B-type Natriuretic Peptide Ability to Predict Mortality After Transcatheter Aortic Valve Replacement

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Abstract

Background: Preoperative risk assessment is a cornerstone of patient's selection for transcatheter aortic valve replacement (TAVR) for severe aortic valve stenosis.

Hypothesis: In this study, we evaluated whether B-type natriuretic peptide (BNP) has a prognostic impact in these patients.

Methods: Data on baseline BNP was available in 348 patients who underwent TAVR. The outcome measures of this study were 30-day and 3-year mortality.

Results: In multivariate analysis, baseline BNP was an independent risk factor for 30-day (logarithmically transformed, OR 2.564, 95%CI 1.288-5.102) and 3-year mortality (logarithmically transformed, HR 1.685, 95%CI 1.280-2.218). According to the Youden's test, the best cutoff of baseline BNP for 30-day mortality was 690 pg/mL (11.7% vs. 1.7%, adjusted OR 7.156, 1.872-27.358), and for 3-year mortality was 290 pg/mL (30.2% vs. 13.4%, adjusted HR 2.094, 95%CI 1.223-3.585). Harrell's C and Somer's D tests showed that baseline BNP improved the predictive ability of the STS score (p=0.040), but not that of the EuroSCORE II (p=0.115), for prediction of 3-year mortality.

Conclusions: BNP is an independent predictor of outcome in patients undergoing TAVR and may be useful in guiding patient's selection and treatment timing. Further studies are needed to assess its potential in increasing the performance of current risk scoring methods.

Clinical Trial Registration: ClinicalTrials.gov, identifier NCT03385915 (https://clinicaltrials.gov/ct2/show/NCT03385915)

Introduction

Transcatheter aortic valve replacement (TAVR) is the preferred treatment strategy of patients with aortic stenosis (AS) at high operative risk. Brain natriuretic peptide (BNP) is released in response to pressure and volume overload (1) and is a reliable biomarker of heart failure (2). Previous studies have shown that high baseline BNP/pro-BNP level is an independent predictor for 30-day and all-cause mortality in high risk patients undergoing TAVR (3-11). However, there is no data on the incremental prognostic effect of using this biomarker in patients undergoing TAVR. This issue has been investigated in present Institutional series.

Methods

Patient population

The study cohort includes 348 patients who underwent TAVR for AS with or without coronary revascularization at the Oulu University Hospital, Oulu, Finland, from January 2008 to September 2017. Data on these patients are from the nationwide FinnValve registry, which included 6463 consecutive

patients who underwent either TAVR or surgical aortic valve replacement (SAVR) with a bioprosthesis for severe aortic stenosis (AS) during the same study period. The Review Board of our Institution approved this study. The exclusion criteria were: 1) any prior TAVR or surgical intervention on the aortic valve; 2) acute endocarditis; and 3) isolated aortic valve regurgitation.

In the present sub-study we included only patients from the Oulu University Hospital in order to avoid bias related to inter-institutional differences in laboratory methods.

Data collection

Data was retrospectively collected from electronic patient records into electronical case report form by experienced clinicians. Mortality data during follow-up time was obtained from the national Population Register Center by linking patient's social security number. Follow-up coverage was 100%.

Definition criteria and study endpoints

Baseline risk factors were defined according to European System for Cardiac Operative Risk Evaluation (EuroSCORE) II criteria (12). In addition to EuroSCORE II, The Society of Thoracic Surgeons (STS) score was calculated (13). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Recent acute heart failure occurring within 60 days from TAVR was defined as new or worsening signs and symptoms requiring hospital admission before TAVR. Stroke was defined as neurological deficit lasting 24 hours or longer confirmed at neuroimaging. Coronary artery disease (CAD) was defined as any stenosis ≥50% of the main coronary branches. Clinical endpoints were defined according to criteria by the Valve Academic Research Consortium -2 (VARC-2) (14).

The primary endpoints were all-cause 30-day and 3-year mortality.

