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ORIGINAL RESEARCH

Cerebrovascular Events in Patients Undergoing Transfemoral Transcatheter Aortic Valve Implantation: A Pooled Patient-Level Study

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BACKGROUND: Cerebrovascular events remain one of the most devastating complications of transcatheter aortic valve implantation (TAVI). Data from real-world contemporary cohorts on longitudinal trends and outcomes remain limited. The aim of this study was to assess incidence, temporal trends, predictors, and outcomes of cerebrovascular events following transfemoral TAVI.

METHODS AND RESULTS: The CENTER2 (Cerebrovascular Events in Patients Undergoing Transcatheter Aortic Valve Implantation With Balloon-Expandable Valves Versus Self-Expandable Valves 2) study includes patients undergoing TAVI between 2007 and 2022. The database contains pooled patient-level data from 10 clinical studies. A total of 24 305 patients underwent transfemoral TAVI (mean age 81.5±6.7 years, 56% women, median Society of Thoracic Surgeon Predicted Risk of Mortality 4.9% [3.1%–8.5%]). Of these patients, 2.2% (n=534) experienced stroke in the first 30 days after TAVI, and 40 (0.4%) had a transient ischemic attack. Stroke rates remained stable during the treatment period (2007–2010: 2.1%, 2011–2014: 2.5%, 2015–2018: 2.1%, 2019–2022: 2.1%; P_{trend}=0.28). Moreover, 30-day cerebrovascular event rates were similar across Society of Thoracic Surgeon Predicted Risk of Mortality risk categories: 2.1% in low-risk, 2.6% in intermediate-risk, and 2.5% in high-risk patients (P=0.21). Mortality was higher in patients with 30-day stroke than without at 30 days (20.3% versus 4.7%; odds ratio, 5.1 [95% CI, 4.1–6.5]; P<0.001) and at 1 year (44.1% versus 15.0%; hazard ratio, 3.5 [95% CI, 3.0–4.2]; P<0.001). One-year mortality rates for stroke did not decline over time (2007–2010: 46.9%, 2011–2014: 46.0%, 2015–2018: 43.0%, 2019–2022: 39.1%; P_{trend}=0.32). At 1 year, 7.0% of patients undergoing TAVI had a stroke.

CONCLUSIONS: In 24 305 patients who underwent transfemoral TAVI, 30-day cerebrovascular event incidence remained ≈2.2% between 2007 and 2022. Thirty-day stroke rates were similar throughout Society of Thoracic Surgeon Predicted Risk of Mortality risk categories. Mortality rates after stroke remain high.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03588247.

Key Words: aortic valve stenosis ■ mortality ■ stroke ■ transcatheter aortic valve replacement

See Editorial by Elkaryoni and Saad.

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CLINICAL PERSPECTIVE

What Is New?

- Rates of cerebrovascular events in patients undergoing transcatheter aortic valve implantation remain high, with a 30-day stroke incidence of 2.2%, which did not decline between 2007 and 2022.
- Stroke rates were similar in patients with low, intermediate, and high surgical risk.
- Mortality in patients with 30-day stroke remains 5-fold higher than in patients without stroke following transcatheter aortic valve implantation.

What Are the Clinical Implications?

- Stroke still occurs in 1 in 50 patients undergoing transfemoral transcatheter aortic valve implantation, and event rates did not decline in the recent years of contemporary transcatheter aortic valve implantation techniques.
- Ongoing efforts to prevent stroke and improve outcomes in patients with stroke remain of high clinical importance.

Nonstandard Abbreviations and Acronyms

CENTER	Cerebrovascular Events in Patients Undergoing Transcatheter Aortic Valve Implantation With Balloon-Expandable Valves Versus Self-Expandable Valves
EuroSCORE	European System for Cardiac Operative Risk Evaluation
STS-PROM	Society of Thoracic Surgeon Predicted Risk of Mortality
TAVI	transcatheter aortic valve implantation
VARC	Valve Academic Research Consortium

