Original Article

Carotid Artery Disease and Periprocedural Stroke Risk after Transcatheter Aortic Valve Implantation

Abstract

Objective/Background: To examine the role of carotid stenosis (CS) and other independent risk factors of perioperative stroke, following transcatheter aortic valve implantation (TAVI). **Materials and Methods:** Using data from the National Inpatient Sample database for analysis, patients who underwent TAVI were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification codes. Various preoperative and perioperative risk factors and their association with perioperative strokes were studied. **Results:** Data on 7566 patients who underwent a TAVI procedure from 2012 to 2013 were extracted. The average age of the patient population was 81.2 ± 0.32 years. The overall perioperative stroke rate in our patient cohort was 2.79%. Majority (94.6%) of the strokes were ischemic. Multivariate analysis showed the following independent risk factors for perioperative strokes after TAVI: female gender odds ratio (OR) = 2.25 (95% confidence interval [CI], 1.42–3.57), higher van Walraven score OR = 6.6 (95% CI = 3.71–11.73), bilateral CS OR = 4.46 (95% CI = 2.03–9.82), and TAVI with a cardiac procedure done under cardiopulmonary bypass OR = 2.84 (95% CI = 1.57–5.14). **Conclusion:** Bilateral carotid disease is a significant risk factor for perioperative strokes following TAVI. Preoperative screening with carotid Doppler to identify high-risk patients appears to be warranted. In addition, patients of female gender were found to have an increased risk for carotid disease.

Keywords: *Carotid disease, carotid stenosis, perioperative stroke, transcatheter aortic valve implantation, transcatheter aortic valve replacement*

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Introduction

Periprocedural strokes, neurological deficits developing within 30 days of transcatheter aortic valve implantation (TAVI), have an incidence rate of 2%–6%,[1] with significant consequences on postoperative mortality and morbidity rates.[1] TAVI is rapidly becoming a common cardiac procedure in the US with 10,000 procedures performed annually,[2] having an operative mortality ranging from 6% to 15%.[3] The growing significance of TAVI in the management of aortic stenosis makes it important for us to examine the risk factors associated with periprocedural stroke.

The Placement of Aortic Transcatheter Valves (PARTNER) trial reports 30-day perioperative stroke rates of 3.8% and 5.5% for TAVI in high-risk and intermediate-risk cohorts, respectively, with procedural events being predominantly in the 1st postoperative week.[4-6] A reported stroke rate of 3%–5% highlights the need for efforts to identify and counter the risk to improve the overall efficacy of TAVI. Periprocedural strokes are also undesirable due to the fact that they eliminate the shorter length of stay (LOS) benefit that is otherwise preferred with TAVI (3 days for TAVI; 5 days for aortic valve replacement).[5] Although the definitive causes for these strokes are yet to be defined, studies postulate intraoperative hypotension, embolic events, and anticoagulation-induced hemorrhage as some of the possible causes for cerebral ischemia.[4,7,8] Cerebral embolization owing to manipulation of guide wires and catheters across stenotic aortic valves and the arch of aorta are likely mechanisms of early strokes following TAVI.[4] Carotid artery stenosis (CAS) is one of the most significant risk factors for perioperative strokes after cardiac operations.[9] The presence of carotid, vertebral,[10] or intracranial arterial stenosis has been shown to accentuate cerebral hypoperfusion, which in the presence of emboli can result in perioperative strokes.

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The primary aim of our study was to identify whether carotid stenosis (CS) is an independent risk factor for perioperative strokes following TAVI. We also examined the relationship of vertebral, basilar, and intracranial stenosis with stroke risk following TAVI. A large-scale analysis of the role of carotid, vertebral, or intracranial stenosis in the etiology of ischemic strokes after TAVI would help us foster improved preoperative screening strategies, intraoperative neuromonitoring of ischemia,[11] prophylactic intensive medical management used in the treatment of intracranial stenosis,[12] and/or carotid revascularization before TAVI.

