JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 3, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.05.025

ORIGINAL INVESTIGATIONS

The Incidence and Predictors of Early- and Mid-Term Clinically Relevant Neurological Events After Transcatheter Aortic Valve Replacement in Real-World Patients

Johan Bosmans, MD, PhD,* Sabine Bleiziffer, MD,† Ulrich Gerckens, MD,‡ Peter Wenaweser, MD,§ Stephen Brecker, MD,‖ Corrado Tamburino, MD, PhD,¶ Axel Linke, MD,# for the ADVANCE Study Investigators

ABSTRACT

BACKGROUND Transcatheter aortic valve replacement (TAVR) enables treatment of high-risk patients with symptomatic aortic stenosis without open-heart surgery; however, the benefits are mitigated by the potential for neurological events.

OBJECTIVES This study sought to determine the timing and causes of clinically relevant neurological events after self-expandable TAVR.

METHODS We enrolled 1,015 patients, of whom 996 underwent TAVR with a self-expandable system at 44 TAVR-experienced centers in Europe, Colombia, and Israel. Neurological events were evaluated for 3 distinct time periods: periprocedural (0 to 1 days post TAVR); early (2 to 30 days); and late (31 to 730 days). In this real-world study, neurological events were first referred to the site neurologist and then reviewed by an independent neurologist.

RESULTS The overall stroke rate was 1.4% through the first day post-procedure, 3.0% at 30 days, and 5.6% at 2 years. There were no significant predictors of periprocedural stroke or stroke/transient ischemic attack (TIA) combined. Significant predictors of early stroke were acute kidney injury ($p = 0.03$), major vascular complication ($p = 0.04$), and female sex ($p = 0.04$). For stroke/TIA combined, prior atrial fibrillation ($p = 0.03$) and major vascular complication ($p = 0.009$) were predictive. Coronary artery bypass graft surgery was the only significant predictor of late stroke ($p = 0.007$) or late stroke/TIA ($p = 0.06$).

CONCLUSIONS Treatment of high-risk patients with aortic stenosis using a self-expandable system was associated with a low stroke rate at short- and long-term follow-up. Multivariable predictors of clinically relevant neurological events differed on the basis of the timing after TAVR. (CoreValve Advance International Post Market Study; NCT01074658) (J Am Coll Cardiol 2015;66:209–17) © 2015 by the American College of Cardiology Foundation.

From the *Antwerp University Hospital, Edegem, Belgium; †German Heart Center, Technical University Munich, Munich, Germany; ‡Gemeinschaftskrankenhaus, Bonn, Germany; §Bern University Hospital, Bern, Switzerland; ‖St. George's Hospital, London, United Kingdom; ¶Ferrarotto Hospital, University of Catania, Catania, Italy; and the #University of Leipzig Heart Center, Leipzig, Germany. Medtronic, Inc., sponsored and funded the CoreValve ADVANCE Study, including support of on site data collection, the independent Clinical Events Committee, and statistical analyses performed by NAMSA; and funded the core laboratory that reviewed ECGs and procedural angiograms. Dr. Bosmans has served as a proctor for Medtronic. Dr. Bleiziffer has served as a consultant to Medtronic; a proctor for Medtronic and JenaValve; and has received travel expenses from Edwards

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CABG = coronary artery bypass grafting

ECG = electrocardiogram

SAVR = surgical aortic valve replacement

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

TIA = transient ischemic attack

VARC = Valve Academic Research Consortium

Aortic valve stenosis is the most common acquired valvular heart disorder in the elderly. Despite advances in cardiac surgery and low mortality rates after surgical aortic valve replacement (SAVR), up to one-third of patients with symptomatic aortic stenosis are not considered for SAVR, often due to frailty or comorbidities (1).

Transcatheter aortic valve replacement (TAVR) enables treatment of aortic stenosis without open-heart surgery. Recently, TAVR using the balloon-expandable Sapien valve (Edwards Lifesciences, Irvine, California) or the self-expanding CoreValve bioprosthesis (Medtronic, Inc., Minneapolis, Minnesota) has been shown to be superior to standard medical therapy for inoperable patients and to be at least noninferior to SAVR in high-risk patients with severe symptomatic aortic stenosis (2–5).

