Prognostic Implications of Baseline B-type Natriuretic Peptide in Patients Undergoing Transcatheter Aortic Valve Implantation

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B-type natriuretic peptide (BNP) levels have been shown to predict outcomes in surgical aortic valve replacement patients. BNP levels have not been well studied in patients undergoing transcatheter aortic valve implantation (TAVI). The purpose of this study is to define the utility of baseline BNP levels in predicting short-term outcomes after TAVI. In this retrospective, observational, study from 2012 to 2019, we reviewed data on 1297 low-risk, intermediate-risk and high-risk patients who underwent TAVI. Patients were dichotomized into those with baseline BNP levels above or below 500 pg/ml. Our primary outcome was a composite of inpatient stroke and death. Our secondary outcome was a composite of 30-day stroke, death and readmission. There were 975 patients with a baseline BNP level of <500 pg/ml and of those, 2% had our primary composite outcome and 13% of patients had our secondary composite outcome. There were 322 patients with a baseline BNP level of ≥500 pg/ml and of those, 6% had our primary composite outcome and 19% of patients had our secondary composite outcome. Those with a baseline BNP level ≥500 pg/ml were 3.47 times more likely (confidence of interval [CI] 1.727, 6.993, p = 0.0005) to have our primary composite outcome and were 1.72 times more likely (CI 1.186, 2.506, p = 0.0043) to have our secondary composite outcome. In conclusion, after adjustments for discrepant baseline characteristics, baseline BNP levels were independently predictive of a composite of inpatient stroke or death and a composite of 30-day stroke, death or readmission after TAVI. Those low, intermediate and high-risk patients whose baseline BNP is ≥500 pg/ml may ultimately require closer post-TAVI monitoring. **(Am J Cardiol 2020;130:94−99)**

Aortic stenosis (AS) is the most frequently encountered valvular disorder in the United States.[1] Transcatheter aortic valve implantation (TAVI) has emerged, as the preferred treatment for patients with severe symptomatic AS deemed inoperable.[2] In the years that followed, TAVI has become an option for those at intermediate-risk with severe symptomatic AS.[3] Recently, the PARTNER-3 trial demonstrated that rates of the composite of death, stroke and readmission were significantly lower in patients undergoing TAVI when compared with SAVR in a low-risk population with severe symptomatic AS.[4] Identification of a noninvasive prognostic tool that can predict outcomes in this growing patient population carries significant clinical implications. B-type natriuretic peptide (BNP) is a hormone that is released by the ventricles, in response to increases in ventricular wall stress in the setting of volume expansion and pressure overload.[5,6] BNP has proven to accurately differentiate patients with severe symptomatic AS from those with severe asymptomatic AS.[7] In SAVR, baseline BNP has been studied extensively and has consistently been shown to be an independent predictor of outcomes after SAVR.[8,9] With regards to TAVI, the prognostic utility of BNP remains unclear. The purpose of this study was to clarify the prognostic utility of baseline BNP levels in predicting short-term outcomes after TAVI in low, intermediate and high-risk patients.

Methods

This is a retrospective, observational study in which we screened 1512 patients who underwent transfemoral-TAVI at our institution from 2012 to 2019. Inclusion criteria for this study were severe symptomatic AS (defined by an aortic valve area of < 1.0 cm^2 plus either a mean gradient ≥ 40 mm Hg or a peak velocity of ≥ 4.0 meters per second on transthoracic echocardiogram) and a low, intermediate or high-risk score for SAVR. Risk was defined by using the Society of Thoracic Surgeons risk score, which uses an algorithm that is based on the presence of comorbidities in order to estimate the 30-day postoperative mortality.[3] All patients had New York Heart Association functional class II, III or IV symptoms at time of TAVI. Pertinent exclusion criteria for our primary composite outcome were patients with aborted TAVI (n = 5), patients previously on hemodialysis (n = 76) or patients who underwent valve-in-valve TAVI (n = 124). Pertinent exclusion criteria for our secondary composite outcome were patients with aborted TAVI (n = 5), patients previously on hemodialysis (n = 76), patients who underwent valve-in-valve TAVI (n = 124) or patients lost to follow up (n = 20) (Figure 1). All patients