Materials and Methods

We used the National Inpatient Sample (NIS) database to select the study population over a period of 2 years (2012–2013) for TAVI. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes was used to identify patients based on their diagnoses and procedures. Patients undergoing TAVI were identified using ICD-9 codes 35.05 and 35.06. The NIS database provides 29 Elixhauser comorbidities based on standard ICD-9 codes.[13] In addition, the ICD-9 codes [Table 1] was used to identify other covariates and the outcomes. The primary outcome studied was perioperative stroke following TAVI. CS was used as the independent variable. Risk stratification was done using van Walraven (VWR) score, which is a summary score for the Elixhauser comorbidities developed by modeling in-hospital mortality with inpatient admission data.[14] The summary score is a weighted combination of the 29 Elixhauser comorbidities, where a larger comorbidity weight correlates with higher in-hospital mortality.

All data are presented as mean ± standard deviation or percentages. Univariate comparisons between groups were done using unpaired *t*-tests for continuous variables and a survey-adjusted Wald test for variables that were categorical in nature. In our multivariable analysis, we included variables that were statistically significant in the univariate analysis, that had a large enough group population, that lacked missing data, and that were established as risk factors in the previous studies. We elected to exclude each individual Elixhauser comorbidity and use the VWR score

Table 1: International Classification of Diseases, Ninth Revision, Clinical Modification codes used to query the National Inpatient Sample database

Risk factors and diagnoses	ICD-9-CM codes
Perioperative stroke	
Perioperative stroke	997.00-997.02, 431, 432, 433.01, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 436
CS and other stenosis	
Unilateral CS	433.10
Bilateral CS	433.30
Vertebral artery stenosis	433.20
Basilar artery stenosis	433.00
Stenosis and occlusion of precerebral arteries (other than carotid/vertebrobasilar or unspecified)	433.80, 433.90
Occlusion of cerebral arteries	434.00, 434.10, 434.90
Aortic atherosclerosis	440.0
Comorbidity factors	
Left ventricular dysfunction and cardiac failure	398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.x
DM	250.0-250.9
Hypertension	401.1, 401.9, 402.10, 402.90, 404.10, 404.90, 405.1, 405.9, 401.0, 402.x-405.x, 642.1, 642.2, 642.7, 642.9
Atrial fibrillation	427.31
Peripheral vascular disease	440.x, 441.2, 441.4, 441.7, 441.9, 443.1-443.9, 447.1, 557.1, 557.9, V43.4
Renal failure	403.11, 403.91, 404.12, 404.92, 585.x, 586.x, V42.0, V45.1, V56.0, V56.8
History of cerebrovascular disease (previous stroke/TIA)	V12.54, 434.91, 434.11
Infective endocarditis	421.0, 421.1
Prior MI and CAD/angina	412 and 414.01, 414.0, 413.9
Previous cardiac surgery	15.1
Previous history of other cardiovascular procedures including CEA and CAS	V45.89, CEA-38.12, CAS-00.61, 00.63
Previous history of CAD with CABG	V45.81
Cardiopulmonary bypass	39.61

DM: Diabetes mellitus, CAD: Coronary artery disease, CABG: Coronary artery bypass graft, CAS: Carotid artery stenosis, CEA: Carotid endarterectomy, MI: Myocardial infarction, ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification, TIA: Transient ischemic attack, CS: Carotid stenosis

as a surrogate as we did not want to risk overloading our model with variables that may have been either statistically insignificant or not relevant to our outcome of interest. Data extraction was performed using SAS 9.3 (SAS Institute, Inc., Cary, NC, USA) as was the creation of the Elixhauser comorbidity index and the generation of the VWR score.[15] All subsequent statistical analyses were performed using Stata version. 14 (StataCorp, College Station, TX, USA).

