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Stroke Prevention With Carotid Compression in Patients Undergoing Transcatheter Aortic Valve Replacement: a Multi-Center Study

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Abstract

***Background*: Transcatheter aortic valve replacement (TAVR) has revolutionized the management of severe aortic stenosis. However, TAVR is associated with several complications, including stroke. Carotid compression has been suggested as a simple maneuver to reduce embolic events during various cardiac procedures. Therefore, we examined the association between carotid compression and the incidence of transient ischemic attack (TIA) and stroke in patients undergoing TAVR.**

***Methods*: This is a retrospective multicenter study of patients who underwent TAVR with and without carotid compression. Primary outcomes were stroke or TIA 72 hours after the procedure and between 72 hours and 30-day follow-up. Data analysis was performed using a propensity score technique with inverse probability weighting.**

***Results*: A total of 306 TAVR patients were included in the study. Group I (n = 188) and II (n = 118) included patients who did not or did undergo carotid compression during TAVR, respectively. The mean age was 82.5 ± 8.2 years in Group I and 78.5 ± 7.6 years in Group II. There was no significant difference in combined stroke or TIA rate 72 hours after the procedure (1.1% vs. 1.9%, P = 0.50) or between 72 hours and 30-day follow-up (2.3% vs 1.6%, P = 0.67).**

***Conclusions*: Carotid compression during the TAVR procedure is not associated with the incidence of composite TIA or stroke after TAVR.**

Key Words

Transcatheter aortic valve replacement • Carotid compression • Stroke • Transient ischemic attack • Severe aortic stenosis

Introduction

Transcatheter aortic valve replacement (TAVR) has emerged in recent years as an attractive option for treating patients with symptomatic severe aortic stenosis (AS) who are deemed to be at intermediate or high risk for surgical aortic valve replacement (SAVR) [1-3]. As TAVR continues to evolve, it requires improvements in device technology and implantation techniques to minimize the rate of complications such as stroke. Stroke is a devastating complication that has been attributed to procedural factors [4]. The 30-day occurrence of all strokes in the PARTNER 1A tri-

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al was significantly higher among TAVR patients than among SAVR patients (5.5% vs. 2.4%, $P = 0.04$) in the high-risk cohort [1]. Published 5-year outcomes of the PARTNER 1 trial showed a similar incidence of stroke or transient ischemic attack (TIA) between TAVR and SAVR patients (15.9% vs. 14.7%, $P = 0.3$) [5]. More recent data show stroke rates of 3.4% at 30 days in the FRANCE 2 Registry study [6] and procedural/in-hospital stroke rates of 1.8% in the Transcatheter Valve Treatment Sentinel Pilot Registry [7]. Although the incidence of stroke is declining [8], stroke is strongly associated increased morbidity and mortality [9, 10].

The mechanism of stroke after TAVR is presumably embolic in most cases and may differ depending on the timing of stroke and route of access. However, a history of carotid disease may be one predictor of post-procedure strokes [11-13]. Multiple studies utilizing magnetic resonance imaging, trans-cranial Doppler, and filtered and retrieved material have documented nearly universal embolic phenomena during TAVR [14-17]. Hypothetically, stroke prevention can be achieved by minimizing the amount of microemboli showering from the aorta to the brain during TAVR implantation. Anecdotally, several TAVR programs in the United States and Europe perform carotid compression during TAVR to minimize the risk of stroke or TIA [18]. The rationale for this concerns both direct occlusion of the arteries during a period of embolic showering and a change in flow diverting emboli from entering cerebral circulation. Here, we examined the association between carotid compression during TAVR and post-procedural incidence of TIA and stroke.

Materials and Methods

Patient Population

The study included patients with symptomatic severe AS who underwent TAVR at the University of Utah Hospital, Washington University Medical Center, or Banner Health Center in Phoenix, Arizona between February 1, 2012 and April 1, 2016. Collected data were part of the Transcatheter Valve Therapy registry. For the purposes of this study, the intervention of interest was whether the patient received carotid compression during the TAVR procedure as documented in the clinical operative report. Patient eligibility for TAVR was decided at each site by the heart team, which included interventional cardiologists, cardiothoracic surgeons, imaging cardiologists, and cardiac anesthesiologists. Members of the heart teams at all three centers were similarly trained and qualified to treat TAVR patients. Enrolled patients were divided into two groups: Group I included patients who underwent TAVR without carotid compression, and Group II included patients who underwent TAVR with carotid compression. The valve technologies included in the study were SAPIEN XT and S3 (Edward Lifesciences, Irvine, California, USA). To control for any potential differences in pathophysiology related to access approach, only patients who underwent a TAVR procedure via the transfemoral access route were included in this study. Patients whose pre-procedure carotid stenosis status had not been measured were not included in the study, nor were patients with bilateral carotid disease. All patients for whom anticoagulation medication was not contraindicated received dual anti-platelet therapy with aspirin and clopidogrel for 6 months after TAVR. Intravenous heparin was administered during the procedure to obtain an activated clotting time goal of >300 s. Taking into account contraindications, there was no significant difference between groups with regard to the administration of anticoagulation medication at discharge (98.4% for Group I vs. 97.5% for Group II, $P = 0.95$).