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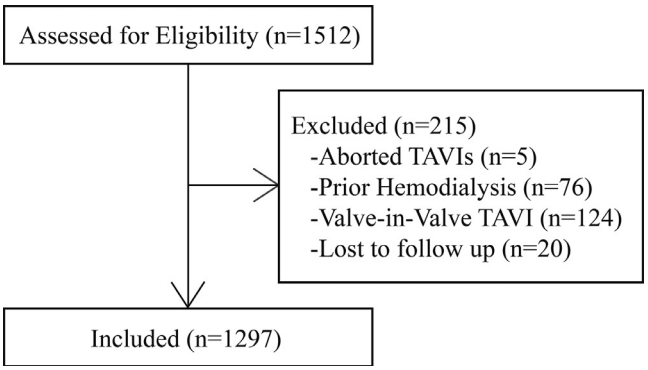

Figure 1. Patients included and excluded in our study.

signed informed consent forms for the TAVI before the procedure.

Of the 1512 patients screened, there were 1297 that were included in the analysis. Baseline plasma BNP levels, which were measured in the days before TAVI, were reviewed for all patients in the study. Patients were then dichotomized into 2 cohorts: cohort 1 included patients whose baseline BNP was <500 pg/ml and cohort 2 included patients whose baseline BNP was ≥500 pg/ml. This cutoff is a simpler number to utilize and allowed for a relatively balanced distribution of both cohorts.

Additionally, our lab's early upper limit for detection of BNP from 2012 to 2015 was 900 pg/ml, thus we could not differentiate patients at higher cutoffs or accurately quantify BNPs above that level.

This retrospective study was reviewed by our institutional review board and deemed exempt. Study data were collected and managed using Research Electronic Data Capture, a secure electronic data capture tool hosted at our institution.[10]

The primary endpoint was a composite of post-TAVI stroke and death during the TAVI hospitalization. The secondary endpoint was a composite of stroke, death and readmission in the 30 days after TAVI. Stroke has been used as an endpoint in studies looking at the prognostic utility in SAVR patients.[8]

The definition of stroke has been standardized by the Valve Academic Research Consortium-2 initiative. Stroke is defined as an episode of focal or global neurological deficit (change in the level of consciousness, hemiparesis, hemiplegia, sensory loss, numbness, aphasia, dysphagia, hemianopia, amaurosis fugax or symptom consistent with stroke) lasting ≥24 hours or <24 hours if neuroimaging demonstrates a new hemorrhage or infarction or if the neurological deficits result in death. The diagnosis of stroke was confirmed on formal consultation by a neurologist or a neurosurgeon.[11]

Readmissions were defined as an admission to a hospital ward or intensive care unit. Visits to the emergency department or admission under observation status were not considered a readmission. Follow up was carried out during prescheduled outpatient clinic visits or by telephone contact at 30 days. In addition, records from referring cardiologists' offices and other hospitals were obtained when necessary to complete follow up. Complete information regarding 30-day follow up was obtained in 98.4% of patients (14 total patients were lost to follow up).

We summarize patients' demographic and clinical characteristics using mean ± standard deviation, and frequency (%). Comparisons between cohorts with respect to continuous variables were performed using two-sample t-test. Comparisons between cohorts with respect to binary variables were performed using Chi-square test. Association of baseline BNP level with variables, which differed between cohorts, was analyzed using logistic regression analysis. Statistical analyses of composite outcomes were performed using multivariate binary logistic regression. The value for entering and staying in the model was set at $p < 0.05$. All analyses were done using SAS 9.4.

Results

The 1297 patients had a mean Society of Thoracic Surgeons score of 7.16% ± 5.25%. Baseline characteristics for the 2 cohorts are listed in Table 1. Baseline characteristics were similar overall, including sex, rates of hypertension, diabetes, coronary artery disease, percutaneous coronary intervention, coronary artery bypass grafting, stroke, transient ischemic attack chronic obstructive pulmonary disease and current tobacco use. Patients in cohort 1 (baseline BNP <500 pg/ml) were younger (81.9 years vs 83.7 years, $p = 0.0002$) and had a lower prevalence of myocardial infarction (MI) (12% vs 21%, $p < 0.0001$). Patients in cohort 1 (baseline BNP <500 pg/ml) had a higher baseline ejection fraction (EF) (55.5% vs 43.6%, $p < 0.0001$) and a lower baseline creatinine (1.1 mg/dL vs 1.2 mg/dL, $p < 0.0001$).