Results

Baseline data on 7566 patients who underwent a TAVI procedure from 2012 to 2013 were extracted [Table 2]. The overall perioperative stroke rate in our patient cohort was 2.79%. The majority (94.6%) of the strokes were found to be ischemic in nature. The average age of the patient population was 81.2 ± 0.32 years. The majority of the patients were categorized as low and moderate risk (45.80% and 46.81%, respectively) according to the VWR scores. The percentage of female (49.28%) and male patients (50.72%) were relatively equal in our study cohort. The average VWR score was 5.62. In the NIS database, 5.25% had unilateral asymptomatic CS and 1.94% had bilateral CS. Patients who suffered a perioperative stroke had an in-hospital mortality rate of 19.6%, whereas patients who did not suffer from stroke had an in-hospital mortality of 4.14%. This difference was highly significant (P = 0.0007). The mean LOS was also significantly higher for the stroke group (12.3 days vs. 8.3 days, $P < 0.0001$).

The univariate analysis of predictors of stroke [Tables 2 and 3] was performed by analyzing the following factors: demographic characteristics, VWR score, cerebrovascular stenosis-related ICD-9 codes, atrial fibrillation, previous history of stroke or transient ischemic attack, infective endocarditis, previous history of myocardial infarction (MI) or angina, previous cardiac surgery, previous carotid endarterectomy (CEA)/CAS, history of coronary artery disease with coronary artery bypass graft, cardiopulmonary bypass, and factors from the Elixhauser comorbidity index (only the significant ones have been shown in the table). The analysis revealed the following significant risk factors ($P < 0.05$): female sex, African-American race, higher VWR score, asymptomatic bilateral CS, previous CEA, CAS, TAVI while on cardiopulmonary bypass, congestive heart failure, multivalvular disease, pulmonary circulation disorders, paralysis, other neurological disorders, weight loss, and drug abuse. Bilateral asymptomatic CS was a significant predictor of perioperative stroke (odds ratio [OR] = 4.019, 95% confidence interval [CI] = 1.859–8.689, $P < 0.05$). In contrast, unilateral CS (OR = 1.571, 95% CI = 0.272–1.964, P = 0.129) and "any CS" (OR = 1.571, 95% CI = 0.876–2.816, P = 0.129) were not found to be significant predictors of perioperative stroke following TAVI. No patients were coded for symptomatic CS, vertebral/basilar stenosis, or intracranial stenosis from the database and were not included in the analysis. Surprisingly, our analysis shows that previous MI or angina (OR = 0.579, 95% CI = 0.398–0.842, $P < 0.05$) and hypertension (OR = 0.535, 95% CI = 0.366–0.782, $P < 0.05$) were both found to be significantly associated with a decreased perioperative stroke risk.

Table 2: Demographic characteristics of study population with univariate analysis

Variables	Percentage of patients	Perioperative strokes		
		Yes, *n* (%)	Unadjusted OR (95% CI)	*P*
Age (mean±SD)				
<65	5.09	7 (3.98)		
65-74	13.58	9 (1.91)	0.471 (0.185-1.198)	0.114
75-84	42.05	32 (2.20)	0.542 (0.237-1.246)	0.150
>85	39.28	50 (3.68)	0.922 (0.020-0.084)	0.837
Gender				
Female	49.28	68 (3.77)	2.100 (1.343-3.283)	0.001
Male	50.72	34 (1.83)		
Race/ethnicity				
White	87.85	75 (2.52)		
African-American	3.52	7 (5.88)	2.413 (1.091-5.341)	0.030
Hispanic	2.72	2 (2.17)	0.858 (0.204-3.612)	0.835
Asian	0.92	1 (3.23)	1.287 (0.175-9.471)	0.804
Native American	0.33	0	N/A	N/A
Other/missing	0.47	2 (1.27)	0.495 (0.123-1.986)	0.321
Risk category				
Low risk (VWR<5)	45.80	32 (1.91)		
Moderate risk (VWR 5-14)	46.81	41 (2.39)	1.260 (0.767-2.069)	0.362
High risk (VWR>14)	7.38	29 (10.74)	6.178 (3.450-11.065)	<0.001

N/A: Not available, VWR: van Walraven, OR: Odds ratio, CI: Confidence interval, SD: Standard deviation