At the University of Utah Hospital, it is standard practice to perform carotid compression on patients receiving SAPIEN valves; however, carotid compression is not used at the other two centers, therefore data from these centers served as a control. Carotid compression is defined as bilateral external compression of the carotid arteries and is performed coincident with rapid pacing. In this study, carotid compression was initiated 2 s before rapid pacing and released 3 s after rapid pacing was discontinued, with the average duration of carotid compression lasting 30–45 s. Carotid compression was completed manually with enough pressure to feel the carotid compressed and was completed by the assisting physician. Stroke and TIA were defined according to Valve Academic Research Consortium (VARC) criteria [19]. TIA was defined as a new focal or global neurological deficit with symptom resolution within 24 hours of onset in the

Table 1. Non-adjusted baseline characteristics.

Variable	No Carotid compression *n=188*	Carotid compression *n= 118*	p value
Age	81.9 ± 8.1	78.8 ± 7.3	**<0.001**
Females	48.5%	39.4%	**0.05**
Caucasian race	93.1%	97.1%	0.06
Diabetes	43.5%	40.6%	0.52
Hypertension	96.1%	89.7%	**0.003**
Atrial fibrillation	48.9%	36.6%	**0.008**
Prior Stroke or TIA	23.8%	18.9%	0.20
Prior MI	36.8%	23.4%	**0.002**
Prior CAD (CABG or PCI)	55.1%	49.4%	0.22
Current Tobacco Use	6.9%	7.4%	0.83
COPD	34.4%	27.4%	0.11
Prior PVD	40.4%	30.3%	**0.02**
Carotid Stenosis (L/R)	22.7%	17.1%	0.14
Baseline LVEF (>30%)	93.3%	96.6%	0.13
BMI	28.5 ± 6.9	28.3 ± 6.2	0.80
STS Score	8.47 ± 4.4	9.24 ±5.9	0.12

Table 2. Non-adjusted procedure characteristics.

Variable	No Carotid Compression	Carotid Compression	p value
LOS Post-Procedure (days)	6.8 ± 5.6	6.3 ± 4.8	0.28
Prior aortic valve procedure	18.3%	8.0%	**0.002**
Pre-procedure anticoagulants	43.8%	28.0%	**<0.001**
Access Site • TF • TA + Other	58.7% 41.3%	70.3% 29.7%	**0.01**
Status • Elective • Urgent/ Emergency	85.0% 15.0%	92.6% 7.4%	**0.01**
NYHA Class • Class I • Class II • Class III • Class IV	2.0% 6.0% 46.0% 46.0%	0% 5.7% 81.7% 12.6%	**<0.001**
Valve-in-valve	6.9%	5.7%	0.60
Annulus size	22.4 ± 2.3	23.4 ± 2.7	**<0.001**
Procedure Time (minutes)	141.2 ± 63.2	116.5 ± 63.2	**<0.001**
ICU Hours	54.5 ± 91.8	72.7 ± 90.7	**0.03**

absence of other possible causes and was confirmed by a neurologist. Stroke was defined as rapid onset of a focal or global neurological deficit lasting ≥24 hours (or <24 hours if therapeutic interventions were performed) in the absence of other identifiable non-stroke causes and was confirmed by a neurologist. In keeping with the VARC recommendation, a disabling stroke (also known as a "major stroke") was defined as a stroke with degree of disability ≥2 on the modified Rankin scale. Post-procedure neurologic events ("post-procedure cardiovascular accidents (CVA)") were defined as any TIA or stroke documented within 72 hours of TAVR, whereas a late neurologic event ("late CVA") was defined as any TIA or stroke documented between 72 hours of TAVR (or at discharge) and 30 days after TAVR. In this study, high-volume TAVR is defined as >100 TAVR cases annually, with all three centers meeting this definition. This study was approved by the institutional review boards at all three centers.