Table 1
Baseline characteristics of patients

Variable	B-type natriuretic peptide (pg/ml)		p Value
	<500 (n = 975)	≥500 (n = 322)	
Age (years)	**81.9 ± 8.0**	**83.7 ± 7.3**	**0.0002**
Men	482 (49%)	142 (44%)	0.1078
Hypertension	934 (96%)	303 (94%)	0.2161
Diabetes mellitus	314 (32%)	92 (29%)	0.2389
Coronary artery disease	426 (44%)	154 (48%)	0.1969
Prior myocardial infarction	**117 (12%)**	**69 (21%)**	**<0.0001**
Prior percutaneous coronary intervention	307 (31%)	99 (31%)	0.8355
Prior coronary artery bypass grafting	168 (17%)	61 (19%)	0.5008
Prior cerebrovascular accident	71 (7%)	28 (9%)	0.4698
Prior transient ischemic attack	70 (7%)	16 (5%)	0.1965
Chronic obstructive pulmonary disease	426 (44%)	150 (47%)	0.4006
Current smoker	36 (4%)	11 (3%)	1.0000
Baseline ejection fraction (%)	**55.5 ± 10.4**	**43.6 ± 15.1**	**<0.0001**
Baseline creatinine (mg/dl)	**1.1 ± 0.4**	**1.2 ± 0.6**	**<0.0001**

Clinical patient characteristics between cohort 1 (baseline BNP <500 pg/ml) and cohort 2 (baseline BNP ≥500 pg/ml).

Of the 975 patients in cohort 1 (baseline BNP <500 pg/ml), 2% of patients (n = 21) had our primary composite outcome (inpatient stroke or inpatient death). In this group, 1% of patients (n = 11) had inpatient stroke and 1% of patients (n = 11) had inpatient death.

Of the 322 patients in cohort 2 (baseline BNP ≥500 pg/ml), 6% of patients (n = 19) had our primary composite outcome. In this group, 2% of patients (n = 5) had inpatient stroke and 4% of patients (n = 14) had inpatient death. When examining our primary composite outcome, there were no associations between baseline BNP level and age (p = 0.8299), MI (p = 0.8895), baseline EF (p = 0.1283) or baseline creatinine (p = 0.8353). After adjustment for discrepant variables (age, MI, baseline EF and baseline creatinine), in the multivariate binary logistic regression analysis of predictors of our primary composite outcome, a BNP ≥500 pg/ml was found to be an independent predictor. Those with a baseline BNP ≥500 pg/ml were 3.47 times more likely (CI 1.727, 6.993, p = 0.0005) to have our primary composite endpoint of inpatient stroke and death (Table 2).

Of the 975 patients in cohort 1 (baseline BNP <500 pg/ml), 13% of patients (n = 125) had our secondary composite endpoint (stroke, death and readmission in the 30 days following TAVI). In this group, 2% of patients (n = 16) had a stroke within 30 days, 2% of patients (n = 19) had death within 30 days and 11% of patients (n = 93) had a readmission within 30 days.

Of the 322 patients in cohort 2 (baseline BNP ≥500 pg/ml), 19% of patients (n = 62) had our secondary composite endpoint. In this group, 2% of patients (n = 5) had a stroke within 30 days, 6% of patients (n = 18) had death within 30 days and 13% of patients (n = 42) had a readmission within 30 days.

When examining our secondary composite outcome, there were no associations between baseline BNP level and age (p = 0.7597), MI (p = 0.5013), baseline EF (p = 0.4822) or baseline creatinine (p = 0.5108). After adjustment for discrepant variables (age, MI, baseline EF and baseline creatinine), in the multivariate binary logistic regression analysis of predictors of our secondary composite outcome, a BNP ≥500 pg/ml was found to be an independent predictor. Those with a baseline BNP ≥500 pg/ml were 1.72 times more likely (CI 1.186, 2.506, p = 0.0043) to have our secondary composite endpoint of stroke, death and readmission in the 30 days after TAVI (Table 3).

Table 2
Multivariate analysis of primary composite outcome of inpatient stroke or inpatient death

Variable	Point estimate	p-Value	95% confidence interval
Baseline BNP ≥500pg/ml	**3.47**	**0.0005**	**1.727, 6.993**
Age	1.01	0.5421	0.970, 1.059
Prior myocardial infarction	0.80	0.6549	0.302, 2.123
Baseline ejection fraction (%)	1.021	0.1382	0.993, 1.049
Baseline creatinine (mg/dl)	1.062	0.8524	0.565, 1.995

Multivariate analysis using discrepant baseline characteristics (age, MI, baseline EF, baseline creatinine) and baseline BNP.