Statistical analysis

Statistical analysis was performed with Stata v. 15.1 (StataCorp LLC, Texas, USA) and SPSS v. 25.0 (IBM Corporation, New York, USA) statistical softwares. Continuous variables were reported as the mean and standard deviation (SD). Categorical variables were reported as counts and percentages. Predictors of baseline BNP have been identified using linear regression with the backward method. Mann-Whitney, Chi-square, Fisher's and Linear-by-linear association tests were used for univariate analyses of early mortality. The area under the curve (AUC) of the receiver operating characteristics (ROC) curve was estimated to assess the discrimination ability of the baseline BNP to predict early and late mortality. The Youden's test was used to identify the best cutoff of baseline BNP in predicting early and late mortality. Logistic regression was used for multivariate analysis of 30-day mortality. The DeLong test was used to determine if the difference between the AUCs of different regression models (DeLong). Kaplan-Meier and Cox proportional hazard tests were used for univariate and multivariate analyses of 3-year mortality. The improvement of discrimination of baseline BNP as compared to the logistic regression model including clinical variables was calculated using the net reclassification index (NRI) and integrated discrimination improvement (IDI) methods. Decision curve analysis was performed to assess the clinical usefulness of

the logistic regression models. The adjusted prognostic impact of baseline BNP on 3-year mortality was evaluated using the Cox proportional hazards method. The proportional hazard assumption was evaluated using the test based on Schoenfeld residuals and by inspecting the survival curves. Global test showed that all regression models held the Cox proportional hazards assumption ($p>0.10$). The Harrel's C and Somers' D were estimated to assess the discriminatory ability of different Cox proportional hazards models. Harrell's C of regression models including clinical variables only and those including also baseline BNP were compared using the linear combination of parameters method taking into consideration censored observations. Significance was set at $p<0.05$ for all statistical tests.

Results

Baseline BNP was not normally distributed (Shapiro-Wilk's test, $p<0.0001$) and skewed to the right. When baseline BNP was transformed into its natural logarithm, it was an independent predictor of 30-day (OR 2.564, 95%CI 1.288-5.102) and 3-year mortality (HR 1.606, 95%CI 1.236-2.085). Increasing quintiles of baseline BNP were associated with increased 30-day (Linear-by-linear association test, $p=0.012$) and 3-year mortality (log-rank test, $p<0.0001$) (Figures 1,2). The ROC AUC for 30-day mortality was 0.703 (95%CI 0.532-0.874) and for 3-year mortality was 0.667 (95%CI 0.596-0.739). According to the Youden's test, the best cutoff of baseline BNP for 30-day mortality was 690 pg/mL (11.7% vs. 1.7%, adjusted OR 7.156, 1.872-27.358), while for 3-year mortality was 290 pg/mL (30.2% vs. 13.4%, adjusted HR 2.094, 95%CI 1.223-3.585).

Logistic regression showed that baseline BNP was an independent predictor of all-cause mortality (OR 2.564, 95%CI 1.288-5.102) (Tab. 1).

Inclusion of baseline BNP as a continuous variable into the regression model with other independent predictors of 30-day mortality (Table 1) improved the discrimination of the model (AUC, 0.885, 95% 0.793-0.977 vs. 0.819, 95%CI 0.703-0.936, DeLong test, $p=0.188$), but the difference was not statistically significant. NRI was 0.702 ($p=0.017$), while IDI was 0.02 and did not reach statistical significance ($p=0.636$). Adding BNP to the EuroSCORE II and STS score did not improve the predictive ability of these risk scores.

Cox proportional hazard analysis showed that baseline BNP was an independent predictor of all-cause mortality (adjusted HR 1.685, 95%CI 1.280-2.218) (Tab. 1). Baseline BNP (Harrell's C 0.691, 95%CI, 0.625-0.757; Somer's D 0.402, 95%CI 0.248-0.557) improved the predictive ability of the STS score (Harrell's C 0.665, 95%CI, 0.596-0.733; Somer's D 0.342, 95%CI 0.188-0.496) (Linear combination of parameters test, $p=0.040$), but not that of EuroSCORE II (Linear combination of parameters test, $p=0.115$).

Table 1. Baseline characteristics of patients undergoing transcatheter aortic valve replacement and risk estimates of 30-day and 3-year mortality.

