26 (7.9)	0.179
35–45%	101 (14.3)	65 (17.3)	36 (11.0)	0.017
45–55%	131 (18.6)	72 (19.1)	59 (18.0)	0.693
>55%	405 (57.5)	198 (52.7)	207 (63.1)	0.005
GFR				
<30 mL/min	76 (10.8)	36 (9.6)	40 (12.2)	0.264
30–45 mL/min	157 (22.3)	79 (21.0)	78 (23.8)	0.378
45–60 mL/min	281 (39.9)	145 (38.6)	136 (41.5)	0.433
>60 mL/min	190 (27.0)	116 (30.9)	74 (22.6)	0.013
History of smoking	157 (22.3)	78 (20.7)	79 (24.1)	0.288
Log. EuroSCORE (%)	18.8 (11.9–28.4)	18.6 (11.6–28.4)	19.0 (12.7–28.5)	0.721
NT-proBNP, pg/mL	1991 (746–4235)	2822 (1113–5575)	1187 (507–2782)	<0.001
AVA, cm^2	0.7 (0.6–0.9)	0.7 (0.5–0.8)	0.8 (0.6–0.9)	<0.001
MPG, mm Hg	37 (28–49)	41 (30–53)	35 (25–43)	<0.001
Diastolic dysfunction ≥ II	442 (62.8)	234 (62.2)	208 (63.4)	0.746
RV dysfunction	110 (15.6)	61 (16.2)	49 (14.9)	0.640
MR III–IV	36 (5.1)	20 (5.3)	16 (4.9)	0.791
TR III–IV	47 (6.7)	23 (6.1)	24 (7.3)	0.525

Values are presented as count (percentage) or median (interquartile range). AVA indicates aortic valve area; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; MPG, mean pressure gradient; MR, mitral regurgitation; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAD, peripheral artery disease; PAH, pulmonary arterial hypertension; RV, right ventricle; TAVI, transcatheter aortic valve implantation; TR, tricuspid regurgitation.

Results

Baseline Patient Characteristics

A total of 704 patients were available for analysis. Based on the NT-proBNP ratio, 376 patients were assigned to the responder group (NT-proBNP ratio <1) and 328 were assigned to the nonresponder group (NT-proBNP ≥1). Baseline patient characteristics are summarized in Table 1. The distribution of the NT-proBNP ratio is visualized in Figure S1.

No significant differences between groups were observed in terms of age (median: 81.6 years), female sex (54.8%), body mass index (median: 26.2), coronary artery disease (72.4%), chronic obstructive pulmonary disease (16.3%), diabetes mellitus (32.7%), dyslipidemia (50.9%), history of smoking (22.3%), and cerebrovascular disease (18.9%).

Table 2. Procedural Variables and Outcomes

	Total (n=704)	Responders (n=376)	Nonresponders (n=328)	*P* Value
Valve size, mm				
23	161 (22.9)	83 (22.1)	78 (23.8)	0.591
26	342 (48.6)	181 (48.1)	161 (49.1)	0.802
29	195 (27.7)	108 (28.7)	87 (26.5)	0.515
34	6 (0.9)	4 (1.1)	2 (0.6)	0.513
TF access	453 (64.3)	288 (76.6)	165 (50.3)	<0.001
Procedural duration, min	66 (50–95)	62 (50–92)	72 (52–101)	0.008
Contrast agent, mL	80 (60–102)	80 (65.0–102)	80 (60–102)	0.904
VARC-2				
Myocardial infarction	6 (0.9)	1 (0.3)	5 (1.5)	0.070
Disabling stroke	10 (1.4)	4 (1.1)	6 (1.8)	0.392
Life-threatening bleeding	27 (3.8)	13 (3.5)	14 (4.3)	0.576
Major access complications	39 (5.5)	22 (5.9)	17 (5.2)	0.699
New pacemaker	57 (8.1)	25 (6.6)	32 (9.8)	0.132
Conversion to open surgery	5 (0.7)	1 (0.3)	4 (1.2)	0.133
AKIN stage 3	23 (3.3)	15 (4.0)	8 (2.4)	0.248
Residual AR ≥ moderate	18 (2.6)	9 (2.4)	9 (2.7)	0.769
NT-proBNP at discharge, pg/mL	1886 (788–4367)	1258 (561–2592)	3009 (1362–6561)	<0.001

