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Perioperative Stroke, In-Hospital Mortality, and Postoperative Morbidity Following Transcatheter Aortic Valve Implantation: A Nationwide Study

Parthasarathy D. Thirumala[a,b]
Felix D. Nguyen[a]
Amol Mehta[a]
John Schindler[c]
Suresh Mulukutla[c]
Vinodh Jeevanantham[d]
Lawrence Wechsler[b]
Thomas Gleason[e]

[a]Departments of Neurological Surgery, [b]Neurology, and [c]Cardiology, University of Pittsburgh, Pittsburgh, PA, USA
[d]Saints Heart and Vascular Institute, St. Anthony Hospital, Oklahoma City, OK, USA
[e]Division of Cardiac Surgery, Department of Cardiothoracic Surgery, University of Pittsburgh, Pittsburgh, PA, USA

Background and Purpose Perioperative stroke is a significant complication of transcatheter aortic valve implantation (TAVI). This study aimed to quantify perioperative stroke as an independent risk factor for in-hospital mortality and postoperative morbidity in patients receiving TAVI.

Methods A retrospective cohort study was conducted using the National Inpatient Sample. Patients undergoing TAVI during 2012 and 2013 were identified using diagnostic codes of International Classification of Diseases, ninth revision. Univariate and multivariate analyses were performed using patient demographics and comorbidities to identify predictors of mortality and morbidity, defined by a length of stay of >14 days and/or discharge to a place other than home.

Results Data were obtained from 7,556 patients undergoing TAVI during 2012 and 2013. The incidence rates of mortality and morbidity were 4.57 and 71.12%, respectively. Perioperative stroke was an independent risk factor for mortality [odds ratio (OR)=3.182, 95% confidence interval (CI)=1.530–6.618, p=0.002], as were infection (OR=17.899, 95% CI=9.876–32.440, p<0.001) and pericardial tamponade (OR=7.272, 95% CI=2.874–18.402, p<0.001). Stroke also predicted morbidity (OR=5.223, 95% CI=2.005–13.608, p=0.001), which was also associated with age, being female, being Asian, moderate and high Van Walraven scores (VWR), and infection.

Conclusions In conclusion, perioperative stroke was found to be independently associated with in-hospital mortality and postoperative morbidity, as are age and high VWR. Our findings support the use of further preoperative, intraoperative, and postoperative management strategies during TAVI.

Key Words stroke, TAVI, mortality, morbidity.

INTRODUCTION

There is growing evidence that transcatheter aortic valve implantation (TAVI) is more effective against severe aortic valve stenosis than is open surgical aortic valve replacement in both patients at high risk [Society of Thoracic Surgeons (STS) risk-of-mortality score >8%] and intermediate risk (STS risk-of-mortality score=4–8%).[1] Indeed, TAVI remains associated with significant morbidity and mortality. Long-term results from the PARTNER trial showed a 1-year mortality rate of approximately 25% in patients treated with the Edwards-Sapien valve.[2] Moreover, those alive at 1 year were likely to experience a decreased quality of life due to long-term complications and functional impairments. While previous studies assessing poor outcomes following TAVI involved large cohorts and were designed as randomized clinical trials (RCTs), none have utilized a large all-payer database such as the

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Correspondence
Parthasarathy D. Thirumala, MD, MS
Center for Clinical Neurophysiology, Department of Neurological Surgery, UPMC Presbyterian-Suite B-400, 200 Lothrop Street, Pittsburgh, PA 15213, USA
Tel +1-412-648-2228
Fax +1-412-383-9899
E-mail thirumalapd@upmc.edu

National Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP).