SEE PAGE 218

The benefits associated with the application of TAVR, however, are mitigated by the potential of major, disabling stroke with associated increased mortality and early reduced quality of life (6). Despite rapid adoption of this technology into clinical practice, reports from recent randomized controlled clinical trials have raised safety concerns regarding an increased risk of neurological events with TAVR compared to both medical treatment and conventional SAVR. In patients undergoing TAVR with the Sapien valve from the PARTNER (Placement of Aortic Transcatheter Valves) trials, 30-day rates of stroke or transient ischemic attack (TIA) of 6.7% for inoperable patients and 5.5% in patients deemed at high risk were reported (7,8). These same studies reported 30-day rates of stroke or TIA of 1.7% with medical management alone and 2.4% with SAVR. In the randomized CoreValve US Pivotal High Risk Trial, the rate of any stroke was numerically higher in the surgical group than in the TAVR group (6.2% vs. 4.9%) at 30 days (4). However, for an already rapidly expanding treatment modality, data coming from carefully monitored, very large "real-world" patient cohorts are still relatively scarce and complementary to randomized trial data. The CoreValve ADVANCE Study was designed to evaluate clinical outcomes, including stroke and TIA, in real-life patients at experienced implanting centers (excluding possible "learning curve" influences). All adverse event adjudication occurred by an independent Clinical Events Committee according to the original definitions of the Valve Academic Research Consortium (VARC-1) (9).

The aim of this specific analysis was to characterize the incidence, timing, type, and predictors of *clinically relevant* neurological events in "real-life" self-expandable system TAVR patients out to 2 years after the procedure.

METHODS

The ADVANCE study methods, procedures, and a detailed description of the study device (CoreValve Transcatheter Aortic Valve, Medtronic, Inc., Minneapolis, Minnesota) have been previously described (5). In brief, ADVANCE is a prospective, multicenter, fully monitored, nonrandomized study that included 44 sites in 12 countries in Europe, Israel, and Colombia. Each investigational site was required to have performed at least 40 TAVR procedures to be considered. A heart team, comprising at least 1 TAVR-experienced interventional cardiologist and 1 cardiothoracic surgeon, determined the surgical risk status and study eligibility of each patient.

The aim of the ADVANCE study was to evaluate clinical outcomes after treatment with a self-expandable system in real-world practice. Therefore the exclusion criteria were limited to patients participating in another trial that would interfere with routine practice and patients who were unwilling or unable to provide written informed consent.

STUDY PROCEDURES AND DEFINITIONS. We sought to determine if the timing of the first neurological

Lifesciences, Medtronic, and Johnson & Johnson. Dr. Gerckens has received consulting and lecture fees as well as study related travel expenses from Medtronic and Edwards Lifesciences; and has served as a proctor for Medtronic and Boston Scientific. Dr. Wenaweser has received consulting fees from Medtronic and Edwards Lifesciences; remuneration for study related travel and for developing education materials from Medtronic; and lecture and proctoring fees as well as travel support from Edwards Life sciences, Boston Scientific, Biotronik, and Cordis. Dr. Brecker has served as a consultant for Medtronic, St. Jude Medical, and Boston Scientific. Dr. Linke has served as a consultant for Medtronic and Bard Vasc, Inc.; has received grant support from Medtronic; has served as a proctor for and received lecture fees from Medtronic, Edwards Lifesciences, and St. Jude Medical; has received lecture fees from Boston Scientific; owns stock options in Claret Medical Inc.; and has received study related travel expenses and lecture fees from Medtronic, St. Jude Medical, and Biosensors. Dr. Tamburino has reported that he has no re lationships relevant to the contents of this paper to disclose.
Listen to this manuscript's audio summary by *JACC* Editor in Chief Dr. Valentin Fuster.

Manuscript received January 20, 2015; revised manuscript received April 1, 2015, accepted May 7, 2015.

event after TAVR was related to unique or competing causes by evaluating the incidence and predictors of stroke, and the composite of stroke and TIA, at 3 distinct time intervals: periprocedural (0 to 1 day post-TAVR); early (2 to 30 days); and late (31 to 730 days). We also evaluated the effect of stroke after TAVR on survival through 2 years.

The implanting physician chose the methods used to evaluate the size of the access vessels and aortic annulus. In this study, a self-expandable system was implanted via an 18-F delivery catheter, and 26 mm and 29 mm valve sizes were implanted to treat native aortic valve annuli of 20 to 27 mm in diameter. Procedural decisions, such as access site, anesthesia type, and, if needed, maneuvers performed after valve placement, such as post-TAVR balloon dilation, were left to the discretion of the heart team and primary operator. Patients received heparin during the procedure and dual antiplatelet therapy (aspirin and clopidogrel) was recommended for 6 months postoperatively. Warfarin anticoagulation and the duration of antiplatelet therapy were left to the discretion of the local physicians and local hospital-based standard protocols.

In the case of a suspected neurological event (stroke/TIA) on the basis of clinical evaluation of the local heart team, a systematic consultation of an on-site neurologist was performed. Finally, these events were then systematically reviewed by an independent neurologist to provide detailed, additional documentation for the Clinical Event Committee to be able to adjudicate the events. Major and minor strokes, as well as TIA, were defined according to VARC-1 (9). Stroke was defined as a rapid onset of a focal or global neurological deficit with change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke and confirmed by a neurology specialist as well as neuroimaging. TIA was defined as a new focal neurological deficit as indicated above with rapid symptom resolution within 24 h in the absence of cerebral tissue injury as evidenced by neuroimaging.