Values are presented as count (percentage) or median (interquartile). AKIN indicates Acute Kidney Injury Network; AR, aortic regurgitation; NT-proBNP, N-terminal pro–B-type natriuretic peptide; TF, transfemoral; VARC-2, Valve Academic Research Consortium 2.

However, patients in the responder group showed significantly lower prevalence of atrial fibrillation (39.4% versus 47.0%, *P*=0.042), arterial hypertension (87.5% versus 94.2%, *P*=0.002), peripheral artery disease (14.6% versus 24.4%, *P*=0.001), pulmonary arterial hypertension (22.6% versus 14.3%, *P*=0.005), and renal impairment (69.1% versus 77.4%, *P*=0.013). With respect to left ventricular ejection fraction (LVEF), responders had higher prevalence of moderately reduced LVEF (17.3% versus 11.0%, *P*=0.017) and significantly higher NT-proBNP levels at baseline (2822 versus 1187 pg/mL, *P*<0.001). Moreover, responders showed lower aortic valve areas (0.7 versus 0.8 cm^2, *P*<0.001) and higher mean pressure gradients (41 versus 35 mm Hg, *P*<0.001) as echocardiographic features of more advanced AS.

Procedural Outcomes, HF Medication, and Their Association With Responder Status

Procedural parameters and patient outcomes are presented in Table 2. Patients in the responder group were treated more frequently using a transfemoral access (76.6% versus 50.3%, *P*<0.001). Median procedural duration was also significantly lower in the responder group (62 versus 72 minutes, *P*=0.008). There were no significant differences regarding VARC-2–related outcomes between groups. Data regarding HF medication at discharge are presented in Table 3 and demonstrate no statistically significant difference between groups.

Kaplan–Meier survival curves are shown in Figure 1 with a median follow-up period of 22.6 months. Survival curves of responders and nonresponders substantially diverged, revealing superior outcomes of NT-proBNP responders in terms of survival (log-rank test, *P*<0.001).

In a further analysis—illustrated in Figure 2—patients with high baseline NT-proBNP levels (upper quartile) and an NT-proBNP ratio ≥1 showed the worst survival.

Variables Significantly Associated With Outcome After TAVI

Table 4 summarizes variables that were significantly associated with mortality after a median follow-up of 22.6 months, using log-rank tests. These included an NT-proBNP ratio ≥1 and elevated baseline and postprocedural NT-proBNP levels (upper quartile, respectively). In addition, age older than the median (81.6 years), atrial fibrillation, chronic obstructive pulmonary disease, diabetes mellitus, dyslipidemia, pulmonary arterial hypertension, and renal impairment were linked to mortality. Regarding VARC-2–

Table 3. HF Medication at Discharge

	Total (n=695)	Responders (n=371)	Nonresponders (n=324)	*P* Value
ACE-I or ARB	550 (79.1)	303 (81.7)	247 (76.2)	0.078
β-Blocker	529 (76.1)	288 (77.6)	241 (74.4)	0.317
MR antagonist	94 (13.5)	54 (14.6)	40 (12.3)	0.395
Loop diuretics	525 (75.5)	271 (73.0)	254 (78.4)	0.102
Other diuretic agents	115 (16.5)	61 (16.4)	54 (16.7)	0.937
ARNI	2 (0.3)	2 (0.5)	0	…
Digitoxin/digoxin	49 (7.1)	23 (6.2)	26 (8.0)	0.348
Ivabradin	5 (0.7)	3 (0.8)	2 (0.6)	0.766
Dihydropyridine CCBs	289 (41.6)	155 (41.8)	134 (41.4)	0.911