Table 3: Univariate predictors of perioperative stroke following transcatheter aortic valve implantation

	Percentage of patients	Perioperative strokes			
		Yes, *n* (%)	No, *n* (%)	Unadjusted OR (95% CI)	*P*
Preoperative risk factors					
Any CS	7.20	11 (4.15)	254 (95.85)	1.571 (0.876-2.816)	0.129
Unilateral asymptomatic CS	5.25	4 (2.08)	188 (97.92)	0.731 (0.272-1.964)	0.534
Bilateral asymptomatic CS	1.94	7 (9.86)	64 (90.14)	4.019 (1.859-8.689)	<0.001
Aortic atherosclerosis	2.79	2 (1.96)	100 (98.04)	0.691 (0.169-2.818)	0.606
Atrial fibrillation	44.46	44 (2.71)	1582 (97.29)	0.946 (0.627-1.428)	0.792
Previous stroke or TIA	10.31	8 (2.12)	369 (97.88)	0.735 (0.331-1.631)	0.449
Infective endocarditis	0.137	1 (20.00)	4 (80.00)	8.790 (0.976-79.192)	0.053
Previous MI or angina	52.34	40 (2.09)	1874 (97.91)	0.579 (0.398-0.842)	0.004
Previous cardiac surgery	0.711	1 (3.85)	25 (96.15)	1.398 (0.185-10.562)	0.745
Previous CEA/CAS	1.01	5 (13.51)	32 (86.49)	5.675 (2.160-14.912)	0.000
History of CAD with CABG	0.027	0	1 (100.00)	N/A	N/A
Cardio pulmonary bypass	7.30	17 (6.37)	250 (93.63)	2.644 (1.539-4.541)	0.000
Significant Elixhauser comorbidities					
CHF	1.59	9 (15.52)	49 (84.48)	6.924 (3.348-14.322)	0.000
Multivalvular disease	0.465	3 (17.65)	14 (82.35)	7.665 (2.049-28.677)	0.002
Pulmonary circulation disorders	0.383	2 (14.29)	12 (85.71)	5.905 (1.310-26.614)	0.021
Paralysis	1.86	29 (42.65)	39 (57.35)	35.815 (20.394-62.895)	0.000
Other neurological disorders	6.29	29 (12.61)	201 (87.39)	6.629 (4.161-10.559)	0.000
Weight loss	5.06	12 (6.49)	173 (93.51)	2.607 (1.443-4.707)	0.001
Drug abuse	0.246	2 (22.22)	7 (77.78)	10.137 (2.051-50.102)	0.005
Hypertension	78.56	68 (2.37)	2805 (2.37)	0.535 (0.366-0.782)	0.001

OR: Odds ratio, CI: Confidence interval, N/A: Not available, CAD: Coronary artery disease, CABG: Coronary artery bypass graft, CAS: Carotid artery stenosis, CEA: Carotid endarterectomy, MI: Myocardial infarction, TIA: Transient ischemic attack, CHF: Congestive heart failure, CS: Carotid stenosis

Multivariate analysis showed the following to be significant ($P < 0.05$) independent risk factors for perioperative strokes after TAVI: female sex, higher VWR score, and bilateral asymptomatic CS. Patients who underwent TAVI or other cardiac surgery while on cardiopulmonary bypass were more likely to develop perioperative strokes. Previous history of MI or angina and hypertension were found to be associated with a decreased risk of perioperative stroke following TAVI. Table 4 displays relevant statistics for these factors as well as other key parameters.

A subgroup analysis was done to identify patients who had CS. Women (OR 11.26, 95% CI = 1.94–65.35, $P = 0.007$) and patients in the high-risk VWR category (VWR >14) were more likely to have bilateral CS, 6.767 (1.30–35.11). Higher risk VWR score was associated with unilateral CS (OR 16.46, 95% CI = 2.10–128.87, $P = 0.008$). No other variables were significantly associated with CS.