See Editorial by Elkaryoni and Saad.Transcatheter aortic valve implantation (TAVI) is a life-saving percutaneous treatment for patients with severe aortic valve stenosis. Since TAVI was approved for commercial use, multiple generations of improved device technology were introduced, and operator experience is continuously growing.[1,2] Further procedural improvements were made such as local anesthesia and smaller sheath sizes.[3] TAVI treatment indication has rapidly expanded from inoperable to low-risk patients.[4,5] Lower-risk patients have a longer baseline life expectancy and may still participate in paid employment. Cerebrovascular events can be even more detrimental to these patients, resulting in more severe impairment in quality of life. Previous randomized clinical trials showed decreasing stroke rates in patients with lower surgical risk, but these results have not been confirmed in real-world patient cohorts.[4,5] Contemporary data from large cohorts evaluating whether improved patient and procedural characteristics result in decreasing stroke rates over the years remain limited to a few studies.[6,7] Cerebrovascular events continue to be one of the most feared complications of TAVI and are associated with increased mortality, discharge to rehabilitation facilities, increased health care costs, and impaired quality of life.[6,8] VARC-3 (Valve Academic Research Consortium 3) states that patients, physicians, and device regulators consider cerebrovascular events as one of the most important adverse events following cardiovascular interventions.[9] Therefore, our aim was to assess cerebrovascular events incidence, temporal trends, and clinical outcomes in patients undergoing transfemoral TAVI between 2007 and 2022 in this large global patient cohort.

METHODS

Patient Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. The CENTER2 (Cerebrovascular Events in Patients Undergoing Transcatheter Aortic Valve Implantation With Balloon-Expandable Valves Versus Self-Expandable Valves 2) study is an international collaboration including patients with severe aortic valve stenosis undergoing TAVI. The initial CENTER study was a patient-level pooled analysis including 12 381 patients treated with transfemoral TAVI between 2007 and 2018.[6] In April 2022, collaborators were asked to add patients to the database. Accordingly, an additional 13 390 patients treated between 2018 and June 2022 were included. As a result, the CENTER2 study comprises a total patient population of 25 771. Baseline and procedural characteristics including outcomes are available on a patient level in the database. Most patients (n=24 321, 94.4%) were treated with a transfemoral approach, 974 (3.8%) with a transapical approach, 393 (1.5%) with a subclavian approach, and 83 (0.3%) with a direct aortic approach. The incidence of 30-day stroke was available in 24 305 (99.9%) patients undergoing transfemoral TAVI, who were included in the current analysis. Additionally, we performed a sensitivity analysis also including patients with nontransfemoral access.

Studies included in the CENTER2 study were selected through a systematic search of the literature, and principal investigators were approached to share patient-level data. Consequently, a pooled database including clinical data from all individual patients was created. The CENTER2 study is previously described.[10] Original studies were: 1 prospective clinical trial, 2 multicenter prospective registries, 3 national registries, and 4 single-center prospective registries. All collaborators provided a dedicated database with baseline patient characteristics, echocardiographic data, procedural information, and long-term follow-up. Included patients had at least 30 days follow-up. Patients were recruited from Spain, United States, Italy, Israel, France, and Brazil. Table S1 presents an overview of included studies. TAVI treatment indication and selection of valve type were made by the heart team of each participating center. Patients were treated with commercially available balloon- and self-expandable devices. All studies were conducted in accordance with the Declaration of Helsinki. Institutional review board approval was obtained at each center. Patients provided written informed consent at their local hospital. The study is registered at ClinicalTrials.gov (NCT03588247).

Study Outcomes

The primary clinical outcome of this study was 30-day stroke incidence. Stroke was defined according to the VARC-2 (Valve Academic Research Consortium 2) definition: "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".[11] Nine studies used the VARC-2 criteria, and 1 study used an equivalent definition. The VARC-2 definition is similar to the more recent VARC-3 and NeuroARC (Neurologic Academic Research Consortium) (1a to 1d) criteria for stroke.[9,11,12] Cerebrovascular events were further categorized per cause: ischemic (NeuroARC 1a) or hemorrhagic (NeuroARC 1b, 1c); disability (fatal, disabling, or nondisabling), and onset timing (acute: ≤24 hours, subacute: >1 day and ≤30 days, and later: >30 days and ≤1 year after TAVI).[9,12] Secondary outcomes were incidence of transient ischemic attack, temporal trends in stroke incidence, stroke incidence per surgical risk category, and stroke incidence in other patient subgroups. In addition, we reported clinical outcomes in patients with 30-day stroke. Lastly, we assessed 1-year stroke incidence and identified clinical predictors for stroke. Surgical risk categories were established according to the Society of Thoracic Surgeons Predicted Risk of 30-Day Mortality (STS-PROM).[13] Patients with STS-PROM <4% were considered low risk; STS-PROM 4% to 8% as intermediate risk, and STS-PROM >8% as high risk. Renal failure was defined as glomerular filtration ratio <30 mL/min per 1.73 m^2.