Values are presented as count (percentage). Data are available for 695 patients. ACE-I indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CCB, calcium channel blocker; HR, heart failure; MR, mineralocorticoid receptor.

defined outcomes, disabling stroke, life-threatening bleeding, periprocedural myocardial infarction, and major access complications were also significant parameters. Following backward selection based on the likelihood criteria, multivariable Cox regression analysis was used to identify variables that show statistically significant associations with adverse TAVI outcome. These data are presented in Table 5. The proportional hazards assumption was met (Schoenfeld individual test for each covariate $P \geq 0.05$, global Schoenfeld test $P=0.250$). Of the aforementioned parameters, both diabetes mellitus and dyslipidemia did not reach statistical significance.

In conclusion, an NT-proBNP ratio ≥1 was significantly associated with mortality after TAVI (hazard ratio: 1.68; 95% CI, 1.27–2.22; $P<0.001$).

Discussion

In this analysis of 704 patients, we examined the association between periprocedural changes of NT-proBNP levels and survival after TAVI. Based on an NT-proBNP ratio (postprocedural NT-proBNP at discharge/preprocedural NT-proBNP) patients were divided into responder (NT-proBNP ratio <1) and nonresponder (NT-proBNP ratio ≥1) groups. Our study shows that the NT-proBNP ratio is significantly associated with survival after TAVI.

NPs and Biomarker-Guided Therapy in Patients With HF

NPs are essential biomarkers in the context of HF because they reflect disease severity and predict adverse

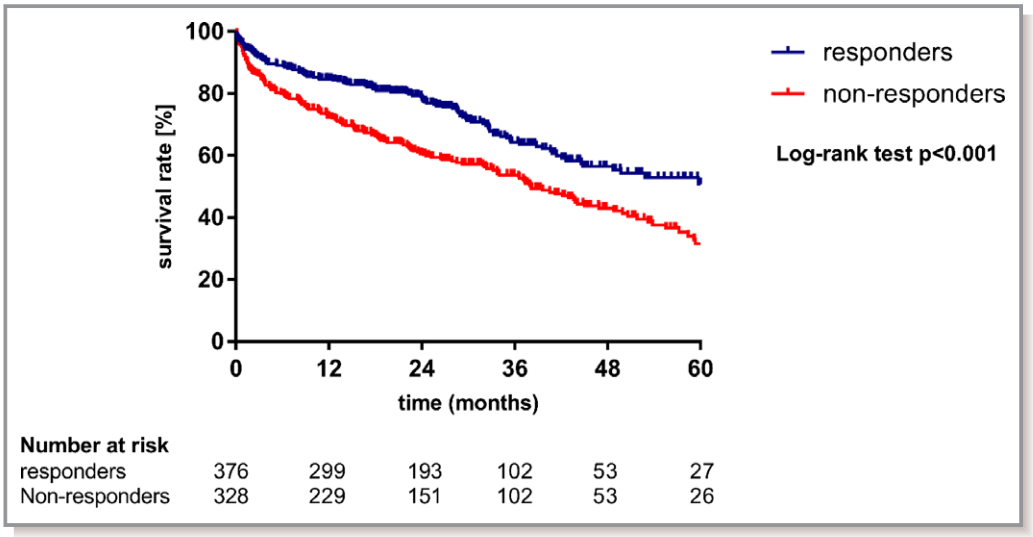

Figure 1. Periprocedural changes in NT-proBNP (N-terminal pro–B-type natriuretic peptide) are associated with survival. Kaplan–Meier survival curves for overall-survival comparing responders (NT-proBNP ratio <1) and nonresponders (NT-proBNP ratio ≥1).