Statistical Analysis

Baseline Comparison of Treatment Groups. Continuous variables are presented as mean ± standard deviation (SD) or percentage based on their distribution. In the overall sample, continuous and categorical variables were compared between groups using Student's *t*-tests and Chi-square tests, respectively. Differences were considered statistically significant if $P < 0.05$.

Development of Propensity Score. One difficulty in using observational data is that there may be different distributions of confounding variables between treatment and control groups. Propensity score analysis with inverse probability weighting (IPW) is a method that can help address imbalances between treat-

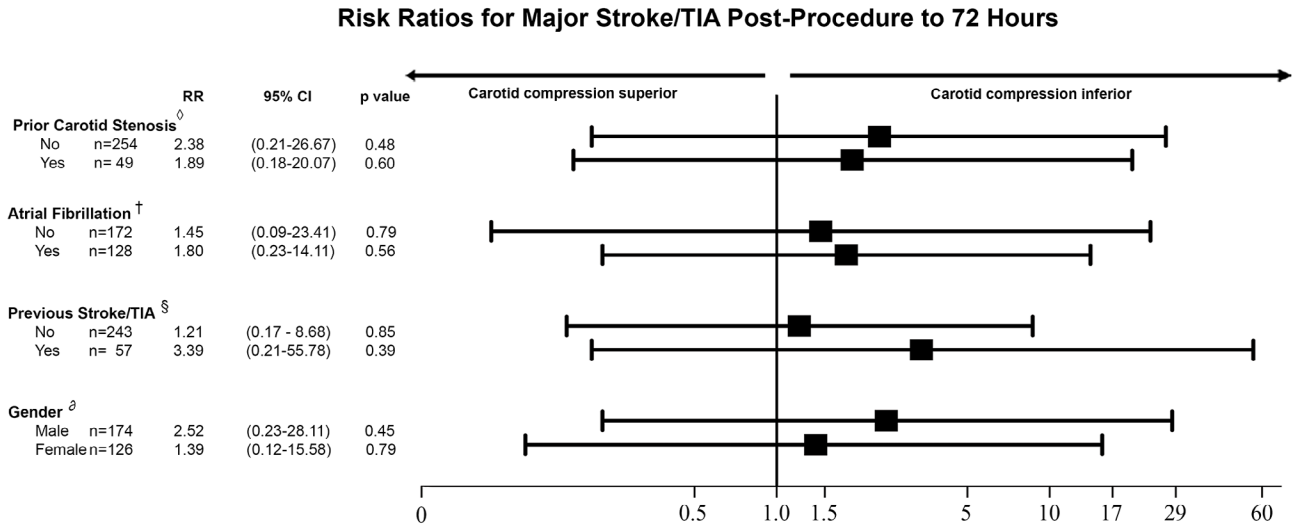

Figure 1. Effects of carotid compression major stroke/TIA post-procedure to 72 hours in subgroups. Carotid compression was shown to be neither superior nor inferior to no carotid compression with regard to combined risk of major stroke or TIA between procedure and 72 hours in subgroups known to have higher risk for stroke or TIA. Due to the low number of overall stroke and TIA events in the population studied, analysis could only be performed on the above subgroups.

◊ Interaction between prior carotid stenosis and carotid compression. p=0.34
† Interaction between atrial fibrillation and carotid compression. p=0.24
§ Interaction between previous stroke/TIA and carotid compression. p=0.38
∂ Interaction between gender and carotid compression. p=0.85

ment and control groups when there is a likelihood of potential selection bias due to nonrandom treatment assignment [20]. As matching is not employed with IPW, this method has the benefit of balancing propensity scores without needing to drop any patients for whom suitable matches cannot be found. A propensity score is the conditional probability of receiving a treatment based on observed potential confounding variables. In this study, the propensity score represents a patient's probability of receiving carotid compression or no carotid compression as a function of baseline and procedural characteristics.

Several covariates that have been linked to the risk of stroke post-TAVR were included in the propensity score model, including new onset of atrial fibrillation, gender, and chronic kidney disease [21]. An initial propensity score model was estimated using 27 variables described in Tables 1 and 2. To estimate propensity scores, logistic regression models were used in which treatment status was regressed on the baseline characteristics listed in Tables 1 and 2. Continuous baseline variables were linearly related to the log-odds of receipt of carotid compression in the initial specification of the propensity score model. Prior research on variable selection for propensity scores suggests that it is desirable to include variables that affect the outcome [22], therefore variables that appeared to impact the outcome were included in the initial propensity score model. Due to our smaller sample size, we chose to remove irrelevant covariates to avoid introducing "noise" into the treatment effect estimates [22]. Propensity scores were modeled as a function of age, pre-procedure hypertension, pre-procedure atrial fibrillation, previous aortic valve procedure, NYHA classification, anticoagulation medication within 24 hours before the TAVR procedure, TAVR procedure time, and pre-procedure aortic valve annulus size. After a propensity score was calculated for each subject, we evaluated the overlap in the range of propensity scores between groups as well as the balance (i.e., distributions) across groups. Although there is no standard guideline for how much imbalance is acceptable, standardized differences for covariates ranging up to 0.25 are acceptable [23]. Balance was achieved with our covariates across groups (Table 3).

