BACKGROUND: Stroke remains one of the most devastating complications of transcatheter aortic valve implantation (TAVI). The aim of this study was to identify the incidence, timing, temporal trends, and predictors of stroke after TAVI and evaluate the outcomes of patients with stroke.

METHODS AND RESULTS: The CENTER-Collaboration is an international collaboration consisting of 3 national registries and 7 local registries or prospective clinical trials, selected through a systematic review. Accordingly, a total of 10,982 patients undergoing transfemoral TAVI between 2007 and 2018 were included in the current patient-level pooled analyses. A total of 261 patients (2.4%) experienced stroke during the first month after TAVI. The median time between TAVI and stroke was 1 day (interquartile range, 0–6 days). The stroke rate was comparable in procedures performed in the early years of TAVI (2007–2012) to those in the more recent years of TAVI (2013–2018; both 2.4%; P=1.0). Independent predictors of stroke at 30 days were a history of cerebrovascular events (odds ratio, 2.2; 95% CI, 1.4–3.6; P=0.0012) and a glomerular filtration rate of <30 mL/min per 1.73 m² (odds ratio, 1.7; 95% CI, 1.0–2.8; P=0.05). Stroke occurring within the first 30 days after TAVI was associated with a 6-fold increase of 30-day mortality (odds ratio, 6.0; 95% CI, 4.4–8.1; P<0.001). Moreover, patients with stroke more frequently had documented new-onset atrial fibrillation (16% versus 3%; P<0.001) and major or life-threatening bleedings (12% versus 7%; P=0.002) at 30-day follow-up.

CONCLUSIONS: In this large, global, patient-level analysis, the incidence of stroke after transfemoral TAVI was 2.4%. Prior cerebrovascular events and a low glomerular filtration rate independently predicted the occurrence of stroke after TAVI. The occurrence of stroke after TAVI was associated with a strikingly 6-fold increase of 30-day mortality; additionally, there was a 5-fold higher rate of new-onset atrial fibrillation in patients with stroke.


VISUAL OVERVIEW: A visual overview is available for this article.
WHAT IS KNOWN

• Stroke remains one of the most devastating complications of transcatheter aortic valve implantation.

WHAT THE STUDY ADDS

• The incidence of stroke after transfemoral transcatheter aortic valve implantation is 2.4% and did not reduce in recent years.
• Patients with prior cerebrovascular events or a low glomerular filtration rate have a higher risk of 30-day stroke.
• Stroke after transcatheter aortic valve implantation is associated with a 6-fold increase in 30-day mortality.
• Patients with stroke after transcatheter aortic valve implantation more frequently experience new-onset atrial fibrillation and major or life-threatening bleedings.

Transcatheter aortic valve implantation (TAVI) is a life-saving and minimally invasive treatment in patients with severe aortic valve stenosis. One and a half decade ago, TAVI was developed for inoperable patients; nevertheless, it’s indication has rapidly expanded from inoperable to intermediate-risk patients. Despite the increase in operator experience and the development of improved valve systems, stroke still remains one of the most detrimental complications of the TAVI procedure. Stroke in TAVI patients increases mortality but also decreases the patient’s quality of life and increases healthcare costs.

In randomized controlled trials, the incidence of stroke in patients undergoing TAVI was 6.7% in inoperable patients and 5.5% in intermediate-risk patients. However, there are limited data and uniformity regarding the incidence and temporal trends of stroke in real-world populations. Moreover, considering the expanding increase in TAVI procedures, it is of importance to identify patients at risk for periprocedural stroke. Currently, the evidence on patient and procedural risk factors is limited because it was mainly derived from meta-analyses and systematic reviews without patient-level data. Accordingly, we believe that a large study with patient-level pooled analysis was to determine the incidence, timing, temporal trend, and predictors of stroke in patients undergoing transfemoral TAVI and evaluate short-term outcomes of patients with stroke.