The Clinical Events Committee used the neurologist's assessment, along with any other patient source data, to adjudicate the events.

The definition of prior atrial fibrillation (AF) was based on medical history from the case report form, site-reported electrocardiograms (ECG), and core lab-analyzed ECGs available prior to the start of the given window (i.e., only considered medical history and baseline ECGs for the 0- to 1-day window; considered medical history, baseline, post-procedure, and discharge ECGs for the 2- to 30-day window; and considered medical history, baseline, post-procedure, discharge, and 1-month ECGs for the 31- to 730-day window). The database does not provide adequate information regarding whether AF was paroxysmal, permanent, or persistent.

STATISTICAL ANALYSIS. We report categorical variables as n and % and continuous variables as mean ± SD. Characteristics were compared between groups using Student *t* tests for continuous variables and chi-square or Fisher exact tests, where appropriate, for categorical variables. Freedom-from-mortality curves were generated by the Kaplan-Meier method and comparisons between groups were calculated using the log-rank test. For Kaplan-Meier curves, time zero is defined as the date of the procedure. For patients without an event, the date of censoring was the latest date of all follow-up visits (including study exit) and events (including death). Hazard ratios, 95% confidence intervals (CIs), and p values are presented for univariable and multivariable predictor analyses on the basis of proportional hazards models.

For the predictor analysis, we identified potential predictors on the basis of clinical judgment for each of the 3 time intervals. Only the first event per patient was evaluated. The number at risk at the beginning of each time period is the number of patients free from a neurological event at the start of the time period and who had follow-up data available. Therefore, patients with an event in an earlier time period are excluded from the risk set in later time periods. For the procedural time interval, we included patient baseline characteristics and medical history in the list of potential predictors. For the early time interval, in addition to the baseline and history variables, we added procedural characteristics (e.g., anesthesia route, procedure duration), procedural complications, and any adverse event that occurred during or after the TAVR procedure but before the neurological event. Last, for the late time interval we included baseline characteristics, medical history, and prior adverse events, but excluded those considered related to the procedure. We only included the first neurological event per patient.

In the selection process of potential predictors, we also excluded rare characteristics or events that occurred in ≤5% of the total risk set for a given time interval. Statistically significant variables with a p value <0.20 from the univariable analyses were included in stepwise selection to determine the final multivariable model. Procedural complications and adverse events were included as time-dependent covariates. The final multivariable model included any predictors with a p value <0.10. All analyses were

performed using SAS version 9.3 software (SAS Institute Inc., Cary, North Carolina).

RESULTS

From March 2010 through July 2011, 1,015 patients were enrolled in the ADVANCE study, of whom 996 had an attempted implant with the self-expandable system. Mean age was 81.1 ± 6.4 years, 51% were female, 79.6% of patients had New York Heart Association functional class III or IV symptoms, and 13.1% had cerebrovascular disease at baseline.

The overall rate of stroke was 1.4% through the first day post-procedure, 3.0% at 30 days, and 5.6% at 2 years; with major stroke rates of 0.5%, 1.2%, and 2.9% for the same time periods, respectively.

No statistically significant differences were found between the patients who developed a stroke or a stroke/TIA and patients who did not develop a periprocedural neurological event (all p >0.05). Online Tables 1 and 2 summarize baseline characteristics for patients with and without a stroke and those with and without stroke/TIA in the immediate post-procedural period (0 to 1 days post-TAVR), along with the univariable proportional hazard models results.

Patients with early stroke were more often female (81.3% vs. 49.8%; p 0.02), had higher Society of Thoracic Surgeons (STS) scores (8.7 ± 4.8% vs. 6.3 ± 4.3%; p 0.04), and more frequently had a major vascular complication (31.3% vs. 11.1%; p 0.01) after TAVR. Patients with early stroke/TIA had similar differences: STS score (8.5 ± 4.7% vs. 6.3 ± 4.4%; p 0.04) and major vascular complication (29.4% vs. 11.0%; p 0.02). Baseline and procedural characteristics are summarized for patients with and without an early (2 to 30 days post-TAVR) stroke or stroke/TIA, and univariable proportional hazards models results are shown in Online Tables 3 and 4.

Patients with late stroke more frequently had prior coronary artery bypass grafting (CABG) (47.6% vs. 21.0%; p 0.003), which was also true for patients with a late stroke/TIA (35.3% vs. 21.0%; p 0.047). Summaries by group and univariable proportional hazards models results are shown in Online Tables 5 and 6.

CLINICALLY RELEVANT NEUROLOGICAL EVENTS. Figure 1 shows Kaplan-Meier freedom from major and minor stroke, and TIA through 2 years. Overall, 14 patients had a stroke in the early periprocedural period, and 2 patients had a TIA. From 2 to 30 days post-procedure, an additional 16 patients experienced a stroke and 1 patient had a TIA. During the late post-procedural period, 21 patients had a stroke and an additional 13 patients had a TIA. At each time point, the majority of stroke events were ischemic in origin (Figure 2).