There are multifactorial causes of mortality following TAVI. Rodés-Cabau et al.[3] found that the presence of several comorbidities such as chronic kidney disease and atrial fibrillation predicted long-term mortality after TAVI in 339 patients. The most devastating causes of death include periprocedural strokes, which have been associated with increases of three- to ninefold in the mortality rate within 30 days in TAVI patients.[4] Dislodgement of calcified plaque from the diseased valve and excess manipulation of the prosthesis have been proposed as etiologies.[5] Significant morbidity−defined as an extended length of hospital stay and/or discharge to a place other than the home−has also been associated with TAVI. One study involving the FRANCE-2 registry showed that TAVI patients who experienced a cerebrovascular event had longer intensive care unit (ICU) and hospital stays and higher rates of new-onset paroxysmal atrial fibrillation.[6] Morbidity following TAVI is an important consideration due to the substantial associated cost burden. Reynolds et al.[7] reported that each treatment regimen with TAVI in the CoreValve Pivotal Trial cost ~$70,000, with a large proportion attributable to the ICU stay.[8] The cost burden of perioperative stroke during valve replacement has yet to be determined, but has been calculated at $24,719 for carotid artery stenting.[9] The emergence of more expensive devices further supports the claim that TAVI remains an expensive procedure with potentially costly complications.

There clearly exists a need to further characterize the association of perioperative stroke with outcomes in order to improve the management of patients with aortic valve disease requiring intervention, especially those susceptible to neurological dysfunction. Furthermore, there is a paucity of evidence demonstrating this relationship in the community setting outside of controlled studies. To this end, we hypothesized that perioperative stroke is an independent risk factor for morbidity and mortality in patients receiving TAVI, and we evaluated this relationship in standard clinical practice as represented by the NIS. Demographic factors including age, sex, and race were also assessed as independent risk factors for morbidity and mortality. The findings of this study will guide the evaluation of strategies aimed at reducing the incidence of perioperative stroke following TAVI through preoperative screening,[10] intraoperative identification,[11,12] and intensive medical management.[13]

METHODS

Data source

The NIS contains details of more than 35 million hospitalizations nationally and 20% of all community hospital discharges yearly in the USA. It is among the largest public databases of all-payer hospital inpatient claims and was ideally suited for the purposes of the present study. Patient data were obtained from the NIS for 2012 and 2013. The patient characteristics reported include diagnosis, procedures, demographics, hospital characteristics, payment source, discharge status, severity, and comorbidity measures. International Classification of Diseases, ninth revision-Clinical Modification (ICD-9-CM) diagnosis codes and procedure codes were used to isolate variables of interest. Projection Clinical Classification Software (CCS) was used to identify comorbidities and procedures associated with TAVI. All NIS data were de-identified, and so institutional review board approval was not required.

Patient population

Inclusion criteria included being aged 18−100 years and having undergone TAVI during 2012 or 2013. Patient data were obtained from the NIS using ICD-9 codes 35.05 and 35.06. Patients who were treated with additional procedures, including carotid endarterectomy, coronary artery bypass surgery, or other concurrent cardiac procedures were excluded using CCS codes 43, 44, and 45 (for percutaneous transluminal coronary angioplasty), respectively.

Covariables

The patient-level covariables in this study included age (stratified into <65, 65−74, 75−84, and 85+ years), sex, race, admission status, admission location, and transfer status. Comorbidities known to have a significant relationship with in-hospital mortality were defined by the Elixhauser Comorbidity Index[14] and were identified using their corresponding ICD-9-CM codes as listed in Supplementary Table 1 (in the online-only Data Supplement). The incidence of perioperative stroke was determined similarly, as described in Supplementary Table 2 (in the online-only Data Supplement). The following additional variables that are not defined within the Elixhauser Comorbidity Index were included in the analysis: prior stroke, perioperative stroke, previous cardiac intervention, heart failure, perioperative cardiac arrest and nonfatal myocardial infarction (MI), previous cardioverter defibrillator or cardiac pacemaker implantation, pericardial tamponade, complications from a heart-valve prosthesis, infections (e.g., endocarditis, sepsis), transfusion, and gastrointestinal (GI) complications.[15,16] The hospital-level characteristics, including teaching status and annual number of TAVIs, were obtained from the STS Adult Cardiovascular Data Specifications. Patients were ultimately stratified into having low, moderate, and high risks of postoperative morbidity using Van Walraven scores (VWRs) of <5, 5−14, and >14, respectively.

Clinical outcomes

Our primary aim was achieved by obtaining outcomes for all patients undergoing TAVI alone within the NIS. Data on mortality during the hospital stay and postoperative morbidity, defined as a length of stay longer than 14 days[17] and/or discharge to a place other than the home, were obtained from the NIS. The demographic factors evaluated include age, sex, and race.