Table 4: Multivariate regression analysis of risk factors

Variables	OR	95% CI	*P*
Age	1.03	1.00-1.061	0.074
Female gender	2.25	1.42-3.57	0.001
VWR score category			
<5 (low risk)	NA	NA	NA
5-14 (medium risk)	1.32	0.80-2.17	0.280
>14 (high risk)	6.60	3.71-11.73	<0.001
Comorbidities			
Unilateral asymptomatic CS	0.88	0.34-2.30	0.797
Bilateral asymptomatic CS	4.46	2.03-9.82	<0.001
Any CS (unilateral asymptomatic, bilateral asymptomatic, symptomatic carotid)	1.82	1.01-3.30	0.047
Previous history of MI or angina	0.61	0.41-0.90	0.012
Cardio pulmonary bypass	2.84	1.57-5.14	0.001
Hypertension	0.56	0.38-0.82	0.003

OR: Odds ratio, CI: Confidence interval, NA: Not available, VWR: van Walraven, MI: Myocardial infarction, CS: Carotid stenosis

Discussion

As noted earlier, TAVI is becoming increasingly popular because of the well-established benefits of minimally invasive procedures with approximately 10,000 procedures performed annually. It is imperative; we better understand and manage complications after this procedure to improve overall safety and efficacy. The study cohort comprised almost equal number of male and female patients although the females had a higher risk of developing strokes. This finding is consistent with other studies, which attribute this higher risk to greater number of associated comorbidities seen in females.[16] African-American patients were at a higher risk for perioperative stroke in our study, a finding which has been reported by others.[17] It is not clear why African-Americans had a higher risk, but the finding

is consistent with abundant data that members of this racial group have elevated risk of stroke in general when compared to Caucasians.[17] TAVI done for patients who had another procedure requiring cardiopulmonary bypass was also a risk factor for stroke. The NIS dataset does not allow us to determine why a small number of patients had this unusual combination of procedures. 2.79% of the patients in our study developed ischemic perioperative strokes. However, only 0.16% of patients had hemorrhagic strokes, which was too small a population to achieve any statistical power to perform subgroup analysis.

Our analysis showed that bilateral asymptomatic CS was a strong predictor of ischemic strokes following TAVI, with patients having a 5-fold greater stroke risk. In contrast, unilateral CS was not a significant predictor. The incidence of unilateral and bilateral CS was lower in our analysis than found in other studies.[18] This difference may be due to differences in intensity of screening for carotid disease between patients in the NIS dataset and those in other studies.

The etiology of strokes in TAVI appears to be multifactorial, but intraoperative embolic events, periprocedural hypotension, and prior history of cerebrovascular disease[8,19] have been reported to play dominant roles.[7] Several transcranial Doppler (TCD) studies have visualized embolic phenomena during manipulation of catheters across the aortic valve and during valve implantation.[20] Our findings suggest a role for preoperative carotid Doppler scanning to screen for asymptomatic CS and risk-stratify the patients based on the diagnosis,[19] and our data also suggest a possible benefit from carotid revascularization before TAVI if patients have bilateral carotid disease.

Other recent publications have suggested that carotid disease is not associated with increased risk for perioperative stroke after TAVI[18,21-24] summarized in Table 5. Our NIS-based analysis and the older studies, which were based on single-institution cohorts of TAVI patients, all find that unilateral CS is not a predictor of post-TAVI stroke. Our study found, however, that bilateral CS was a significant predictor of stroke. Of the previous papers, only one[18] specifically reported on the prevalence of bilateral CS. This study had an unusually low rate of periprocedural stroke (0.5%). The other studies[21-24] reported stroke rates (1.5%–6.8%) more in line with our findings, but they did not specifically analyze the possible predictive role of bilateral carotid disease. Thus, the previous data do not definitively address the issue of bilateral CS as a possible predictor of post-TAVI stroke.