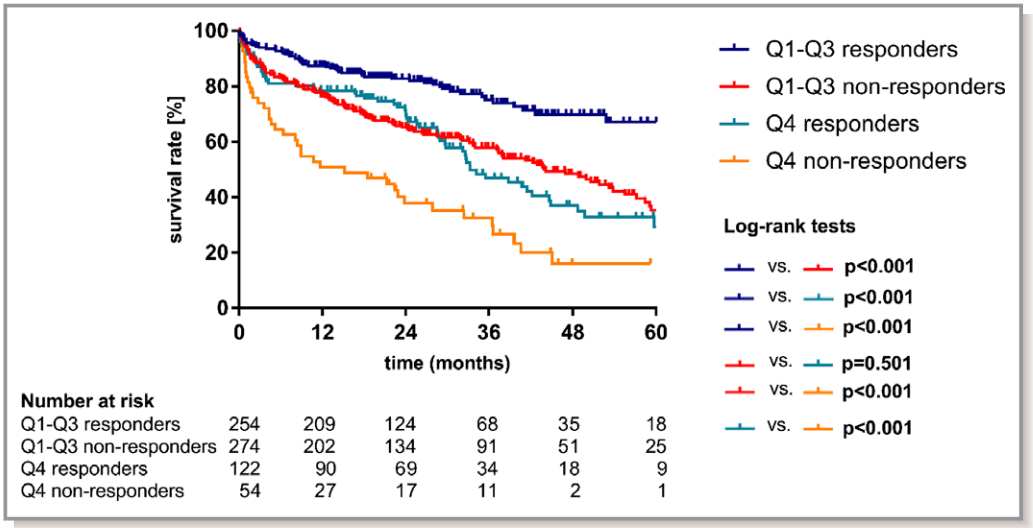

Figure 2. Relevance of a combination of periprocedural NT-proBNP (N-terminal pro–B-type natriuretic peptide) changes and baseline NT-proBNP levels. Kaplan–Meier survival curves for overall survival of subgroups based on responder status and baseline NT-proBNP levels. (Q4=upper quartile). Q indicates quartile.

outcomes.[15–17] Although normal plasma concentrations of NPs (cutoff for NT-proBNP <125 pg/mL in a nonacute setting and <300 pg/mL in an acute setting) have an excellent predictive value for excluding HF,[8] elevated NPs may be associated with various cardiovascular and noncardiovascular diseases including valvular heart disease.[18,19] In addition to the prognostic implications of NPs, the concept of a biomarker-guided treatment strategy has also been evaluated in HF patients. In the UPSTEP (Use of Peptides in Tailoring Heart Failure Project) study,[20] 279 patients with worsening HF, LVEF <40%, and elevated levels of BNP were randomized to either conventional HF treatment or BNP-guided therapy. Although no significant differences were noted between groups regarding morbidity and mortality, the study demonstrated that treatment responders (>30% decrease in baseline BNP levels) had significantly better outcomes compared with nonresponders. Moreover, the GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure) study,[21] which enrolled 894 high-risk HF patients with reduced LVEF who were randomized to either an NT-proBNP-guided strategy or usual care, also failed to show superiority of an NP-based approach and was terminated for futility.

NPs in AS and Aortic Valve Replacement

NPs have been shown to correlate with AS severity, symptom-free survival, optimal timing of aortic valve replacement, and mortality.[22–25] BNP is recognized in the current European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease[2] as the only biomarker with prognostic value in AS. Regarding risk stratification, elevated NPs at baseline have been identified as predictors of postoperative mortality in patients undergoing surgical aortic valve replacement.[9,10]

Consequently, NPs have also been evaluated for their prognostic implications in the context of TAVI. In a study comprising 340 TAVI patients, O'Sullivan et al[26] showed that

Table 4. Significant Mortality-Associated Factors (Log-Rank Test)

	P Value
Nonresponder status (NT-proBNP ratio ≥1)	<0.001
Preprocedural NT-proBNP >4235 pg/mL (Q4)	<0.001
Postprocedural NT-proBNP >4367 pg/mL (Q4)	<0.001
Age older than median (81.6 y)	0.009
Atrial fibrillation	<0.001
COPD	<0.001
Diabetes mellitus	0.048
Dyslipidemia	0.007
PAH	0.015
Renal impairment (GFR <60 mL/min)	<0.001
Disabling stroke	<0.001
Life-threatening bleeding	<0.001
Myocardial infarction	0.003
Major access complication	0.013

COPD indicates chronic obstructive pulmonary disease; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; Q, quartile; Q4, upper quartile.