		30-day mortality		3-year mortality	
	No. (%) / Mean (SD)	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Age (years)	82.3 (6.0)	0.485		0.652	
Female	188 (54.0)	0.382		0.021	
Brain natriuretic peptide (pg/mL)	459 (552)	0.017	2.564, 1.288-5.102	<0.0001	1.685, 1.280-2.218
Anemia	131 (37.6)	0.007		<0.0001	1.606, 1.236-2.085
eGFR (mL/min/1.73 m^2)	62 (18.0)	0.004		<0.0001	0.983, 0.970-0.997
Diabetes	105 (30.2)	0.377		0.008	1.721, 1.027-2.882
Coronary artery disease	133 (38.2)	0.002	9.909, 1.981-49.551	0.007	1.915, 1.150-3.186
Prior myocardial infarction	2 (0.6)	0.001		<0.0001	
Prior cardiac surgery	63 (18.1)	0.163		0.238	
Prior percutaneous coronary intervention	83 (23.9)	0.141		0.009	1.872, 1.110-3.156
Critical preoperative state / acute heart failure	36 (10.3)	0.004		0.032	
Prior aortic balloon valvuloplasty	20 (5.8)	0.147		0.003	
Prior stroke	35 (10.1)	1.000		0.409	
Extracardiac arteriopathy	79 (22.7)	0.003	5.375, 1.3440-20.067	0.084	
Atrial fibrillation	141 (40.5)	0.557		0.084	
Prior pacemaker	39 (11.2)	0.748		0.158	
Pulmonary disease	91 (26.1)	0.010	4.836, 1.310-1.288	0.043	1.853, 1.086-3.159
NYHA class 4	16 (4.6)	0.001		0.002	
LVEF≤50%	83 (23.9)	<0.0001		<0.0001	
Moderate/severe mitral valve reurgitation	67 (19.8)	0.584		0.363	

SPAP		0.806	0.402
31-55 mmHg	164 (47.1)		
>55 mmHg	52 (14.9)		
EuroSCORE II (%)	7.8 (9.4)	<0.0001	<0.0001
STS score (%)	4.1 (2.4)	<0.0001	<0.0001

Continuous variables are reported as means±standard deviation (SD) and categorical variables as counts and percentages. a, logarithmically transformed; Clinical variables are according to the EuroSCORE II definition criteria. eGFR, glomerular filtration estimated according to the CKD-EPI equation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SPAP, systemic pulmonary artery pressure; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons.

Discussion

The main result of the present study is that BNP was an independent predictor of 30-day (logarithmically transformed, OR 2.564, 95%CI 1.288-5.102) and 3-year mortality (logarithmically transformed, HR 1.685, 95%CI 1.280-2.218) when adjusted for other significant variables. Thirty-day and 3-year mortality increased along with quintiles of baseline BNP. The best cut off value for 30-day mortality was 690 pg/mL and for 3-year mortality 290 pg/mL.

BNP has been used to assess the outcome and cardiovascular risk in patients with chronic heart failure (15). Furthermore, it has been observed to be a predictor of outcome in AS patients undergoing surgical aortic valve replacement (16). Moreover, there are prior data showing the association between BNP levels and outcome in patients with AS treated with TAVR (3-10). However, one of their limitation is that most of those studies included symptomatic AS patients with high surgical risk (STS score >10%). In these studies the cut-off value of baseline BNP for increased risk for either 30-day or long-term mortality were in the range of 453-596 pg/mL. In our study the operative risk of this series was much lower than previous studies (mean STS score 4.1% and mean EuroSCORE II 7.8%). We observed that the baseline BNP cut-off value for the 30-day mortality was 690 pg/mL and it was as low as 290 pg/mL for 3-year mortality. Chen et al. (17), showed a J-curved association between BNP levels and mortality. The investigators speculated that also low BNP values may reflect a decreased capability of the left ventricle to adapt with severe AS (17). In our study we did not observed no such a phenomenon as the risk of mortality increased significantly only in the highest quintiles of baseline BNP (Figs. 1,2).

Optimal timing of TAVR is important for the outcome of the patient. Early intervention may expose patients to the risk for adverse events related to invasive treatments, whereas late intervention carries the risk of irreversible remodeling of the left ventricle and of unfavorable recovery. Interestingly, also in

asymptomatic patients with severe AS the cumulative 5-year incidence of AS-related events (heart failure hospitalization or aortic-valve related death) was significantly higher with increasing BNP level (BNP <100 pg/mL 14.2%, 100<BNP<200 pg/mL 29.6%, 200<BNP<300 pg/mL 46.3% and BNP>300 pg/mL 47.0%, p<0.001) (18). Currently, there are ongoing studies evaluating the TAVR treatment of AS already at the asymptomatic phase, and recent study suggested favorable outcome for SAVR patients with high degree of AS treated in an asymptomatic phase (19). Based on our results, early intervention may prove to be a valuable strategy. Given the progressive nature of AS this means that, once the decision to perform TAVR is made, the operation should be performed without significant delay.