Statistical snalysis

Our population of interest was obtained from the NIS using SPSS (version 23, IBM Corp., Armonk, NY, USA). The Elixhauser Comorbidity Index and VWRs were calculated using SAS Student Edition (version 9.3 TS1M2 revision 15w25, SAS Institute, Cary, NC, USA) and Cleveland Clinic's Van Walraven macro.[18] The Elixhauser Comorbidity Index was created using the comorbidity software available from the HCUP.[19] Exploratory, univariate, and multivariate analyses were performed using Stata Student Edition (version 14.0 SE. StataCorp., College Station, TX, USA). We used Stata's survey command grouping by hospital ID, weighted using the trend weights provided by the HCUP and stratified using Strata.

Univariate comparisons between groups were performed using unpaired *t*-tests for continuous variables and adjusted Wald tests for categorical variables. We applied a multivariate regression model adjusting for various variables. Variables that were missing or associated with small groups were excluded. Individual comorbidities were not included as many of them had too few instances, were statistically insignificant, and/or were not relevant to our primary outcome.

RESULTS

Patient characteristics

The analysis was applied to 7,566 patients from the NIS were treated with TAVI during 2012 and 2013. The TAVI patients were aged 81.20±0.32 years (mean±SD) at the time of treatment. Of the patient sample, 50.72% were male, 87.85% were white, and the overall VWR was 5.62±0.25, corresponding to a moderate risk. The patients mainly comprised those at low risk (45.80%) and moderate risk (46.81%), with markedly fewer high-risk patients (7.38%). The overall procedural mortality rate was 4.57%. The mortality rate was highest among those aged 85+ years (6.25%), females, Native Americans, and at a high risk (VWR >14). The postoperative morbidity rate was 71.12% over the entire cohort. The morbidity rate was similarly highest among those aged 85+ years, females, and Hispanics. High-risk patients (VWR >14) had the highest rates of morbidity, as expectedly. Table 1 lists the patient characteristics in detail.

Table 1. Patient characteristics and rates of mortality and morbidity

Characteristic	Proportion of patients (*n*=7,566)	In-hospital mortality	Postoperative morbidity
Age, years			
<65	5.41	4.04	54.04
65–74	12.85	4.68	62.13
75–84	39.79	3.16	67.84
85+	37.16	6.25	79.25
Sex			
Male	50.72	4.37	63.94
Female	49.28	4.77	78.52
Race			
White	87.85	4.38	71.29
African American	3.52	5.04	73.11
Hispanic	2.72	5.43	75.00
Asian	0.92	6.45	51.61
Native American	0.33	18.18	63.64
Other/missing	4.67	3.80	74.68
Van Walraven risk category			
Low (VWR <5)	45.80	2.87	67.28
Moderate (VWR=5–14)	46.81	5.24	73.01
High (VWR >14)	7.38	11.11	82.96

VWR: Van Walraven score.

Comorbidities and clinical outcomes

The rate of procedural perioperative stroke during 2012 and 2013 was 2.76%. Those experiencing a perioperative stroke had high rates of in-hospital mortality (16.83%) and postoperative morbidity (93.07%). Subjects had characteristic indications for TAVI with frequent comorbidities. Of note were high incidence rates of cardiovascular comorbidities including complicated hypertension (78.56%), peripheral vascular disease (30.11%), and coagulopathy (24.36%). Renal disease was common, with high proportions of renal failure (34.89%) and fluid and electrolyte disorders (27.59%). Chronic diseases such as chronic pulmonary disease (34.13%) and uncomplicated diabetes (28.47%) were similarly frequent within the patient population. The incidence of mortality was highest among those who experienced endocarditis, sepsis, and other infections (43.06%), followed by pulmonary circulation disorders (35.71%), congestive heart failure (35.48%), and pericardial tamponade (30.30%). Of those who died in hospital, complicated hypertension, renal failure, and fluid and electrolyte disorders were the most common comorbidities (Fig. 1). Prior cardiac procedures, infection, and perioperative MI/cardiac arrest were similarly frequent (Fig. 2). A complete list of comorbidities and associated rates of morbidity and mortality is shown in Supplementary Table 3 (in the online-only Data Supplement).