Statistical Analysis

Baseline continuous variables were visually tested for normality with distribution plots. Accordingly, variables were reported as mean with standard deviation or median with interquartile range (IQR), and differences were tested with the *t* test or Mann-Whitney U test. Baseline categorical variables were reported as frequencies and percentages, and differences were tested with the χ^2 test. A total of 3.8% of the baseline medical history values (patients × variables) were missing in the total data set. We assessed the frequency and distribution of the missing values according to 30-day stroke status and per included study center. Under the assumption that data were missing at random, we applied multiple imputation methods according to the Rubin protocol to estimate missing data in baseline medical history. Table S2 lists more information on the frequency and distribution of the missing data for the observed values and results of the imputation model. The primary outcome of stroke incidence was assessed 30 days after TAVI. For secondary outcome analyses, the study period was divided into 4 time periods: 2007 to 2010, 2011 to 2014, 2015 to 2018, and 2019 to 2022. Differences in stroke incidence between these time periods were tested with the Mantel-Haenszel test for trend. Differences in stroke incidence between groups (such as sex, presence of baseline atrial fibrillation, valve type, predilatation, postdilatation, valve in valve, and bicuspid valves) were tested with a χ^2 test.

Differences in clinical outcomes in patients with versus without 30-day stroke were tested with a χ^2 test, and odds ratios (ORs) with 95% CIs were established using logistic regression. Time to mortality curves were made with Cox regression, and hazard ratios (HRs) were reported. Proportional hazards assumption was tested with Schoenfeld residuals. To assess the effect of 30-day stroke on mortality in patients surviving the initial acute postprocedural period, we censored patients who did not survive 30 days and performed a Cox regression analysis with landmark time at 30 days. Baseline patient characteristics were explored as potential predictors with the Akaike information criterion. If the Akaike information criterion value for a variable was lower than the model with intercept only, the variable was added to a multinominal regression model. Multivariable logistic regression calculated the OR with 95% CI for independent predictors. Multivariable models were created for acute stroke (≤24 hours), 30-day stroke, and later stroke (>30 days and ≤1 year). In addition to the complete case analysis, we performed sensitivity analyses for stroke predictors with the imputed baseline values. One-year cerebrovascular event rates were evaluated

similarly to 30-day stroke analyses with a χ^2 test, and subgroup analyses were performed. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. All statistical tests were 2-tailed, and $P<0.05$ was considered statistically significant. Calculations were performed using SPSS software (version 28.0 for Windows; IBM, Armonk, NY). Authors A.C.v.N., H.M.A., K.I.H., and R.D. had full access to all data.

RESULTS

Baseline Characteristics

A total of 24 305 patients undergoing transfemoral TAVI were included in the current cohort. Mean age was 81.5±6.7 years, 13 585 (56%) were women, and median STS-PROM was 4.9% (IQR, 3.1–8.5). Median follow-up was 365 days (IQR, 40–653). Table 1 presents baseline characteristics of the included cohort. Approximately half of patients (51%) presented with New York Heart Association functional class 3 or 4. Balloon-expandable devices were used in 43% of patients. Table S3 lists the types of transcatheter heart valves that were used in these patients. According to STS-PROM score, 40% (n=5624) were classified as low-risk patients, 32% (n=4554) as intermediate-risk patients, and 28% (n=3908) as high-risk patients. Table S4 presents baseline characteristics according to estimated surgical risk.