Previous studies (3-10) demonstrated that baseline BNP/pro-BNP level is associated with mortality after TAVR. However, there is no data on the incremental prognostic effect of using this biomarker in patients undergoing TAVR. A few studies investigated whether such biomarkers may increase the predictive ability of current risk scoring methods in patients undergoing other cardiovascular interventions (20-24). However, not all studies were able to demonstrate an incremental predictive ability when BNP/pro-BNP was added to the EuroSCORE or STS risk scores (21,22). The present study showed that adding baseline BNP to these risk scores provided an increase of the predictive ability for 3-year mortality only for the STS score. We speculate that the relatively small size of this series might lead to type II error in the evaluation of the incremental prognostic value of BNP in this patient population. Furthermore, only the highest quintile of baseline BNP was associated with a marked increase of early and late death, therefore limiting the ability of this biomarker to identify only a rather small proportion of high-risk patients.

Limitations

The main limitation is the retrospective nature of this study. Secondly, we do not have data on BNP levels after the procedure. This prevented an analysis of the potential prognostic impact of post-procedural BNP level changes on the mid-term outcome after TAVR. Finally, this institutional series is of limited size and this may lead to type II error in the evaluation of the incremental prognostic value of BNP in this patient population.

Conclusion

Baseline BNP is an independent predictor of 30-day and 3-year mortality in patients undergoing transcatheter aortic valve replacement. These findings suggest that patients with severe aortic stenosis may most benefit from TAVR before signs of heart failure subside. Further studies are needed to assess the potential of BNP in increasing the predictive performance of current risk scoring methods.

Declarations

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Availability of data and materials

Data is available upon a reasonable request from the corresponding author.

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Contributions

FB, TM and MN conceived the study design. JP and TT collected the data. HL, JP, MN, FB, TT, JJ, TJ and TM read, provided feedback on, and approved the final manuscript.

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Ethics declarations

The study conforms to the Declaration of Helsinki.

Ethics approval and consent to participate

The study protocol was approved by the Medical Ethics Committee of the Oulu University Hospital. Inform consent was not required because of the registry nature of the study.

Competing interests

The authors declare that they have no competing interests.