Table 3
Multivariate analysis of secondary composite of stroke, death and readmission 30 days post-TAVI

Variable	Point estimate	p-Value	95% confidence interval
Baseline BNP ≥500pg/ml	**1.72**	**0.0043**	**1.186, 2.506**
Age	1.00	0.6359	0.985, 1.026
Prior myocardial infarction	0.92	0.7194	0.580, 1.455
Baseline ejection fraction (%)	1.008	0.2450	0.995, 1.022
Baseline creatinine (mg/dl)	1.155	0.3767	0.839, 1.591

Multivariate analysis using discrepant baseline characteristics (age, MI, baseline EF, baseline creatinine) and baseline BNP.

Discussion

The main results from our retrospective, observational study of 1297 low, intermediate and high-risk patients with severe symptomatic AS who underwent TAVI can be summarized as follows. After adjusting for discrepant baseline characteristics, patients with a baseline BNP ≥500 pg/ml were 3.47 times more likely to develop our composite primary endpoint (inpatient stroke or inpatient death) and were 1.72 times more likely to develop our secondary composite endpoint (stroke, death and readmission in the 30 days following TAVI). Stroke is a devastating complication associated with severe disability and high mortality.[12] It is one of the most feared complications after TAVI. Stroke early after TAVI is predominantly due to debris embolization during implantation, whereas later events are associated with patient specific factors. Despite the steady decrease in clinical strokes compared with initial TAVI experience, it remains one of the most significant contributors to morbidity and mortality in these patients.[13] Identifying patients at higher risk for stroke is of paramount importance. Recognition and careful patient selection, using noninvasive testing with BNP can help tailor antithrombotic strategies in this fragile population with calcified aortic arches. Additionally, those with elevated baseline BNPs may warrant closer post-TAVI monitoring for such events. In our study, there was a trend toward higher inpatient strokes and 30-day strokes in patients whose baseline BNP was <500pg/ml. Validation using larger prospective cohorts may clarify the true prognostic value of baseline BNP in predicting stroke after TAVI. BNP have been found to be acutely elevated in patients with acute ischemic stroke.[14] We postulate that patients with elevated baseline BNPs are chronically ill, with numerous risk factors for cardiovascular disease including acute ischemic stroke.

Unplanned readmissions after the index TAVI hospitalization are frequent.[15] They negatively affect patient quality of life, clinical outcomes and healthcare cost. It has been estimated that nearly 20% of Medicare beneficiaries who

had been discharged were readmitted within 30 days.[16] Unplanned readmissions account for more than $17 billion in healthcare costs.[16] Certain procedural complications have been found to be associated with unplanned 30-day readmissions, including major bleeding and anemia post-TAVI.[15] Identification of patients before TAVI who are at higher risk for readmission can allow for implementation of closer follow up in the days after TAVI similar to patients with recurrent heart failure hospitalizations.[17,18]

While SAVR has traditionally offered excellent results for patients with severe symptomatic AS, those who are declined for surgery have poor survival.[1] As mentioned earlier, the onset of symptoms portends a poor prognosis. One study reports the mean survival after the onset of angina to be 45 months, syncope to be 27 months and heart failure 11 months.[1] The emergence of TAVI offers an additional treatment option to patients who are at prohibitive risk for SAVR. Mortality of high-risk patients with severe symptomatic AS undergoing TAVI in the PARTNER-I trial was 5.0% after 30 days and 30.7% after 1 year.[19] Despite increase in experience, improvements in technique, mortality have remained the most feared complication of TAVI. Mortality of intermediate-risk patients with severe symptomatic AS undergoing TAVI in the PARTNER-2 trial was 3.9% after 30 days and 12.3% after 1 year.[3] Mortality of low-risk patients with severe symptomatic AS undergoing TAVI in the PARTNER-3 trial was 0.4% after 30 days and 1.0% after 1 year.[4] In low, intermediate and high-risk patients undergoing TAVI, identification of patients at higher risk for short-term death can allow for additional risk stratification before TAVI and closer follow-up post-procedure.