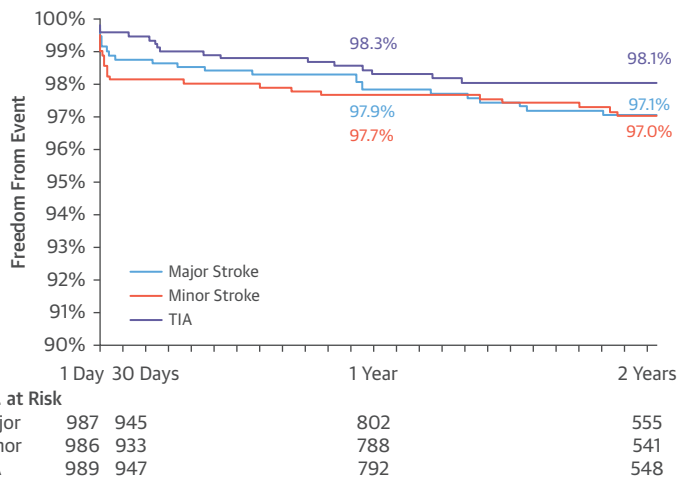
We also evaluated the effect of valve implant access route on stroke and stroke/TIA events in the early time period after TAVR. There were no significant differences in the rate of stroke or in the rate of stroke or TIA on the basis of access (Online Table 4).

Survival through 2 years for patients with and without a stroke, and for those with and without a stroke/TIA, within the first 30 days post-TAVR is shown in Figure 3.

PREDICTORS OF STROKE OR STROKE/TIA. None of the univariable predictors examined (Online Table 1) met the alpha level criterion of <0.20 to be considered for the multivariable predictor analysis for periprocedural stroke. The predictors of early and late stroke are reported in Table 1. In the multivariable model, besides female sex, the occurrence of acute kidney injury and major vascular complication were identified as significant independent predictors of early stroke. Prior CABG was the only significant independent predictor of late stroke.

We also did not identify any multivariable predictors of periprocedural stroke/TIA events combined on the basis of our model selection criteria. The predictors of early and late stroke or TIA are reported in Table 2. In the multivariable model, prior AF and major vascular complication were identified as significant independent predictors of early stroke/TIA. Prior CABG was also a significant independent predictor of late stroke/TIA.

FIGURE 1 Freedom From Stroke and TIA



As these Kaplan Meier curves demonstrate, incidence of any type of neurological event was low through 2 years in the ADVANCE study. TIA transient ischemic attack.

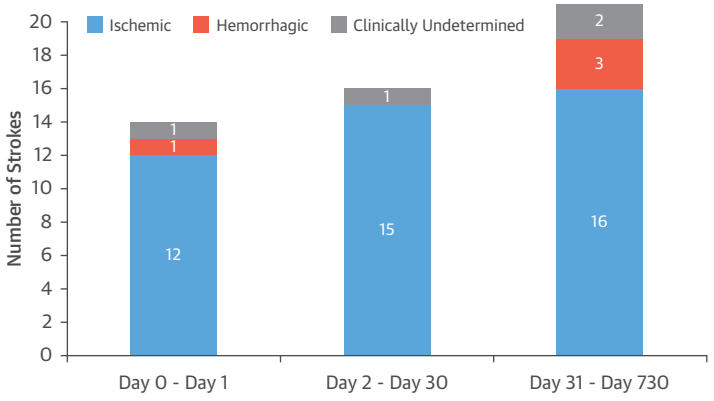
DISCUSSION

The CoreValve ADVANCE study, the largest, multicenter, prospective, fully monitored, VARC-reported "real-world" CoreValve study, has already reported improvement in aortic valve function and quality of life with low mortality rates at 1 and 12 months after TAVR (5). In our analyses, the incidence of stroke or stroke/TIA during the immediate periprocedural time period, as well as within 1 month or through 2 years after valve replacement, all proved to be relatively low, taking into account the age and risk profile of this high-risk patient cohort. However, we found that the occurrence of a clinically relevant neurological event within the first month post-procedure significantly affected long-term survival, highlighting the importance of these types of analyses to uncover clinically meaningful predictors that can aid in patient selection for TAVR.

Of the neurological events that occurred within the first month after TAVR, only one-half occurred in the periprocedural time period (days 0 to 1), with the remainder documented on days 2 to 30 post-procedure. Most strokes, regardless of the time since the procedure, were ischemic and only rarely hemorrhagic (**Figure 2**). We were not able to identify any predictors of periprocedural stroke. For the early time period (days 2 to 30), acute kidney injury, female sex, and major vascular complication predicted stroke. When considering stroke and TIA together, history of AF and major vascular complication were significant predictors (**Central Illustration**). History of CABG was the only predictor of late neurological events.