Table 3. Covariate balance across control and treatment groups after weighting on the propensity score.

Covariate	No Carotid Compression (standardized mean)	Carotid Compression (standardized mean)	Standardized Difference (%)
Age	80.96	80.29	8.5
Female	0.45	0.45	0.0
Hypertension	0.94	0.93	3.8
Atrial fibrillation - pre-procedure	0.44	0.48	-9.6
COPD	0.31	0.29	5.3
Baseline EF (<30%)	0.05	0.03	11.4
BMI	28.74	28.19	7.9
Chronic Kidney Disease	0.54	0.53	2.5
Prior aortic valve procedure	0.14	0.08	19.9
Anticoagulants pre-procedure	0.40	0.46	-13.3
Procedure time	131.27	133.77	-4.0
Annulus size	22.80	22.65	5.8
Atrial fibrillation – new, post-procedure	0.02	0.00	10.0

Data Analysis. Adjusted risk ratios for post-procedure and late stroke were estimated with 95% confidence intervals (CIs) using a Poisson regression model. All statistical analyses were performed with STATA software (Stata Statistical Software: Release 14, StataCorp, College Station, Texas, USA).

Results

Patient Demographic and Procedural Characteristics

A total of 306 TAVR patients from three high-volume TAVR centers were included in the study. Group I consisted of 188 patients, and Group II consisted of 118 patients. There were 118 patients (38.6%) from the University of Utah, 142 (46.4%) from the University of Washington, and 46 (15.0%) from Banner Health Center. Patient demographic characteristics are shown in Table 1. Mean age was 82.5 ± 8.2 years in Group I and 78.5 ± 7.6 years in Group II. There were more males in both Group I and II (54.3% and 63.6%, respectively). Procedural characteristics are shown in Table 2. The average length of stay was 5.8 ± 4.6 days in Group I and 5.1 ± 3.8 days in Group II.

Unadjusted Results

Before propensity adjustment, post-procedure CVAs were observed in 1.6% of patients in Group I and 2.5% of patients in Group II, with a risk ratio (RR) of 1.59 (95% CI, 0.33–7.78, $P = 0.57$). Late CVA rates were 2.7% in Group I and 2.5% in Group II, with a RR of 0.96 (CI 95%, 0.23–3.94, $P = 0.95$).

Adjusted Results

After propensity adjustment, post-procedure CVAs were observed in 1.1% of patients in Group I and 1.9% of patients in Group II, with a RR of 1.77 (95% CI, 0.34–9.39, $P = 0.50$). Late CVA rates were 2.3% for Group I and 1.6% for Group II, with a RR of 0.72 (95% CI, 0.16–3.18, $P = 0.67$).

Subgroup Analysis

We evaluated the association between specific clinical characteristics and carotid compression with regard to disabling stroke and TIA risk after the procedure. Due to the small number of events, subgroup analysis could be completed only for the following baseline characteristics: carotid stenosis, atrial fibrillation, previous stroke or TIA, and gender. There were no changes in risk of disabling stroke at discharge among analyzed subgroups (Figure 1).

Discussion

We found that patients who received or did not receive carotid compression during TAVR exhibited no significant difference in risk of disabling stroke after the procedure. While the data do not show any benefit in the use of carotid compression, they also do not show evidence of harm associated with carotid compression. It is possible that carotid compression may limit microemboli. The clinical significance, of any, of microemboli detected by transcranial Doppler that do not manifest in overt TIA or stroke is still unknown [24].