Predictors of morbidity and mortality

The final model used in the multivariate analysis comprised 15 variables as summarized in Tables 2 and 3. Perioperative stroke was determined to be an independent risk factor for mortality [odds ratio (OR)=3.182, 95% confidence interval (CI)=1.530–6.618, p=0.002] following TAVI. The other variables that were found to be particularly strong predictors of mortality included infections (e.g., endocarditis and sepsis) (OR=17.899, 95% CI=9.876–32.440, p<0.001), pericardial tamponade (OR=7.272, 95% CI=2.874–18.402, p<0.001), and being Native American (OR=7.170, 95% CI=2.566–20.033, p<0.001). Additional factors associated with mortal-

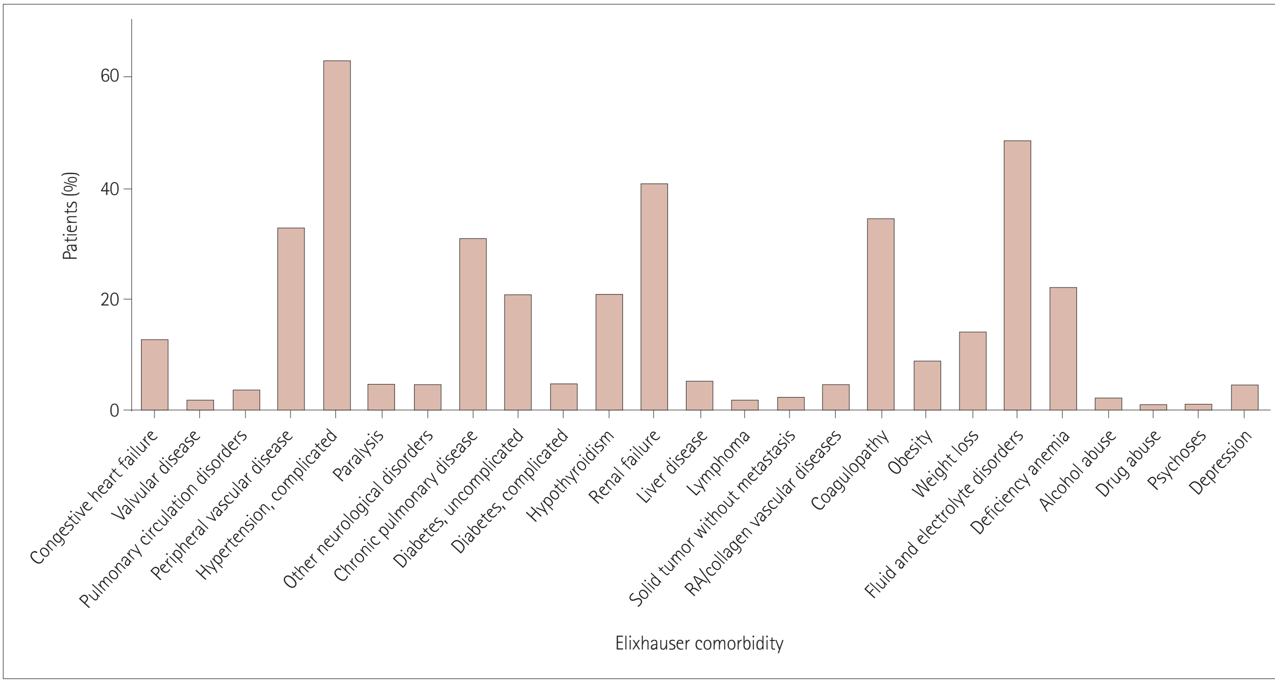

Fig. 1. Proportion of overall mortality delineated by Elixhauser comorbidities. The most common Elixhauser comorbidities among the patients who died were hypertension, fluid and electrolyte disorders, and renal failure. RA: rheumatoid arthritis.