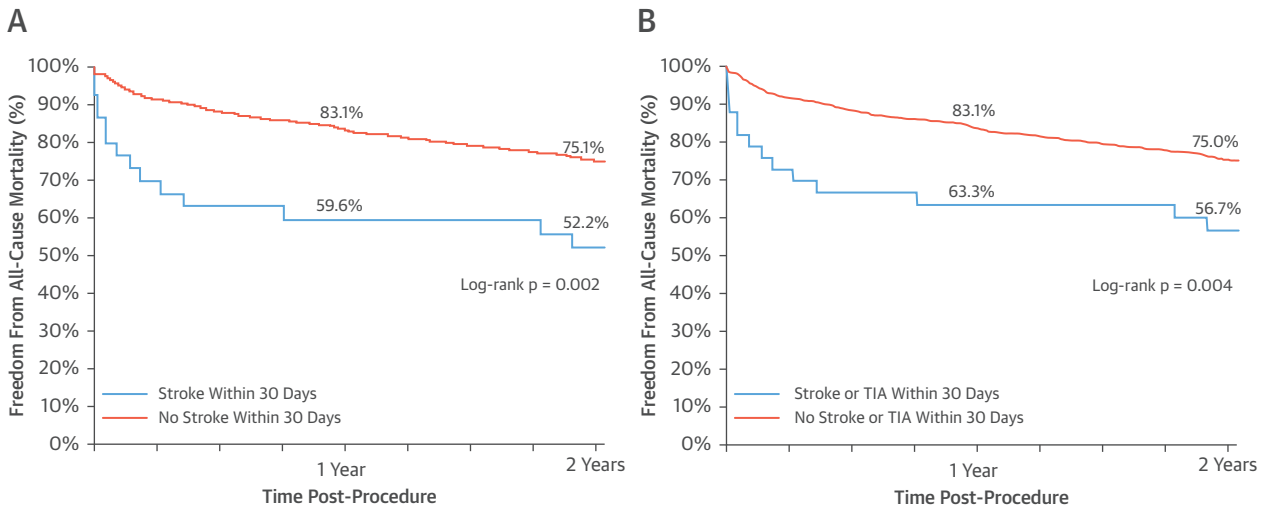
In the ADVANCE study, the incidence of stroke after (mostly transfemoral) TAVR, even in "real-world" patients, was lower compared to the relatively recently published stroke data from both the PARTNER and CoreValve US Pivotal trials (2–4). In the PARTNER trial, the rate of neurological events in high-risk patients treated transfemorally was 3 times higher after TAVR than after SAVR: 4.6% versus 1.4%

FIGURE 2 Type of Stroke Over Time



The majority of stroke events were classified as ischemic at each time point.

FIGURE 3 Survival on the Basis of Neurological Event Status



These Kaplan Meier curves illustrate 2 year survival for patients with and without a stroke event **(A)** or a stroke/transient ischemic attack (TIA) event **(B)** within the first 30 days after transcatheter aortic valve replacement (TAVR). Patients who did not experience a stroke or TIA within the first 30 days post TAVR had significantly better survival through 2 years.

TABLE 1 Predictors of Early and Late Stroke After TAVR*

	Event	No Event	Univariable Analysis† HR	95% CI	p Value	Multivariable‡ HR	95% CI	p Value
Predictors of early (2 30 days) stroke post TAVR (event, n 16; no event, n 959)								
Male (vs. female)	18.8 (3/16)	50.2 (481/959)	0.23	0.07 0.82	0.023	0.26	0.07 0.92	0.037
STS mortality, %§	8.7 ± 4.8 (16)	6.3 ± 4.3 (958)	1.62	0.82 3.22	0.129			
STS mortality <4% (vs. 4% 10%)	6.3 (1/16)	31.1 (298/958)	0.17	0.02 1.28	0.085			
STS mortality 4% 10% (vs. >10%)	68.8 (11/16)	56.3 (539/958)	0.63	0.20 1.98	0.631			
STS mortality >10% (vs. <4%)	25.0 (4/16)	12.6 (121/958)	9.60	1.07 85.85	0.043			
Prior AF	56.3 (9/16)	37.2 (357/959)	2.18	0.81 5.85	0.122			
Prior CABG	6.3 (1/16)	21.5 (206/956)	0.25	0.03 1.86	0.174			
Acute kidney injury	18.8 (3/16)	7.4 (71/959)	5.04	1.43 17.77	0.012	4.32	1.19 15.64	0.026
Major vascular complication	31.3 (5/16)	11.1 (106/959)	4.47	1.55 12.85	0.006	3.12	1.04 9.31	0.042
Predictors of late (31 730 days) stroke post TAVR (event, n 21; no event, n 905)								
Age	78.7 ± 7.9 (21)	81.0 ± 6.4 (905)	0.96	0.90 1.01	0.137			
Prior CABG	47.6 (10/21)	21.0 (189/902)	3.26	1.38 7.67	0.007	3.26	1.38 7.67	0.007
Acute kidney injury	14.3 (3/21)	6.7 (61/905)	3.61	1.06 12.26	0.040			