METHODS

Study Design and Patient Population

The CENTER trial (Cerebrovascular Events in Patients Undergoing Transcatheter Aortic Valve Implantation With Balloon-Expandable Valves Versus Self-Expandable Valves) is an international collaboration, including patients with severe aortic valve stenosis undergoing transfemoral TAVI with balloon-expandable valves from Edwards Lifesciences, Inc (Irvine, CA), or self-expandable valves from Medtronic, Inc (Minneapolis, MN). The CENTER trial is registered at https://www.clinicaltrials.gov (NCT03588247). Institutional review board approval was obtained, and all patients provided written informed consent for the procedure and data collection according to the policy of each participating hospital. The data will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because substudies are currently ongoing. Details on the study design, study eligibility inclusion criteria, systematic search, and data collection have been reported previously. In summary, the CENTER-Collaboration consists of 3 national registries, 2 multicenter registries, 4 single-center registries, and 1 prospective trial selected through a systematic online search on PubMed (flowchart of study selection and selected studies are included in Supplemental Materials 1 and 2 in the Data Supplement). Hence, the CENTER-Collaboration includes a global patient population with patients treated in the United States, Brazil, Israel, and several European countries. All collaborators provided a dedicated database with baseline patient characteristics, echocardiographic data, procedural information, and follow-up data. Accordingly, a total of 12,381 patients undergoing transfemoral TAVI between 2007 and 2018 with balloon-expandable or self-expandable valves were included in the dataset of the CENTER-Collaboration. The incidence of 30-day stroke rates was available in 10,982 patients (89%); these patients were included in the current patient-level pooled analysis.

Study End Points and Definitions

The primary end point of the current study was the incidence and timing of stroke occurring within the first 30 days after TAVI. In the updated criteria of the Valve Academic Research Consortium (VARC-2), stroke is defined as the duration of focal or global neurological deficit >24 hours, or <24 hours if any hemorrhage or infarct is documented using neuroimaging, or if the neurological deficit results in death. In the first VARC criteria, stroke was subdivided according to the modified Rankin score as minor (<2) versus major (≥2) at 30 and 90 days. Transient ischemic attack is defined as the duration of a focal or global neurological deficit <24 hours. The VARC criteria for stroke were used in 9 of 10 studies; the OBSERVANT trial (Observational Study of Effectiveness of SAVR–TAVI Procedures for Severe Aortic Stenosis Treatment) defined stroke as following: the occurrence of any new persistent neurological deficit.
Secondary outcomes included the 30-day incidence of transient ischemic attacks and the subdivision of minor stroke versus major stroke. Minor stroke was defined as a modified Rankin score of <2 at 30 and 90 days after the stroke, and major stroke was defined as a modified Rankin score ≥2 at 30 and 90 days. Furthermore, the difference in the 30-day stroke rate between procedures performed in the early years of TAVI (2007–2012) compared with the more recent years of TAVI (2013–2018) was evaluated. Additionally, the difference in the 30-day stroke rate in studies that had stroke adjudication (6 studies) compared with studies without stroke adjudication (4 studies) was determined. Also, the results of the individual studies were pooled using weighted meta-analysis. Moreover, multiple regression analyses were performed to identify baseline variables predictive of stroke occurring on the day of TAVI and stroke occurring during the first month after TAVI. Finally, the impact of postprocedural stroke on mortality and the occurrence of other clinical outcomes in patients with stroke was assessed.