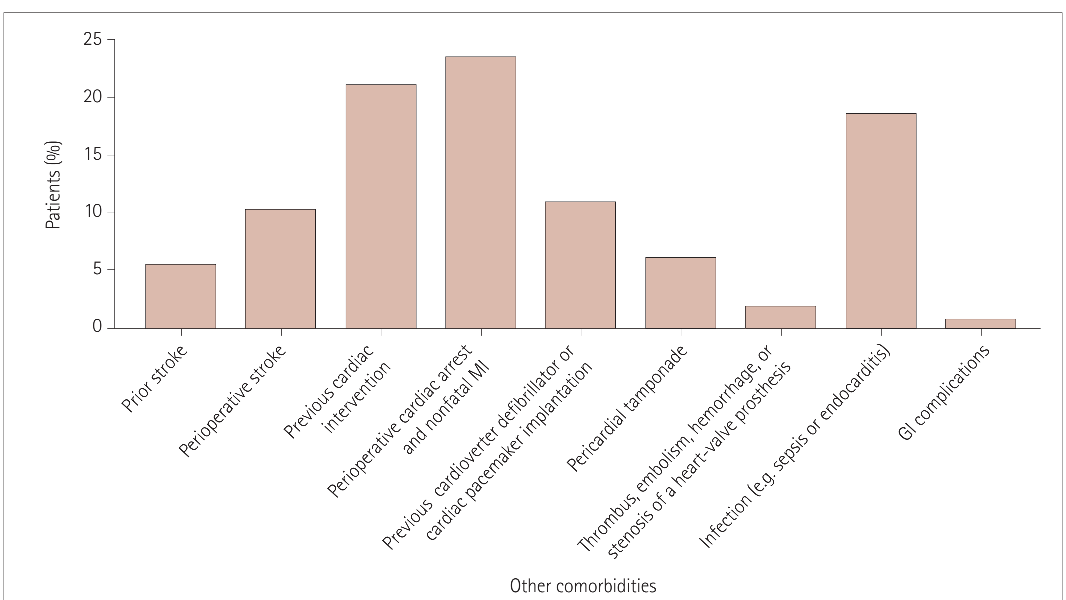

Fig. 2. Proportion of overall mortality delineated by non-Elixhauser comorbidities. The most common non-Elixhauser comorbidities among the patients who died were perioperative cardiac arrest, a previous cardiac intervention, and infection (e.g., sepsis or endocarditis). GI: gastrointestinal, ICD: International Classification of Diseases, MI: myocardial infarction.

ity included advanced age (OR=1.039, 95% CI=1.011–1.067, p=0.005), high VWR (OR=2.324, 95% CI=1.305–4.141, p=0.004), previous cardiac intervention (OR=0.568, 95% CI=0.357–0.903, p=0.017), and postoperative cardiac arrest and nonfatal MI (OR=2.621, 95% CI=1.719–3.995, p<0.001). The comorbidities that were statistically significant predictors of mortality are presented in Fig. 3. The univariate analysis for mortality is shown in Supplementary Tables 4 and 5 (in the online-only Data Supplement).

The multivariate model describing outcomes of morbidity comprised variables similar to those used for mortality, including GI complications and delirium and excluding prior stroke and previous cardiac intervention due to lack of statistical significance and group smallness. Perioperative stroke

Table 2. Predictors of mortality in multivariate analysis

Predictor	Adjusted OR	95% CI	*p*
Perioperative stroke	3.182	1.530–6.618	0.002
Age	1.039	1.011–1.067	0.005
Being female	0.966	0.666–1.402	0.856
Race			
African American	1.127	0.446–2.848	0.801
Hispanic	0.851	0.308–2.350	0.756
Asian	1.415	0.274–7.298	0.678
Native American	7.170	2.566–20.033	0.000
Other/missing	0.571	0.194–1.680	0.309
Moderate risk (VWR=5–14)	1.384	0.964–1.987	0.078
High risk (VWR >14)	2.324	1.305–4.141	0.004
Prior stroke	0.599	0.285–1.261	0.177
Previous cardiac intervention	0.568	0.357–0.903	0.017
Postoperative cardiac arrest and nonfatal MI	2.621	1.719–3.995	0.000
Pericardial tamponade	7.272	2.874–18.402	0.000
Endocarditis, sepsis, and other infections	17.899	9.876–32.440	0.000

CI: confidence interval, MI: myocardial infarction, OR: odds ratio, VWR: Van Walraven score.