Values are % (n/N) or mean ± SD (n). *For the very early time period of days 0 to 1 post-transcatheter aortic valve replacement (TAVR), no predictors of stroke were found. †An alpha level of 0.20 was used to select univariable predictors. ‡Hazard ratios and p values are adjusted for the other covariates in the final model. §The p value is from Type III tests for comparisons across categorical groups.

AF atrial fibrillation; CABG coronary artery bypass grafting; CI confidence interval; HR hazard ratio; STS Society of Thoracic Surgeons.

at 30 days and 6.1% versus 1.9% at 1 year (10). However, the patients in the ADVANCE real-world study were at lower risk (as expressed by lower mean STS score) than in either PARTNER trial, with a lower incidence of pre-existing cerebrovascular disease. Also, the relatively good survival, even in the patient cohort that sustained a neurological complication (**Figure 3**), compared to that in the PARTNER studies, may reflect the fact that ADVANCE patients were less sick, frail, or debilitated. Moreover, in ADVANCE, all patients were treated in relative high-volume TAVR sites. In the CoreValve US Pivotal High Risk trial, which included somewhat higher-risk patients treated at less experienced TAVR sites, the cumulative frequency of all strokes at 1 year was 8.8% compared to 12.6% in the surgical group (4). Yet in the CoreValve US trial at least all patients had a National Institutes of Health stroke status assessment before and after the procedure and any change triggered a neurological evaluation and imaging. This also may contribute to the higher rate seen compared with ADVANCE.

The SOURCE XT Registry, which enrolled "real-world" patients treated with the Sapien XT transcatheter valve (Edwards Lifesciences) at about the same time as the ADVANCE study, recently reported

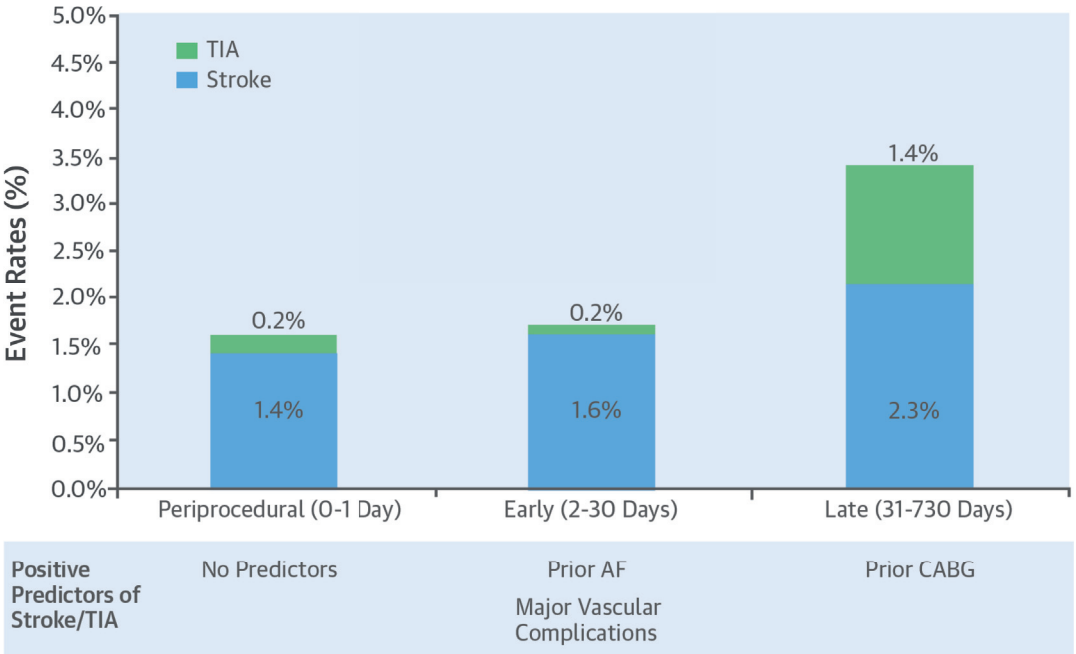
TABLE 2 Predictors of Early and Late Stroke or TIA After TAVR