TAVR is the gold standard therapy for inoperable patients with symptomatic severe AS [1, 3]. Recently, TAVR has been indicated for intermediate risk patients [2]. The use of TAVR in a wider range of patient populations has paralleled improvements in valve technology aimed at reducing the risk of complications such as vascular injury and stroke [25]. The 30-day stroke rate in the PARTNER 1A trial was significantly higher among patients in the TAVR group than among patients in the medical therapy group (6.7% vs. 1.7%, $P = 0.04$) or the SAVR group (5.5% vs. 2.4%, $P = 0.04$) [1, 3]. In the PARTNER 1A trial, 38% of strokes occurred within 2 days and 58% within 30 days in patients undergoing TAVR. Risk factors for stroke in the PARTNER 1A trial were use of TAVR and small native aortic valve area [9]. The risk of post-TAVR stroke in other studies ranged between 1.7% and 8.4% [7, 26, 27]. This wide difference in reported stroke rate in the literature is likely secondary to inconsistencies in the definitions of acute neurological events. However, a systematic review of the literature shows that stroke rates have declined over the last decade as delivery systems have become smaller, the systematic use of heparin has increased, and technical experience has improved [7, 25, 28].

The mechanism of stroke in TAVR is multifactorial but largely thought to be secondary to embolization. This may be in part due to liberation of calcific material during valve implantation. Other factors contributing to the development of stroke are manipulation of wires and catheters at the level of the aortic arch and root during the transfemoral approach and manipulation of the apex during the transapical approach [29]. Although studies have implicated embolization during the procedure as a potential cause of stroke [30], and bilateral carotid disease is a predictive factor for post-procedure stroke [12], the main source of emboli remains unclear. Clinically silent emboli to the brain have been detected in the majority of patients after TAVR [14, 16, 24, 31]. Several studies have used transcranial Doppler to identify high-intensity transient signal (HITS) as a surrogate for microembolization. Procedural HITS was identified in all patients, with the highest HITS detected for the transfemoral approach with the self-expanding Medtronic Core Valve, mainly during implantation [14, 29, 30]. In our study, neuroimaging testing was not used to determine the impact of carotid compression on the burden of asymptomatic microembolization. The valve design did not seem to alter the risk of stroke after TAVR. The FRANCE 2 Registry showed no statistically significant difference between the balloon-expanding Edwards SAPIEN valve and the self-expanding Core Valve in terms of stroke outcome [32].

The use of carotid compression to influence cerebral embolization during cardiac procedures is controversial, with little published data in support of this practice. Asahi et al. [33] used magnetic resonance angiography to examine the effects of unilateral carotid compression on cerebral flow patterns in two human volunteers. They demonstrated clear changes in perfusion patterns and flow directions within the cerebral vasculature that recovered with decompression. Hillebrand et al. [18] studied 20 patients undergoing a variety of open cardiac surgeries and performed transcranial Doppler of the middle cerebral artery. They found that digital carotid compression reduced the incidence of cerebral emboli during aortic cannulation and declamping. The lack of efficacy of carotid compression during TAVR in the present study may be explained by the fact that microemboli occur during every step of TAVR, not just during valve deployment, as shown by TCD monitoring [14], although there is clearly a peak during valve positioning and deployment. In addition, there is no consensus on the timing and level of pressure that should be applied to potentially prevent stroke.

Another approach to preventing stroke after TAVR is the use of embolic protection devices. There is evidence to suggest that the use of embolic protection devices is associated with a smaller volume of silent ischemic lesions and a smaller total volume of lesions, but there is no related decrease in clinically relevant strokes [34] and no significant change in neurocognitive function [15, 16, 24].

Although the specific causes of ischemic stroke in TAVR patients have yet to be fully identified, several factors may increase a patient's risk of post-procedure stroke, including chronic kidney disease, new onset atrial fibrillation [11, 21], post-deployment balloon dilation, and pure aortic stenosis without regurgitation [26]. Because stroke increases a patient's risk for mortality [35] and can negatively impact quality of life for patients and their families [36], and there is evidence

that early treatment of ischemic stroke results in better patient outcomes [37], it might be worthwhile to consider post-procedure treatment plans specifically designed for patients determined to be at a higher risk of post-procedure stroke.

Some limitations of this study must be considered. This study is a retrospective analysis of a relatively small number of patients. Although this is a multi-center study, carotid compression was performed at only one of the three study sites, and the overall number of outcome events was small. The study did not involve neuroimaging testing to verify the impact of carotid compression on the burden of clinically silent emboli. Larger cohort trials are needed to validate the results of this study.

In conclusion, stroke prevention by means of the non-invasive technique of using carotid compression during TAVR may not impact the incidence of TIA or disabling stroke after TAVR. Further research into the relationship between carotid disease and post-procedure stroke in TAVR patients is warranted.

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Conflict of Interest

The authors have no conflict of interest relevant to this publication.

Comment on this Article or Ask a Question

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