Table 3. Predictors of morbidity in multivariate analysis

Predictor	Adjusted OR	95% CI	*p*
Perioperative stroke	5.223	2.005–13.608	0.001
Age	1.042	1.031–1.053	0.000
Being female	2.080	1.773–2.439	0.000
Race			
African American	1.119	0.728–1.719	0.609
Hispanic	1.264	0.755–2.116	0.372
Asian	0.409	0.189–0.883	0.023
Native American	0.760	0.280–2.061	0.590
Other/missing	1.038	0.710–1.516	0.848
Moderate risk (VWR=5–14)	1.291	1.091–1.528	0.003
High risk (VWR >14)	2.402	1.656–3.485	0.000
Postoperative cardiac arrest and nonfatal MI	1.841	1.376–2.464	0.000
Pericardial tamponade	7.364	0.949–57.160	0.056
Endocarditis, sepsis, and other infections	9.286	1.981–43.525	0.005
GI complications	9.551	1.257–72.555	0.029
Delirium	2.174	0.690–6.854	0.185

CI: confidence interval, GI: gastrointestinal, MI: myocardial infarction, OR: odds ratio, VWR: Van Walraven score.

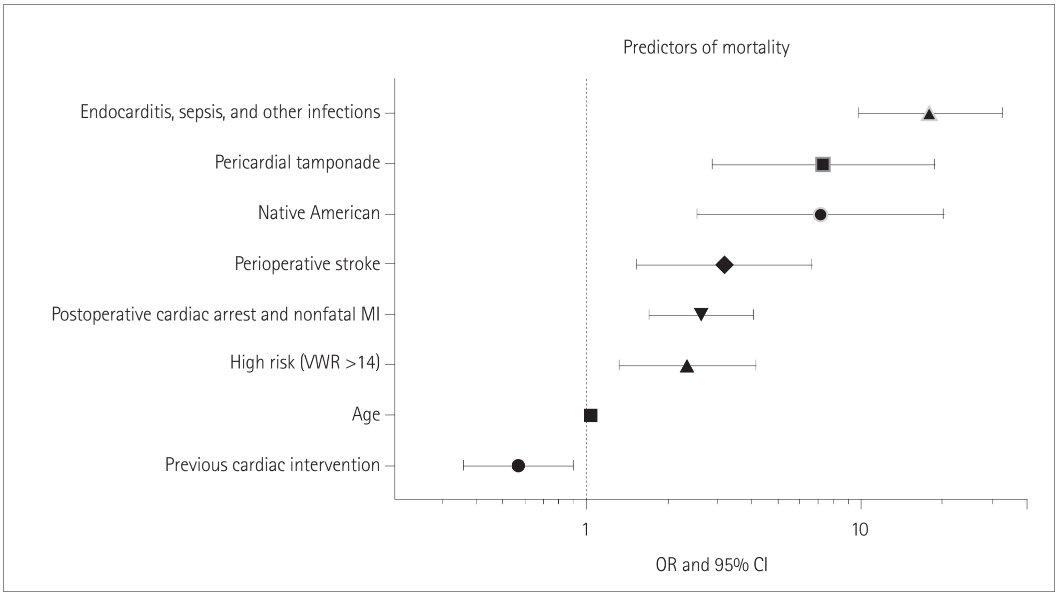

Fig. 3. Significant comorbidities that predict mortality. Comorbidities that were significant predictors of in-hospital mortality. Previous cardiac intervention was negatively associated with mortality. CI: confidence interval, MI: myocardial infarction, OR: odds ratio, VWR: Van Walraven score.

was found to be a more significant risk factor for morbidity (OR=5.223, 95% CI=2.005–13.608, p=0.001) than were the other variables. Additional factors that were significantly associated with morbidity included age (OR=1.042, 95% CI=1.031–1.053, p<0.001), being female (OR=2.080, 95% CI=1.773–2.439, p<0.001), being Asian (OR=0.409, 95% CI=0.189–0.883, p=0.023), having a moderate VWR (OR=1.291, 95% CI=1.091–1.528, p=0.003), and having a high VWR (OR=2.402, 95% CI=1.656–3.485, p<0.001). As for mortality, infection was found to be a significant predictor of morbidity (OR=9.286, 95% CI=1.981–43.525, p=0.005) and GI complications (OR=9.551, 95% CI=1.257–72.555, p=0.029). Univariate analysis of outcomes of morbidity is shown in Supplementary Tables 4 and 6 (in the online-only Data Supplement).