	Event	No Event	Univariable Analysis* HR	95% CI	p Value	Multivariable† HR	95% CI	p Value
Predictors of early (2 30 days) stroke or TIA post TAVR (event, n 17; no event, n 956)								
Male (vs. female)	29.4 (5/17)	50.1 (479/956)	0.42	0.15 1.20	0.105			
STS mortality (%)‡	8.5 ± 4.7 (17)	6.3 ± 4.4 (955)			0.129			
STS mortality <4% (vs. 4% 10%)	5.9 (1/17)	31.1 (297/955)	0.15	0.02 1.17	0.070			
STS mortality 4% 10% (vs. >10%)	70.6 (12/17)	56.2 (537/955)	0.69	0.22 2.14	0.521			
STS mortality >10% (vs. <4%)	23.5 (4/17)	12.7 (121/955)	9.56	1.07 85.55	0.043			
Prior AF	64.7 (11/17)	37.1 (355/956)	3.11	1.15 8.40	0.026	3.02	1.12 8.17	0.030
Acute kidney injury	17.6 (3/17)	7.4 (71/956)	5.16	1.47 18.13	0.011			
Bleeding event	41.2 (7/17)	32.8 (314/956)	1.99	0.76 5.24	0.162			
Major vascular complication	29.4 (5/17)	11.0 (105/956)	4.15	1.46 11.77	0.008	3.99	1.41 11.34	0.009
Predictors of late (31 730 days) stroke or TIA post TAVR (event, n 34; no event, n 889)								
Prior CABG	35.3 (12/34)	21.0 (186/886)	1.96	0.97 3.95	0.062	1.96	0.97 3.95	0.062
Major bleed	2.9 (1/34)	12.3 (109/889)	0.27	0.04 1.95	0.193			

Values are % (n/N) or mean ± SD (n). *An alpha level of 0.20 was used to select univariable predictors. †Hazard ratios and p values are adjusted for the other covariates in the final model. ‡p value is from Type III tests for comparisons across the categorical groups.

TIA transient ischemic attack; other abbreviations as in **Table 1**.

CENTRAL ILLUSTRATION **Timing, Number, and Predictors of Clinically Relevant Stroke/TIA**



Bosmans, J. et al. J Am Coll Cardiol. 2015; 66(3):209-17.

Approximately the same number of neurological events occurred within the periprocedural time period (days 0 to 1) as did during the remainder of the first month after transcatheter aortic valve replacement (TAVR). Unsurprisingly, such events rose over the next 2 years post TAVR. History of atrial fibrillation (AF) and major vascular complication were significant predictors of early neurological events, and a history of coronary artery bypass graft surgery (CABG) was a significant predictor of late neurological events. Percentages represent the number of patients with an event out of the number at risk at the beginning of the time interval. These are simple proportions and will not completely align with the Kaplan Meier rates, which censor patients and take into account events over time. TIA transient ischemic attack.

higher stroke rates through 2 years (11). These discrepancies are not easily explained by differences in patient risk profile given that the logistic EuroSCORE in ADVANCE was similar to the SOURCE XT Registry, although our study included fewer patients implanted via a noniliofemoral access route. The fact that ADVANCE and SOURCE XT were performed exclusively in high-volume TAVR sites excludes the effect of possible "learning-curve" influences, at least for these 2 studies, and standard clinical practice would have been similarly applied. Access route, delivery system size, and valve type as well as the criteria for stroke assessment varied among these studies and may have contributed alone or in combination to the differences in overall event rates.

MECHANISMS OF STROKE AFTER TAVR. Periprocedural stroke, accounting for about 30% of strokes after implantation, has a multifactorial etiology. In our analysis, no specific patient or procedure-related characteristics could be identified as a significant predictor for periprocedural stroke. However, most probably, catheter manipulations of the calcified and diseased aortic valve and aortic arch cause embolization of aortic debris or thrombotic material, resulting in stroke or TIA (12). Therefore, embolic protection devices currently under evaluation might offer potential benefit in reduction of at least some of TAVR-related neurological complications.

Remarkably, in ADVANCE, 50% of the strokes that occurred within the first 30 days after TAVR were recognized after the first 2-day periprocedural window. Also in the PARTNER trial TAVR-treated high-risk patients, 6 of the 18 neurologic events (TIA, minor or major stroke) that occurred within the first month presented after the 0- to 2-day window (10). These observations strongly suggest that other determinants, apart from procedural aspects, are significantly related to final neurological outcome. Indeed, female sex (most probably by smaller arterial vessel diameter and increased risk of vascular

complications), history of AF, acute kidney injury, or major vascular complication after TAVR (most likely due to prolonged hypotensive episodes) all significantly predicted early neurological events.

ADVANCE suggests that a history of AF may be an important risk factor for neurological events (stroke/TIA) early after TAVR. These results strongly suggest that, in order to reduce neurological complications after TAVR, anticoagulation therapy should be started immediately after diagnosis of the AF episode and continued for several months. No clear guidelines actually exist on anticoagulation therapy after short episodes of postoperative AF (13). However, patients undergoing TAVR are at high risk for thromboembolism in cases of atrial arrhythmia, and a more aggressive antithrombotic treatment should probably be implemented in these cases. Although dual antiplatelet therapy with aspirin and clopidogrel has been empirically recommended after TAVR, future randomized studies will have to evaluate the more appropriate antithrombotic treatment after these procedures and the potential role for systematic anticoagulant therapy either with warfarin or direct thrombin inhibitors in this setting.