BNP is frequently used in prognostic assessment across various cardiac conditions. With regards to AS, it has been extensively studied in SAVR patients with consistent results. One small study of 109 patients with severe symptomatic AS who underwent SAVR demonstrated that pre-operative BNP correlates with worsening New York Heart Association functional class late. This study also showed that a preoperative BNP >312 pg/ml was strongly predictive of major adverse cardiac events, cerebrovascular events and readmission at 36 months.[8] Another small study of 113 patients with severe symptomatic AS and preserved EF found that BNP levels after SAVR were related to LV diastolic dysfunction at 12 months.[20] This finding suggests BNP can be used to complement echocardiographic findings when after patients postoperatively.[20] Additionally, preoperative BNP levels have been shown to predict short-term and long-term major adverse cardiovascular events including mortality after SAVR.[9] In a study of 89 patients undergoing SAVR, preoperative BNP levels and early post-operative BNP levels were shown to predict short-term and long-term major adverse cardiovascular events including mortality after SAVR.[9]

Until recently, SAVR was the only definitive treatment for severe symptomatic AS. In recent years, TAVI has emerged as treatment option for low, intermediate or high-risk patents.[3,4,19] As a result, it is a rapidly expanding structural intervention worldwide. There have been only a few smaller studies, with conflicting results, which have investigated the prognostic value of BNP in the initial high-risk patients undergoing TAVI. One study comparing n-terminal prohormone BNP (NT-proBNP) in 462 SAVR and TAVI patients demonstrated that NT-proBNP was associated with 1-year mortality.[21] In the multicentered PARTNER-I trial, increases in BNP after transfemoral TAVI were found to independently predict 1-year mortality.[22] However, a single centered study of high-risk patients with severe symptomatic AS who underwent transapical TAVI showed that increases in NT-proBNP did not predict 2-month mortality.[23] One smaller single centered study examined baseline BNP levels. This single centered study of 151 high-risk patients showed that baseline NT-proBNP was not associated with mortality but 1-year NT-proBNP was.[24]

Our study is the largest single center study (1297 patients) and only study of low, intermediate and high-risk TAVI patients demonstrating a strong correlation between baseline BNP levels and important clinical short-term outcomes (stroke, death and readmission) (Table 4). We elected to use an endpoint of 500 pg/ml, rather than the

Table 4
Comparison of BNP and NT-proBNP studies in aortic valve replacement

Study	Patients	Marker	Results
TAVI studies			
Our study*	1297	pre-TAVI BNP ≥500 pg/ml	Increased short term death, stroke and readmission
O'neil et al.[22]	1097	increases in BNP following TAVI	Increased 1-year mortality
Pfister et al.[23]	31	decreases in NT pro-BNP prior to TAVI	Improved functional class not mortality
Vale et al.[24]	151	pre-TAVI NT-proBNP >1350 pg/ml post-TAVI NT-proBNP >2500 pg/ml	Not predictive of 1-year mortality predictive of 1-year mortality
SAVR studies			
Iwahashi et al.[8]	109	pre-SAVR BNP >312 pg/ml	Increased major adverse cardiovascular events
Mannacio et al.[20]	113	1 year BNP >120 pg/ml	Moderate or severe diastolic dysfunction
Fellahi et al.[9]	189	pre-TAVI BNP	Increased major adverse cardiovascular events
TAVI + SAVR Studies			
Hultkvist et al.[21]	462	increases in NT-proBNP post-AVR	Increased 1-year mortality in SAVR not TAVI

Comparison of AVR studies examining BNP or NT-proBNP as a prognostic marker.
* The only study which included low, intermediate and high-risk patients with severe symptomatic aortic stenosis undergoing TAVI.

previously used endpoint of 312 pg/ml. This study was limited to one high-volume TAVI centers and the results require prospective validation in a larger multicentered cohort of patients. The BNP level most closely preceding TAVI was selected, instead of a BNP level at a standardized time before TAVI. Additionally, composite outcomes were utilized because of our sample size. Longer follow up was more limited in our study population, and thus 1-year follow up was not analyzed.

Using a baseline BNP cutoff of 500 pg/ml in low, intermediate and high-risk patients, our data suggest that BNP can provide a noninvasive, objective tool with broad application across all risk groups in patients with severe symptomatic AS undergoing TAVI. Our study provides evidence that measuring baseline BNP before TAVI can help identify which patients require closer postprocedural monitoring in an attempt to reduce rates of short-term stroke, death or rehospitalization.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Credit Author Statement

Giorgio A. Medranda: conceptualization of ideas, methodology, formal analysis, investigation and data collection, data curation, writing the original draft, visualization of data, project administration.

Khaled Salhab: conceptualization of ideas, methodology, project administration.

Richard Schwartz: conceptualization of ideas, methodology, project administration.

Stephen J. Green: conceptualization of ideas, methodology, project administration.

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