Statistical Analysis
The study population was divided into 2 groups: patients who experienced stroke during the first 30 days after TAVI versus patients who did not. Values of continuous variables were tested for normal distribution and reported as mean±SD or median (25th–75th percentile) where applicable. Accordingly, either the independent t test or Mann-Whitney U test was used to determine differences between the 2 groups. Categorical variables were presented as frequencies and percentages; differences between the 2 groups were tested with χ². Cumulative incidence of stroke was estimated through Kaplan-Meier survival curves. In the current study, the overall 30-day stroke rate was derived from individual patient-level pooled data. However, this may not reflect the heterogeneity of the various study populations. Accordingly, we performed an additional meta-analysis of the 30-day stroke incidence of the 10 individual studies using weighing according to a random effects model; the results were presented in a forest plot. Moreover, baseline patient characteristics were explored as predictors of stroke occurring on the day of TAVI and at 30 days using logistic regression. Continuous predictors were subdivided in subintervals for interpretational purposes. Accordingly, age was subdivided into >85 years versus ≤85 years, and the Logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) was subdivided into ≤20% (high risk) versus >20%. The glomerular filtration rate (GFR) was subdivided as <30 versus ≥30 mL/min per 1.73 m²; body mass index was subdivided as <25 versus ≥25, and the aortic valve area (AVA) as measured with echocardiography was subdivided as <0.7 versus ≥0.7 cm²; all 3 variables were analyzed reciprocally as lower body mass index, GFR, and AVA all indicated a higher risk of stroke. Each potential predictor was tested in a univariate model, and those that were P <0.2 were simultaneously entered, to create a multiple regression model. The results of these models are reported as odds ratios (ORs) with a 95% CI. The association between 30-day stroke and mortality at 30 days was assessed with logistic regression and presented as OR (95% CI). All statistical tests were 2 tailed, and a value of P <0.05 was considered statistically significant. Calculations were generated by SPSS software (version 25.0, for Windows; SPSS, Inc, Chicago, IL).

RESULTS
Baseline Patient Characteristics
A total of 10,982 patients undergoing transfemoral TAVI between 2007 and 2018 were included in the current analysis. The mean age of the total population was 81.6±6.8 years, and 58% of all patients were women (Table 1). The median STS-PROM score (Society of Thoracic Surgeons Predicted Risk of Mortality) was 6.5% (interquartile range, 4.0%–13.2%). Approximately half of the patients underwent TAVI with a balloon-expandable valve (n=5345; 49%), whereas the other half was treated with a self-expandable valve (n=5637; 51%). Patients treated with balloon-expandable valves were either treated with the early-generation Edwards SAPIEN (4%), the early-generation SAPIEN XT (31%), or the new-generation SAPIEN 3 valve (12%). Patients treated with self-expandable valves were either treated with the early-generation Medtronic CoreValve (39%) or the new-generation Evolut series (14%).

Incidence of Stroke in the First Month
A total of 261 patients (2.4%) undergoing transfemoral TAVI experienced stroke during the first month after TAVI, with a median time between TAVI and stroke of 1 day (0–6 days; Figure). The meta-analyzed 30-day stroke rate, calculated using weighing according to a random effects model, was comparable with the pooled stroke rate (2.3%; 95% CI, 1.8–2.7; Supplemental Material 3 in the Data Supplement). Moreover, 34% of the strokes occurred on the day of the TAVI procedure, and 80% of the strokes occurred within the first week after TAVI. The stroke rate did not differ between procedures performed in the early years of TAVI (2007–2012) compared with those performed in the more recent years of TAVI (2013–2018; 2.4% versus 2.4%; P=1.0). Stroke was defined as major in three-quarters of all patients with stroke and as minor in the remainder. The incidence of transient ischemic attack at 1-month follow-up was 0.6%. Additional analysis showed that the rate of 30-day stroke was comparable in patients participating in studies with stroke adjudication versus patients participating in studies without stroke adjudication (2.5% versus 2.3%; P=0.56).

Baseline Risk Factors for Stroke After TAVI
Significant univariate predictors of 30-day stroke were age >85 years (OR, 1.3; 95% CI, 1.0–1.7; P=0.03), previous cerebrovascular events (prior stroke or transient ischemic attack: OR, 1.8; 95% CI, 1.3–2.6; P=0.001), a GFR of <30 mL/min per 1.73 m² (OR, 1.5; 95% CI, 1.1–2.3; P=0.03), and an AVA <0.7 cm² (OR, 1.5; 95% CI, 1.1–2.0; P=0.01; Supplemental Material 4A in the Data Supplement). In
multiple regression analysis, previous cerebrovascular events (OR, 2.2; 95% CI, 1.4–3.6; \(P=0.002\)) and a GFR of <30 mL/min per 1.73 m² (OR, 1.7; 95% CI, 1.0–2.8; \(P=0.05\)) independently predicted 30-day stroke. Patient characteristics that independently predicted stroke occurring on the day of TAVI were age >85 years (OR, 2.1; 95% CI, 1.1–4.1; \(P=0.03\)), body mass index <25 (OR, 2.2; 95% CI, 1.1–4.2; \(P=0.02\)), history of coronary artery disease (OR, 2.1; 95% CI, 1.0–4.1; \(P=0.04\)), and an AVA <0.7 cm² (OR, 2.1; 95% CI, 1.0–4.2; \(P=0.04\); Supplemental Material 4B in the Data Supplement).