DISCUSSION

This study found that perioperative stroke is an independent risk factor for death or discharge to a place other than the home. The rates of stroke in the NIS were found to be similar to those determined in previous studies. Tchetche et al.[6] assessed outcomes from the FRANCE-2 registry and found a stroke rate of 3.98%, while Jilaihawi et al.[20] determined the rate of stroke to be 2.6% in a meta-analysis of TAVI complications. The overall rates of mortality and morbidity in the present study were 4.57 and 71.12%, respectively, which is consistent with the findings of recent studies.[1,21] A particularly interesting finding was that the rate of mortality in those experiencing a perioperative stroke was notably high at 16.83%.

There have been few reports of specific rates of stroke-related death. The first PARTNER trial[22] and Tamburino et al.[23] found low rates of stroke-related death (3.5%), while Stortecky et al.[24] reported a significant mortality rate of 42.3% following a periprocedural stroke in a prospective study of 389 high-risk elderly patients undergoing TAVI. Indeed, the definitive causes of death can be difficult to ascertain. Other causes of mortality associated with stroke (e.g., ischemic heart disease) or not related to stroke (e.g., cancer) during the hospital stay may have contributed to our reported values and inflated the true rate of mortality. Thus, identifying and delineating death from stroke and death from related complications will be valuable for characterizing the features of mortality following TAVI.

Other baseline comorbidities and procedural complications were found to be predictors of short-term mortality. The preoperative conditions included congestive heart failure, uncomplicated diabetes, and pulmonary disease. Periprocedural events such as perioperative stroke, infection, MI, and pericardial tamponade were factors that significantly increased the risk of mortality, corroborating the previous study of Saia et al.[15] identifying similar factors additional to acute kidney injury. The use of in-hospital mortality as an outcome makes it possible to identify events that are directly related to the procedure and subsequent tailor interventions that minimize the complications of TAVI. Long-term outcomes were difficult to analyze using NIS data due to a lack of relevant CCS codes and the novelty of TAVI. The addition of in-hospital mortality could provide insight into the sequelae that follow complications of TAVI beyond the in-hospital period. Studies have found high rates of mortality (near to 20%) at 3 years following treatment,[15] with varying mortality rates due to comorbidities that include both cardiovascular and noncardiovascular illnesses.

It is equally important to evaluate measures of morbidity such as length of stay and discharge status given the cost burden of TAVI.[7] Infections and GI complications are among the comorbidities that significantly predict morbidity. The need for antibiotics and resuscitative measures in the event of sepsis require increased resource utilization and ICU care that prolong the length of hospitalization. Being female was found to be a demographic variable that was significantly associated with postoperative morbidity. This finding may be explained by outcomes from the Pooled-RotterdAM-Milano-Toulouse In Collaboration (PRAGMATIC) registry,[6] which attributed being female to increased bleeding and the need for transfusion following TAVI, perhaps requiring an extended hospital stay or rehabilitation. Race was also implicated as affecting outcomes, since being Asian was associated with morbidity. There have been few studies of racial disparities in the setting of TAVI or indeed any cardiac procedure, so the present results may indicate that future work is needed in this area.

These findings have significant implications for modifying the management of patients with severe aortic stenosis. Preoperative conditions could be included in an extensive screening test to evaluate patients at risk of poor outcomes following treatment and to minimize the risk of unsuccessful treatment. Those identified as being at high risk based on their preoperative status could be managed further. The SAMMPRIS trial[13] showed that medical therapy was effective at minimizing the stroke rate in patients with intracranial atherosclerotic disease. Similarly, the CREST-2 trial[25] that is comparing pharmacological strategies to surgical and endovascular therapies for carotid stenosis will further elucidate the efficacy of medical management for vascular pathologies. Thus, existing recommendations for antithrombotic treatment in TAVI could be modified to include higher dosages of antiplatelets and more aggressive lifestyle modification in order to minimize the risk of stroke. Addressing the occurrence of intraoperative events requires a broad range of strategies, but could include intraoperative neurophysiological monitoring to assess for stroke and other disturbances in the cerebral perfusion.[26] Somatosensory evoked potentials and electroencephalograms have been used previously to identify cerebral hypoperfusion and guide intraoperative decision-making during carotid endarterectomies,[11,12] and these modalities might also be suitable for applying during TAVI.