Table 5. Cox Regression Analysis

Variable	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Nonresponder status (NT-proBNP ratio ≥1)	1.67 (1.32–2.11)	<0.001	1.68 (1.27–2.22)	<0.001
Preprocedural NT-proBNP >4235 pg/mL (Q4)	1.83 (1.43–2.33)	<0.001	1.46 (1.06–1.99)	0.019
Postprocedural NT-proBNP >4367 pg/mL (Q4)	2.48 (1.96–3.14)	<0.001	1.52 (1.12–2.05)	0.007
Age older than median (81.6 y)	1.36 (1.08–1.72)	0.010	1.38 (1.08–1.76)	0.010
Atrial fibrillation	1.77 (1.41–2.24)	<0.001	1.48 (1.17–1.88)	0.001
COPD	2.14 (1.64–2.79)	<0.001	2.19 (1.66–2.88)	<0.001
PAH	1.40 (1.07–1.85)	0.016	1.47 (1.10–1.96)	0.009
Renal impairment (GFR <60 mL/min)	2.23 (1.62–3.07)	<0.001	1.63 (1.17–2.28)	0.004
Disabling stroke	4.57 (2.43–8.6)	<0.001	3.57 (1.83–6.97)	<0.001
Life-threatening bleeding	2.34 (1.45–3.78)	<0.001	2.63 (1.58–4.38)	<0.001
Myocardial infarction	3.57 (1.47–8.69)	0.005	4.81 (1.92–12.02)	<0.001
Major access complication	1.69 (1.11–2.57)	0.014	1.69 (1.07–2.65)	0.024
Diabetes mellitus	1.27 (1.0–1.62)	0.048	1.22 (0.95–1.57)	0.113
Dyslipidemia	0.73 (0.58–0.92)	0.007	0.80 (0.63–1.02)	0.076

COPD indicates chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HR, hazard ratio; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAH, pulmonary arterial hypertension; Q, quartile; Q4, upper quartile.

patients in the upper tertile group (BNP ≥596 pg/mL) had higher rates of all-cause mortality and major adverse cardiac and cerebrovascular events (death, major stroke, and myocardial infarction) at 30 days compared with patients in the lower tertile group (BNP ≤201 pg/mL). With respect to long-term outcome, Koskinas et al[27] demonstrated in a study of 340 TAVI patients that high preprocedural BNP levels predict all-cause mortality and cardiovascular death at 2 years. In 219 of those patients, both BNP and NT-pro-BNP were measured serially before and after the procedure. In their study, NT-proBNP levels after TAVI showed the highest prognostic discrimination for 2-year mortality. In a study of 333 TAVI patients by Ribeiro et al,[28] elevated NT-proBNP at baseline (cutoff value ≥2000 pg/mL) emerged as a predictor of all-cause mortality, cardiovascular death, and rehospitalization for HF at a median follow-up of 2 years. The authors concluded that NT-proBNP levels should be included in the decision-making process and in clinical patient follow-up.

The prognostic implications of periprocedural changes of BNP were investigated by O'Neill et al. Based on data from the PARTNER (Placement of Aortic Transcatheter Valve Trial Edwards SAPIEN Transcatheter Heart Valve) trial,[11] comprising 933 patients with baseline and serial BNP measurements, the authors demonstrated that an increase of BNP level at 30 days was associated with death and the combined end point of death or rehospitalization. Furthermore, data from the multicenter OCEAN-TAVI (Optimized Catheter valvular intervention) registry[13] presented by Mizutani et al showed that elevated BNP levels at discharge were significantly associated with 2-year mortality and thus might aid in risk stratification of TAVI patients. In addition, a study of 504 patients regarding the prognostic value of periprocedural NT-proBNP levels after TAVI[29] has been reported recently by Liebetrau et al. The authors showed that elevated postprocedural NT-proBNP is a predictor of mortality if interpreted in the context of transapical access with concomitant aortic regurgitation and in transfemoral patients with concomitant aortic regurgitation and reduced LVEF.