Thirty-Day Cerebrovascular Event Incidence

The primary outcome of 30-day stroke occurred in 534 (2.2%) patients. A total of 205 (1.1%) of these were acute strokes (≤24 hours after TAVI). Median time to stroke was 1.0 days (IQR, 0.0–6.0). Most strokes were of ischemic cause (94.3%, n=166), and 5.7% (n=10) were hemorrhagic. Strokes were fatal in 21.4% (n=59) of patients, disabling in 37.7% (n=104), and nondisabling in 40.9% (n=113) of patients. Another 0.4% (n=40) patients had a transient ischemic attack. Thirty-day stroke rates did not decrease during the study period: from 2.1% between 2007 and 2010; 2.5% between 2011 and 2014; 2.1% between 2015 and 2018; to 2.1% between 2019 and 2022 (*P* for trend *P*=0.28, Figure 1). Thirty-day stroke rates were consistent through STS-PROM risk categories: 2.1% in low-risk patients, 2.6% in intermediate-risk patients, and 2.5% in high-risk patients (*P*=0.21). Thirty-day stroke rates were similar in men and women (both 2.2%, *P*=0.90; Figure 1). There was no difference in 30-day stroke rates between patients with known preexisting atrial fibrillation versus those without known atrial fibrillation (2.4% versus 2.2%, *P*=0.45). Patients receiving self-expandable valves had higher rates of 30-day stroke than those receiving balloon-expandable valves (2.4% versus 1.9%; OR, 1.3 [95% CI, 1.1–1.5]; *P*=0.004). There were no higher rates of stroke after predilatation compared with direct implantation (2.3% versus 2.1%, *P*=0.37). However, postdilatation was associated with higher 30-day stroke rates (3.1% versus 2.0%; OR, 1.6 [95% CI, 1.3–2.0]; *P*<0.001). Thirty-day stroke rates were comparable in patients with bicuspid versus tricuspid valves (1.6% versus 2.1%, *P*=0.79) and valve-in-valve versus native valve TAVI (1.9% versus 2.3%, *P*=0.50).

Clinical Outcomes in Patients With 30-Day Stroke

Table 2 presents clinical outcomes in patients with 30-day stroke. Patients with stroke had higher bleeding rates than patients without stroke (9.5% versus 6.5%; OR, 1.5 [95% CI, 1.1–2.0]; *P*=0.005). Moreover, patients with stroke had a higher mortality risk during the first year than patients without stroke (44.1% versus 15.0%; HR, 3.5 [95% CI, 3.0–4.2]; *P*<0.001). Figure 2 presents corresponding landmark time to mortality curves. Mortality rates declined over time in patients without stroke; however, in patients with stroke, mortality rates remained stable: 46.9% between 2007 and 2010; 46.0% between 2011 and 2014; 43.0% between 2015 and 2018; to 39.1% between 2019 and 2022 (*P* for trend *P*=0.32, Figure 3). New-onset atrial fibrillation was not more frequent in patients with 30-day stroke (6.1% versus 5.8%; OR, 1.0 [95% CI, 0.6–1.7]; *P*=0.85), and neither was permanent pacemaker implantation (18.3% versus 17.5%; OR, 1.1 [95% CI, 0.7–1.5]; *P*=0.76). Procedure times were longer in patients with 30-day stroke (106±58 versus 99±46 minutes, *P*=0.04). In particular, procedure times were longer for patients with stroke in those treated with self-expandable valves (111±59 minutes versus 103±44 minutes, *P*=0.08), but not in patients treated with balloon-expandable valves (98±55 versus 94±47 minutes, *P*=0.40).

One-Year Stroke Incidence

One-year stroke incidence was 7.0% (n=754). In these patients, median time to stroke was 4.0 days (IQR, 1.0–63.8). Figure 4 presents the number of days between TAVI and stroke onset. There was a trend to lower 1-year stroke incidence in patients with low surgical risk compared with intermediate- and high-risk patients: 5.9% versus 7.7% and 6.8% (*P*=0.05). One-year stroke incidence was comparable in men and women (7.4% versus 6.7%, *P*=0.17) and in patients receiving self- and balloon-expandable valves (7.2% versus 6.7%, *P*=0.38). There was no difference in stroke rates between patients with known atrial fibrillation versus those without known atrial fibrillation (7.2% versus 6.9%, *P*=0.57).