**Mortality and Other Short-Term Outcomes in Patients With Stroke**

Stroke occurring within the first 30 days after TAVI was associated with a 6-fold increase of 30-day mortality (OR, 6.0; 95% CI, 4.4–8.1; \(P<0.001\); Table 2). Moreover, patients with stroke more frequently had new-onset atrial fibrillation (16% versus 3%; \(P<0.001\)) and experienced major or life-threatening bleedings (12% versus 7%; \(P=0.003\)) at 30 days or follow-up. The incidence of myocardial infarction (0.8% versus 0.9%; \(P=0.79\)) and permanent pacemaker implantation (14% in both groups; \(P=0.81\)) was not different among patients who experienced stroke compared with patients who did not.

**DISCUSSION**

**Main Findings**

In this large, global, patient-level analysis, the 30-day incidence of stroke after transfemoral TAVI was 2.4%; this rate was equal in patients treated in the early years of TAVI compared with those treated in more recent years. In 80% of patients, the stroke occurred within...
the first week after TAVI. Prior cerebrovascular events independently predicted the occurrence of stroke after TAVI, whereas low GFR was a borderline significant predictor. Moreover, there was a 5-fold higher rate of new-onset atrial fibrillation and a 2-fold higher rate of major or life-threatening bleedings in patients with stroke. Finally, the occurrence of stroke after TAVI was associated with a strikingly 6-fold increase of 30-day mortality rates.

**Risk Factors for Stroke in TAVI Patients**

An earlier, large meta-analysis including >72,000 patients concluded that female sex, performance of TAVI during the first half of centers experience, chronic kidney disease, and new-onset atrial fibrillation were associated with an increased risk of short-term cerebrovascular events. In accordance with Auffret et al, we found that there was a strong association between the occurrence of new-onset atrial fibrillation and stroke after TAVI. Because of the timing of the end points in the current analysis, a conclusion on causality between new-onset atrial fibrillation and stroke after TAVI cannot be made. Nevertheless, we believe the findings of the current study warrant future studies to further evaluate the impact of new-onset atrial fibrillation in TAVI patients, as well as the optimization of fast detection of new-onset atrial fibrillation and adequate anticoagulation strategies. In contrast to the new-onset atrial fibrillation, there was no relation between atrial fibrillation before TAVI and the occurrence of stroke after TAVI. This may indicate that patients with prior atrial fibrillation undergoing TAVI received adequate antithrombotic therapy and are not exposed to an increased risk of stroke after TAVI, despite a brief interruption of anticoagulation therapy. Furthermore, similar to the current study, low GFR was a predictor for stroke. The presence of chronic kidney disease may function as a marker for the general cardiovascular risk profile of a patient.

Moreover, in the current study, prior cerebrovascular events independently predicted the occurrence of 30-day stroke. Likewise, risk factors for the occurrence of stroke on the day of TAVI were a small AVA before TAVI and a history of coronary artery disease. It is likely, that these patients have a relatively large calcification burden of the aortic arch and native valve, resulting in cerebral embolizations both spontaneously and triggered by cardiovascular interventions. This was confirmed by previous research, which showed that a high

**Table 2. Thirty-Day Outcomes in the Patients With or Without Stroke in the First Month After Transcatheter Aortic Valve Implantation**