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Figures

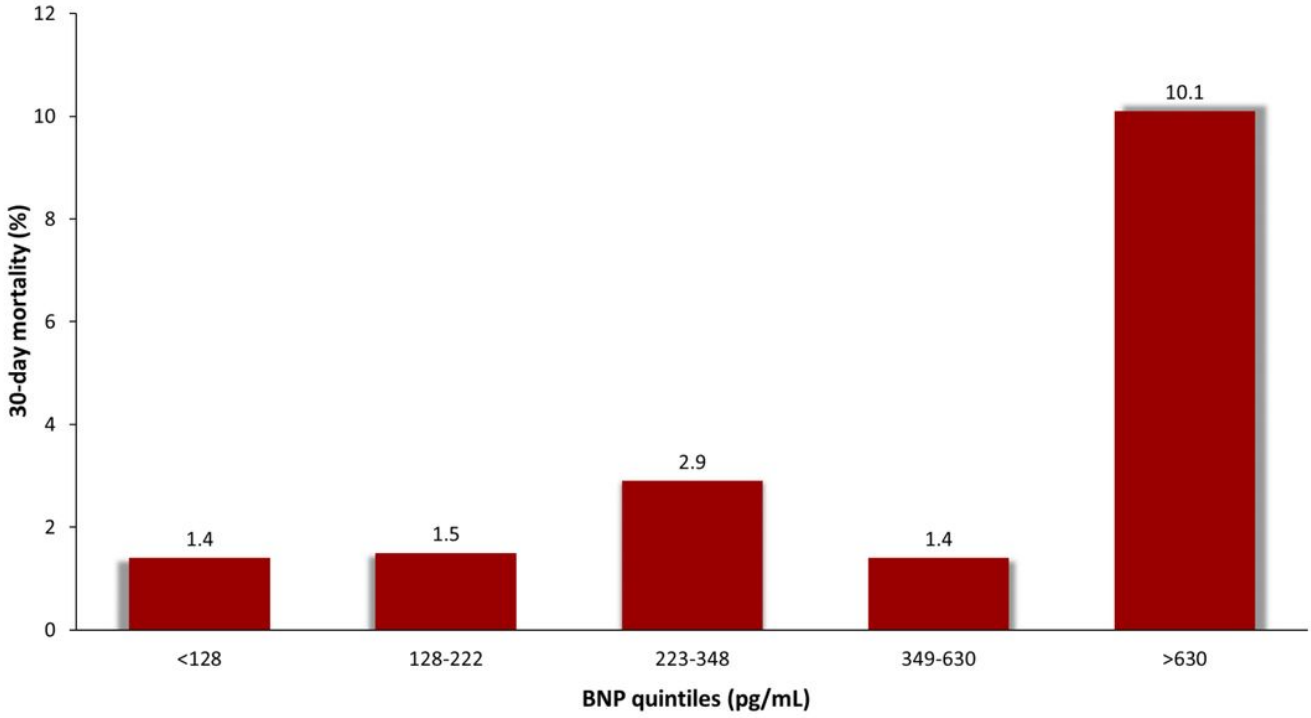

Figure 1

Thirty-day mortality according to baseline brain natriuretic peptide (BNP) quintiles.

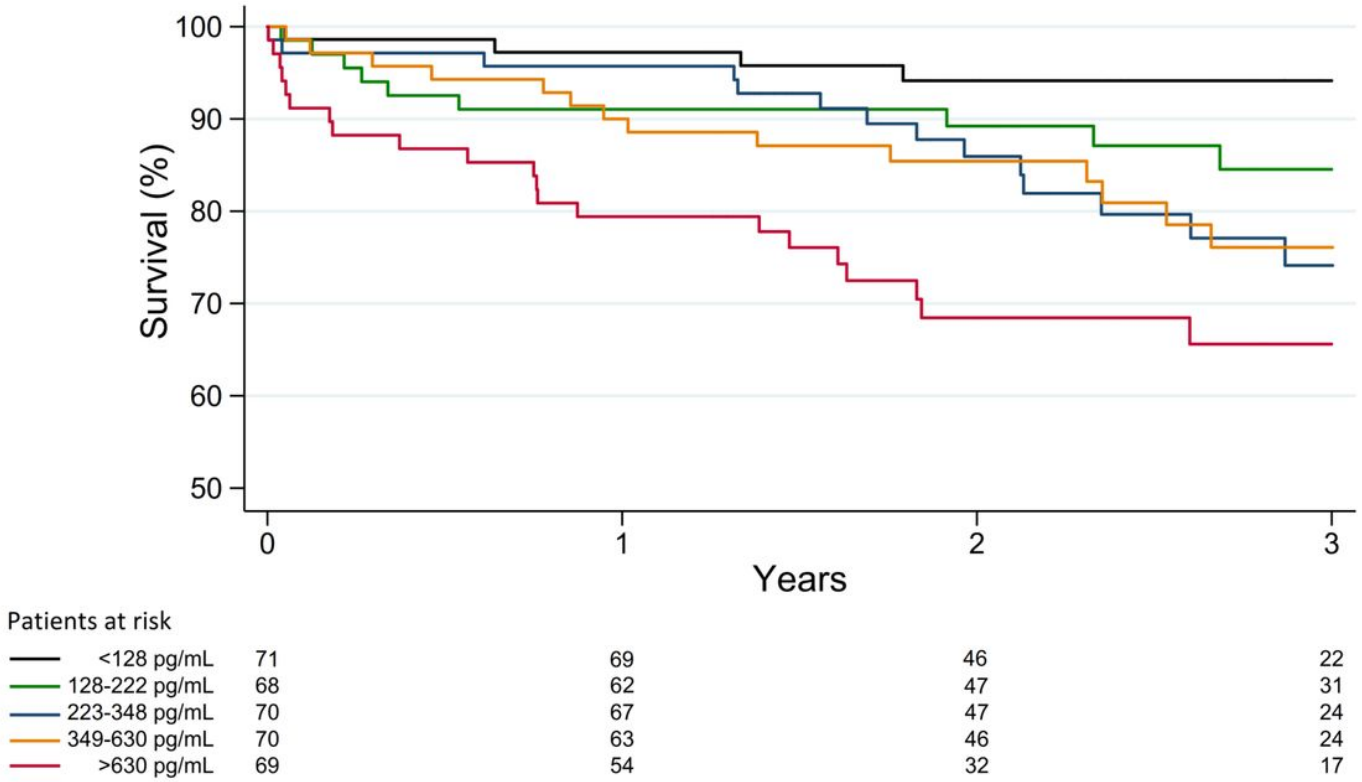

Figure 2

Survival according to baseline brain natriuretic peptide (BNP) quintiles.