Given that perioperative stroke is related to poor outcomes following TAVI, it can be surmised that interventions aimed at minimizing risk factors for stroke will reduce the rates of mortality and morbidity after TAVI. One such intervention is carotid artery stenosis, with there being evidence from the NIS that bilateral asymptomatic carotid stenosis predicts events of stroke during TAVI.[27] Thus, prior to aortic valve replacement, patients could undergo preoperative carotid Doppler imaging followed by a carotid artery intervention such as stenting to reduce the rates of stroke and other adverse events. A study by Kleiman et al.[28] involving data from the CoreValve Pivotal Trial revealed other risk factors for stroke, including a body mass index below 21 kg/m^2 and falling within the previous 6 months; both of these factors could be modified preoperatively through adequate weight and dietary management and fall-prevention strategies. That group also described intraoperative predictors of stroke, such as length of time in the operating room/catheterization laboratory and snare manipulation in the CoreValve Pivotal Trial. Improved efficiency and operative techniques are logical solutions to these issues.

The present study found that higher VWRs were associated with increased risks of mortality and morbidity, as expected. The VWR is an established method for modeling poor outcomes by weighting Elixhauser comorbidities by their association with in-hospital mortality. There are also other measures of mortality and morbidity risk, and in the setting of aortic valve stenosis, the STS risk-of-mortality score and the EuroSCORE are commonly used to assess the suitability of patients for surgical interventions. These scores are widely used as inclusion and exclusion criteria in prospective clinical studies, as seen in the PARTNER trial[1] and the CoreValve Pivotal Trial.[29] Both scores are based on various baseline characteristics including demographics, presence of chronic diseases, surgical history, and the preoperative cardiac and hemodynamic status. Hemmann et al.[30] found the scores to be strong predictors of 30-day mortality. Thus, given their value and ubiquity as a tool for risk stratification, their inclusion in the present study would have been warranted. Unfortunately, neither score is reported in the NIS and, to our knowledge, it is not possible to convert VWRs into these measures. Commonly used metrics of neurological function, including the National Institutes of Health Stroke Scale (NIHSS), were similarly not reported in the NIS. NIHSS scores quantify the magnitude of neurological dysfunction and have been shown to predict mortality,[31,32] with higher scores associated with worse outcomes.

Strengths and limitations

The use of the NIS provides an opportunity to characterize the implications of TAVI in a nationally representative sample of patients. Unlike current RCTs, such as the PARTNER and SURTAVI trials, the use of the NIS will include patients treated in all settings with no strict inclusion or exclusion criteria being applied. This means that it is more generalizable and better reflects the outcomes of patients treated in community settings.

While no previous study has utilized the largest inpatient database available in the USA, using the NIS is associated with limitations. The NIS is based on claims data that can be vulnerable to billing errors. The NIS only provides information related to in-hospital events. We were therefore unable to report on events beyond the hospital stay, including readmission or complications outside the hospital. Commonly used quality metrics such as 30-day mortality cannot be identified from existing NIS codes. As mentioned above, more specific measures of operative risk that characterize cardiac function and hemodynamic status (e.g., STS risk-of-mortality score and EuroSCORE) as well as neurological impairment (e.g., NIHSS) were not found in the database. Despite these shortcomings, this study has yielded valuable data that can guide future research.

Conclusion

Perioperative stroke is a significant event during TAVI and is associated with increased risks of in-hospital mortality and postoperative morbidity. High VWR and advanced age were also found to be important risk factors for mortality. These findings will guide future strategies for improving screening and postoperative management for TAVI.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2017.13.4.351.

Conflicts of Interest

The authors have no financial conflicts of interest.

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