<table>
<thead>
<tr>
<th></th>
<th>No Stroke at 30 d (n=10721)</th>
<th>Stroke at 30 d (n=261)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>570 (5%)</td>
<td>61 (25%)</td>
<td>6.0 (4.4–8.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major or life-threatening bleeding</td>
<td>592 (7%)</td>
<td>24 (12%)</td>
<td>1.9 (1.3–3.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>71 (0.9%)</td>
<td>2 (0.8%)</td>
<td>1.2 (0.3–5.0)</td>
<td>0.79</td>
</tr>
<tr>
<td>New-onset atrial fibrillation</td>
<td>51 (3%)</td>
<td>5 (16%)</td>
<td>5.2 (1.9–14.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Permanent pacemaker implantation</td>
<td>1178 (14%)</td>
<td>24 (14%)</td>
<td>1.0 (0.6–1.5)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Incidence and OR (95% CI). OR indicates odds ratio.

**Figure.** The number of days between transcatheter aortic valve implantation (TAVI) and the stroke was documented in 198 of 261 patients with stroke (76%).
calcium score of the native valve, representing the calcification burden, was associated with a high number of cerebral embolizations during the TAVI procedure.\textsuperscript{18} We hypothesize that patients >85 years of age are at risk for stroke during TAVI because of a higher calcification burden associated with the cumulative increase of atherosclerosis caused by age. In the current study, the risk of stroke remained constant throughout the years (2007–2018). The enhancement of procedural techniques, increased operator experience, and healthier TAVI populations seem to have reduced patient mortality but not stroke.\textsuperscript{19} The current study highlights that the prediction of stroke in patients undergoing transfemoral TAVI remains challenging for the larger part.

**Pathophysiology of Stroke During TAVI**

The finding of the current study that patients with a more extensive calcification burden of the aortic arch and native valve had a higher risk of stroke is in accordance with the pathophysiology. During TAVI, the use of large-sized catheters and delivery systems, balloon valvuloplasty, positioning and implantation of the new valve as well as post-dilation, manipulates both the calcified native valve as well as the often calcified aortic wall. Consequently, dislodgement and embolization of crushed calcified native valves and aortic debris can take place. This is confirmed by studies that extracted debris from cerebral protection filters used during TAVI and quantified the origin of the captured embolizations.\textsuperscript{20–22} Frequently found types of debris consisted of arterial wall tissue (52%–94%), native valve tissue (20%–60%), calcifications (50%–73%), and alarmingly also foreign body material, detached from percutaneous devices (10%–36%). Interestingly, histopathologic debris was found in nearly all cerebral protective devices.

In the current study, outcomes in patients with stroke were poor. The risk of mortality was 6-fold higher in patients with stroke, and patients with stroke experienced twice as much major or life-threatening bleedings. The high bleeding rates among patients with stroke may partly be explained by a small portion of hemorrhagic strokes, which by default is defined as a life-threatening bleeding, according to the VARC criteria. However, only 1 of 11 strokes after TAVI is of a hemorrhagic origin.\textsuperscript{21} Moreover, patients with atrial fibrillation treated with anticoagulants are at higher risk for both stroke and bleedings. Lastly, the concomitant occurrence of both stroke and bleeding may reflect a general frail patient population.