The only significant predictor of late neurological events, occurring >1 month after TAVR, was a history of CABG, most likely reflecting more extensive or complex atherosclerotic disease. Also in the PARTNER trial TAVR-treated high-risk patients, the likelihood of late neurologic events was linked to patient-related factors. Late strokes after TAVR therefore seem to be mostly related to patient-dependent characteristics and not to valve- or procedure-related factors, at least through 2 years after implantation.

STUDY LIMITATIONS. The relatively low rate of cerebrovascular events, despite this large patient cohort, has to be considered when interpreting the results of the present study. The low number of events may result in difficulty identifying predictors and cause overfitting of the proportional hazards models. In this real-world study, a neurologist was consulted after a clinically relevant neurological event was first suspected by the local heart team—much as would occur in standard clinical practice—which could have also contributed to the low documented cerebrovascular event rate, especially compared to other large trials. It is possible that the comorbid condition of our study population might have diluted the impact of TAVR on stroke. In addition, the "real-life" nature of this study did not include close monitoring of patient compliance with anticoagulation and antiplatelet medications; therefore we were not able to determine any relationship with the timing or type of stroke events.

CONCLUSIONS

Multivariable analyses of time-related potential predictors were not able to identify any predictors of periprocedural neurological events. During the early post-procedural period, predictors of neurological events varied depending on whether stroke was considered alone or stroke and TIA were considered together. The only predictor of late events was a history of CABG, probably reflecting patient risk and not the TAVR procedure. The overall incidence of clinically relevant neurological events was low in the ADVANCE Study through 2 years after TAVR with the self-expandable system.

ACKNOWLEDGEMENTS Under the direction of Prof. Bosmans, Jane Moore, MS, ELS, an employee of the trial sponsor, drafted the study Methods, developed the tables and figures, and performed minor copy-editing. Stacia Kraus, MPH (NAMSA, Minneapolis, Minnesota), performed all statistical analyses for this report and ensured the accuracy of the data presented. Francesca Barbieri, MD, PhD; Rijk de Jong, MSc; and Maarten Hollander, MSc, from Medtronic Bakken Research Center (Maastricht, the Netherlands), were responsible for overall study management.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Johan Bosmans, Department of Cardiology, University Hospital Antwerp, Wilrijkstraat 10, 2650 Edegem, Belgium. E-mail: johan.bosmans@uza.be.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Although TAVR has become a standard management strategy for patients with symptomatic aortic valve stenosis facing a high risk of complications with SAVR, a history of atrial fibrillation or CABG identify patients with a higher risk of stroke during the month after TAVR with a self-expandable valve prosthesis at centers with experience performing ≥40 TAVR procedures.

TRANSLATIONAL OUTLOOK: Additional study is needed to evaluate the generalizability of these correlations to patients undergoing TAVR at less experienced centers requires, and large registry databases could be employed for this purpose as the technique becomes more widely employed.

REFERENCES

1. Iung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J 2005;26:2714–20.

2. Kodali SK, Williams MR, Smith CR, et al. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.

3. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012; 366:1696–704.

4. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic valve replacement with a self-expanding prosthesis. N Engl J Med 2014; 370:1790–8.

5. Linke A, Wenaweser P, Gerckens U, et al. Treatment of aortic stenosis with a self-expanding transcatheter valve: the International Multi-centre ADVANCE Study. Eur Heart J 2014;35:2672–84.

6. Walters DL, Mang GC, Platts DG, et al. Characterization of neurological injury in transcatheter aortic valve implantation. How clear is the picture? Circulation 2014;129:504–15.

7. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.

8. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364: 2187–98.

9. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011;57:253–69.

10. Miller DC, Blackstone EH, Mack MJ, et al. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. J Thorac Cardiovasc Surg 2012;143: 832–43.

11. Windecker S. Two-year outcomes from the SOURCE XT post approval registry. Paper presented at: Annual Meeting of EuroPCR; May 22, 2014; Paris, France.

12. Omran H, Schmidt H, Hackenbroch M, et al. Silent and apparent cerebral embolism after retrograde catheterisation of the aortic valve in valvular stenosis: a prospective, randomised study. Lancet 2003;361:1241–6.

13. Amat-Santos IJ, Rodés-Cabau J, Urena M, et al. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. J Am Coll Cardiol 2012;59:178–88.

KEY WORDS aortic stenosis, self-expanding transcatheter aortic valve, stroke, transient ischemic attack

APPENDIX For supplemental tables, please see the online version of this article.