In conclusion, our results are in line with previously published data emphasizing that both pre- and postprocedural NPs including NT-proBNP are of predictive value in patients undergoing TAVI and thus might be incorporated into clinical practice.

NT-proBNP Ratio and Variables Associated With Responder and Nonresponder Status

To the best of our knowledge, this study is the first to investigate the prognostic value of a biomarker ratio based on NT-proBNP levels at discharge and at baseline in patients undergoing TAVI.

Although we acknowledge the important aforementioned scientific data demonstrating that NPs aid in risk stratification of TAVI patients during follow-up (eg, at 30 days or 1 year), we strongly support a strategy of early risk stratification. Implementation of an NT-proBNP ratio as a simple tool might

be beneficial in identifying those patients in need of closer follow-up or optimized medical treatment. Notably, in our analysis, there was no statistically significant difference in HF medication at discharge between groups, perhaps suggesting that a large proportion of TAVI patients did not receive optimal therapy. This may be attributed in part to the fact that medical treatment of TAVI patients was not routinely guided by NT-proBNP; however, the best explanation seems to be the well-known underuse of recommended HF therapy in elderly patients.[30] Notably, responders had higher preprocedural NT-proBNP levels compared with nonresponders, and that finding seems to be attributed mainly to the higher rates of chronic HF and more severe AS in this group.

Our data also show that highly elevated NT-proBNP levels—both at baseline and at discharge (upper quartile, respectively)—are significantly associated with survival regardless of a postprocedural decrease of NT-proBNP after TAVI.

In our study, parameters associated with nonresponder status included atrial fibrillation, arterial hypertension, peripheral artery disease, and impaired renal function, all of which are conditions known to be associated with increased levels of baseline NT-proBNP.[19,31] It seems obvious that these patients may display persistently elevated NT-proBNP levels, reflecting myocardial damage that is not fully reversible by TAVI. In contrast, the responder group had higher mean pressure gradients and smaller aortic valve areas as echocardiographic parameters of AS severity. This finding supports the idea that TAVI in this patient group yields immediate effects in terms of ventricular unloading and decrease of myocardial stretch, leading to an acute postprocedural decrease of circulating NT-proBNP levels. Our findings also suggest the intuitive assumption that patients whose elevated NT-proBNP levels are driven mainly by severe AS benefit the most from TAVI.

Interestingly, the responder group in our study included more patients with impaired LVEF. An adequate explanation seems to be beyond the scope of our study, but these patients might constitute an important subgroup for future studies.

Limitations

Our study is limited mainly by its retrospective single-center design with the focus on survival. End points such as HF symptoms, physical capacity, cardiac-related rehospitalization, and quality of life are not accounted for. In addition, both measured and unmeasured confounding factors may limit the conclusions that can be drawn from our analysis. Echocardiography data were partially analyzed in retrospect, and follow-up echo data were not sufficiently available, which may under- and overestimate differences between groups. However, our study cohort represents a typical, unselected, real-world TAVI population with a considerable sample size and a relatively long follow-up period. We acknowledge that ≥ 1 might not be the perfect cutoff value, but we chose to dichotomize the ratio because, from a clinical point of view, this approach seems to be the most reasonable and keeps our analysis simple. Because risk stratification of TAVI patients constitutes a major clinical challenge, implementing an NT-proBNP ratio might be of great value.

Conclusion

Periprocedural changes of NT-proBNP are significantly associated with survival in patients undergoing TAVI. Patients who fail to respond to TAVI with a postprocedural decrease of NT-proBNP should be carefully monitored and evaluated for optimized medical treatment. Future studies are necessary to determine the potential role of NT-proBNP in risk stratification and therapeutic management of patients after TAVI.

Disclosures

Kuhn received speaker's honoraria from Medtronic. D. Frank works as a proctor for and has received speaker's honoraria as well as travel support from Medtronic and Edwards. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Figure S1. Distribution of the NT-proBNP ratio.