**Reduction of TAVI-Related Stroke**

In inoperable patients undergoing TAVI, the 30-day stroke rate increased from 6.7% to 10% at 1 year of follow-up (Δ3.3%).\textsuperscript{2} Inoperable patients who received standard therapy had a considerably lower 30-day stroke rate (1.7%). However, similar to TAVI patients, the stroke rate increased with Δ2.8% between 30 days and 1 year. These findings emphasize that stroke occurring after the first 30 days is a natural event in these elderly patients. Moreover, the current study stresses that more than one-third of the strokes occurs on the day of the TAVI procedure. When considering this time frame and the higher risk of stroke in patients with a high calcification burden, in theory, cerebral protection devices might be a solution to reduce TAVI-related stroke.\textsuperscript{24} Because of the relatively low stroke rates, all current available randomized studies examining the efficacy of cerebral protection devices were underpowered for clinical end points. However, in a relatively large propensity-matched study (n=802), use of the Sentinel cerebral embolic protection device (Boston Scientific Corporation, Natick, MA) was associated with a significant reduction of stroke (1.4% versus 4.6%; OR, 0.3; 95% CI, 0.1–0.9; \(P=0.03\)), as well as a tendency to a reduction in mortality (0.7% versus 2.9%; OR, 0.3; 95% CI, 0.1–1.2; \(P=0.06\)).\textsuperscript{25} Nevertheless, the outcomes of currently ongoing larger randomized trials are needed to confirm these results (PROTECT-TAVI [Prospective Randomized Outcome Study in TAVI Patients Undergoing Periprocedural Embolic Cerebral Protection With the Claret Sentinel Device], NCT02895737 and REFLECT trial [Randomized Evaluation of the TriGuard Embolic Deflection Device to Reduce the Impact of Cerebral Embolic Lesions After Transcatheter Aortic Valve Implantation], NCT02536196). However, if in the future these randomized controlled trials confirm this 3-fold reduction of stroke, the costs of these cerebral protection devices will be the second barrier for the standard use of cerebral protection devices. Nonetheless, the long-term financial burden of stroke should not be underestimated. Patients in the current trial with stroke had a 60% longer hospital stay compared with patients without stroke. The costs for the longer hospital admission and the acute care for stroke are only the tip of the iceberg. As three-quarters of all stroke after TAVI is considered major, many patients return to their home with moderate or severe disability and increased healthcare consumption.

**Limitations**

The current study represents a global and real-world patient population. However, even though the populations of the current collaboration were selected through a systematic search, the willingness of principle investigators to collaborate may be the result of preconceived beliefs about the incidence of stroke, and this may have influenced the final study population. The current study only included patients who underwent transfemoral
TAI; accordingly, the predictor model for stroke cannot be applied to all patients with severe aortic valve stenosis and, therefore, does not provide information that may influence the decision-making process between transfemoral TAVI, other approach routes, or surgical aortic valve replacement. Moreover, the current collaboration includes various types of studies, including registries without adjudication of clinical events. Accordingly, occurrence of events such as stroke may have been underestimated. However, in the current study, the rate of stroke was comparable in studies with adjudication of strokes compared with those without adjudication. Furthermore, in the current study, stroke definitions using VARC-1 or VARC-2 criteria were both used. The definition of stroke has not changed in the updated VARC-2 criteria. However, the subdivision of stroke was changed from major/minor into disabling/non-disabling, which is equivalent to major/minor but corrects for the patient’s baseline functioning. Moreover, the current patient population underwent TAVI between 2007 and 2018. Accordingly, this study does not provide conclusions on stroke in low-risk patients treated with the newest valve types. However, this study does reflect the real-world practice of TAVI, across the globe during the past decade.

Conclusions

In this large, global, patient-level pooled analysis, the 30-day incidence of stroke after transfemoral TAVI was 2.4%. In 80% of patients, the stroke occurred within the first week after TAVI. Prior cerebrovascular events and a low GFR independently predicted the occurrence of stroke after TAVI. There was a 5-fold higher rate of new-onset atrial fibrillation in patients with stroke, and the occurrence of stroke after TAVI was associated with a strikingly 6-fold increase of 30-day mortality. The current findings highlight the importance of stroke reduction during the TAVI procedure.

ARTICLE INFORMATION

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Dr de Brito and Sarmento-Leite are proctors for Edwards Lifesciences and Medtronic. Dr Barbanti is a consultant for Edwards Lifesciences and received speaker honoraria from Medtronic and Biotronik. Dr Latib is a consultant for Medtronic and has received honoraria from Abbott Vascular. Dr D’Onofrio is a proctor for Edwards Lifesciences and Symetis. Dr Baan receives an unrestricted research grant from Edwards Lifesciences and is a proctor for Edwards Lifesciences. The other authors report no conflicts.

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