Aortic arch atherosclerosis and calcification were reported to be a significant risk factor for strokes following TAVI due to aortic plaque disruption with resultant atheroembolic debris occluding cerebral. However, no patients who underwent TAVI from the NIS database identified this diagnosis. This finding suggests that the patients were not screened for aortic atherosclerosis despite the significant stroke risk it poses[4,25] or that the diagnosis is grossly underreported in patients undergoing TAVI. The NIS database does not allow us to determine whether patients routinely underwent chest computed tomography before TAVI, and even if they did, those findings may not have been coded in the hospital billing records. The SAMMPRIS[26] and CAVATAS[10] trials signify the role of vertebral, basilar, and other intracranial artery stenosis on perioperative strokes. We were unable to analyze for these risk factors as we could not find any patients who were identified to have vertebral or intracranial stenosis. Preoperative screening of patients with carotid Doppler and transesophageal echocardiography to risk-stratify patients and intraoperative neuromonitoring with TCD may help reduce perioperative strokes rates. Other preventive strategies for embolic strokes such as adequate antiplatelet and anticoagulant medication,[27] embolic protection devices such as deflection,[28] and filtering devices have been studied, but a definitive role is yet to be established.[8,29]

Multivariate analysis showed a higher VWR score to be an independent predictor for strokes. Higher scores implicate greater associated comorbidities and necessitate better preoperative screening and patient selection. These results were similar to the findings of the PARTNER trial in the high-risk inoperable group.[4] Ideally, Society of Thoracic Surgeons score and Euroscore stratification of patients would give us more information to correlate

Table 5: Summary of other studies which have examined carotid stenosis among transcatheter aortic valve implantation patients

References	Author	Year	CS		Stroke rate (%)	Conclusions
			≥50%	≥70%		
[18]	Steinvil *et al*.	2014	33	9	0.5	CS was not independently associated with 30-day mortality or stroke rates
[21]	Ben-Shoshan *et al*.	2017	31.1	6.4	1.5	CS not associated with worse outcomes following TAVI
[22]	Huded *et al*.	2016	19	Not reported	6.8	Carotid or vertebral artery stenosis was not significantly related to the occurrence of stroke after TAVI
[23]	Condado *et al*.	2017	Not reported	5.2	3.4	No significant association between CS severity and stroke after TAVR

TAVR: Transcatheter aortic valve replacement, TAVI: Transcatheter aortic valve implantation, CS: Carotid stenosis

results with the current prospective studies, but we were limited in our ability to access this information through the database.[4,6,30] The finding that previous history of angina/MI and hypertension is associated with a decreased stroke risk was unexpected. It is possible that patients with these conditions benefited from receiving aggressive preoperative medical therapy (e.g., antiplatelet therapy and statins). However, the nature of our data does not allow us to analyze this possible explanation.

This study was conducted using the NIS, a database that allows for analysis of large number of patients treated in the "real-world" general hospital setting and therefore relies on ICD-9 codes. Coding is an imperfect science because the diagnoses associated with different ICD-9 codes can overlap with one another, leading to potential inconsistency of coding. For example, a patient with bilateral CS may sometimes receive only code 433.30 or both 433.10 and 433.30. Moreover, coders may apply 433.30 to patients when multiple noncarotid precerebral arteries have stenosis. However, because it is unusual for coders to have any data on the precerebral vasculature besides carotid duplex data, the use of 433.30 generally implies bilateral carotid disease. Our finding that very few patients were coded as having vertebral and/or basilar artery disease and no patients have been coded for aortic atherosclerosis supports this assumption. Any data on strokes which occurred after discharge but within the 30-day postoperative mark are unavailable. We were unable to analyze the role of subclinical cerebral infarcts detected by postoperative magnetic resonance imaging, seen in almost 93% of patient's post-TAVI. Our study conclusions are pertaining to clinically evident strokes following TAVI.

Conclusion

We found that bilateral carotid disease is a significant risk factor for perioperative strokes following TAVI. Preoperative screening with carotid Doppler to identify high-risk patients appears to be warranted. In addition, patients of female gender were found to have an increased risk for carotid disease.

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Conflicts of interest

There are no conflicts of interest.

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