Table 1. Baseline Procedures and Procedural Characteristics

Variable	Total population (n=24 305)	Stroke at 30 d (n=534)	No stroke at 30 d (n=23 771)	*P* value
Demographics				
Age, y	81.5±6.7	82.4±6.8	81.4±6.7	0.001
Women	13 585 (56%)	300 (56%)	13 285 (56%)	0.90
Body mass index, kg/m^2	27.5±4.9	27.0±4.6	27.5±4.9	0.50
Medical history				
Cerebrovascular events	2425 (10%)	95 (18%)	2330 (10%)	<0.001
Myocardial infarction	2994 (13%)	66 (13%)	2928 (13%)	0.92
Previous PCI	4857 (21%)	105 (20%)	4752 (21%)	0.77
Previous CABG	2062 (9%)	44 (9%)	2018 (9%)	0.74
Hypertension	19 418 (81%)	427 (80%)	18 994 (81%)	0.70
Dyslipidemia	13 988 (59%)	305 (58%)	13 683 (59%)	0.77
Peripheral vascular disease	2854 (12%)	76 (15%)	2778 (12%)	0.10
Coronary artery disease	8949 (38%)	216 (41%)	8733 (38%)	0.14
Atrial fibrillation	6578 (28%)	155 (30%)	6423 (28%)	0.45
Renal failure	2632 (12%)	70 (15%)	2562 (12%)	0.06
GFR, mL/min per 1.73 m^2	52.6 (38.9–69.3)	50.3 (38.1–65.4)	52.6 (38.9–69.3)	0.05
NYHA ≥3	8799 (51%)	217 (57%)	8582 (51%)	0.02
Bicuspid aortic valve	62 (1%)	1 (1%)	61 (1%)	0.79
Frailty	3640 (42%)	92 (45%)	3548 (42%)	0.35
Risk scores				
STS-PROM, %	4.9 (3.1–8.5)	5.3 (3.2–8.8)	4.9 (3.1–8.4)	0.14
Logistic EuroSCORE, %	13.5 (8.5–21.4)	14.0 (8.9–22.7)	13.5 (8.5–21.5)	0.29
EuroSCORE II, %	3.6 (2.2–6.0)	3.8 (2.5–6.1)	3.7 (2.2–6.0)	0.31
CHA_2DS_2-VASc	4 (4–5)	5 (5–5)	4 (4–5)	0.04
Echocardiographic characteristics				
LVEF, %	56.9±13.1	57.0±13.3	56.9±13.1	0.79
Maximum gradient, mm Hg	77.8±23.2	76.7±20.9	77.8±23.3	0.31
Mean gradient, mm Hg	49.0±16.5	49.4±15.8	48.9±16.5	0.53
Aortic valve area, cm^2	0.67±0.20	0.67±0.20	0.67±0.20	0.49
Device type				
Balloon-expandable valve	10 535 (43%)	199 (37%)	10 336 (44%)	0.004
Self-expandable valve	13 770 (57%)	335 (63%)	13 435 (57%)	0.004
Third-generation valve	13 768 (57%)	277 (53%)	13 491 (57%)	0.04
Valve in valve	593 (3%)	11 (2%)	582 (3%)	0.50
Valve size, mm	26 (25–29)	26 (26–29)	26 (25–29)	<0.001
Baseline medication				
Aspirin	3915 (62%)	105 (69%)	3810 (62%)	0.07
Clopidogrel	1588 (38%)	33 (35%)	1555 (38%)	0.63
Oral anticoagulation	735 (23%)	16 (23%)	719 (23%)	0.99
Statin	1691 (63%)	44 (65%)	1647 (63%)	0.76
Discharge medication				
Aspirin	10 126 (78%)	216 (79%)	9910 (78%)	0.95
Clopidogrel	6639 (54%)	135 (54%)	6504 (54%)	0.96
Oral anticoagulation	4799 (39%)	98 (39%)	4701 (39%)	0.94
Statin	1689 (63%)	38 (56%)	1651 (63%)	0.22

CABG indicates coronary artery bypass graft; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention; and STS-PROM, Society of Thoracic Surgeon Predicted Risk of Mortality.

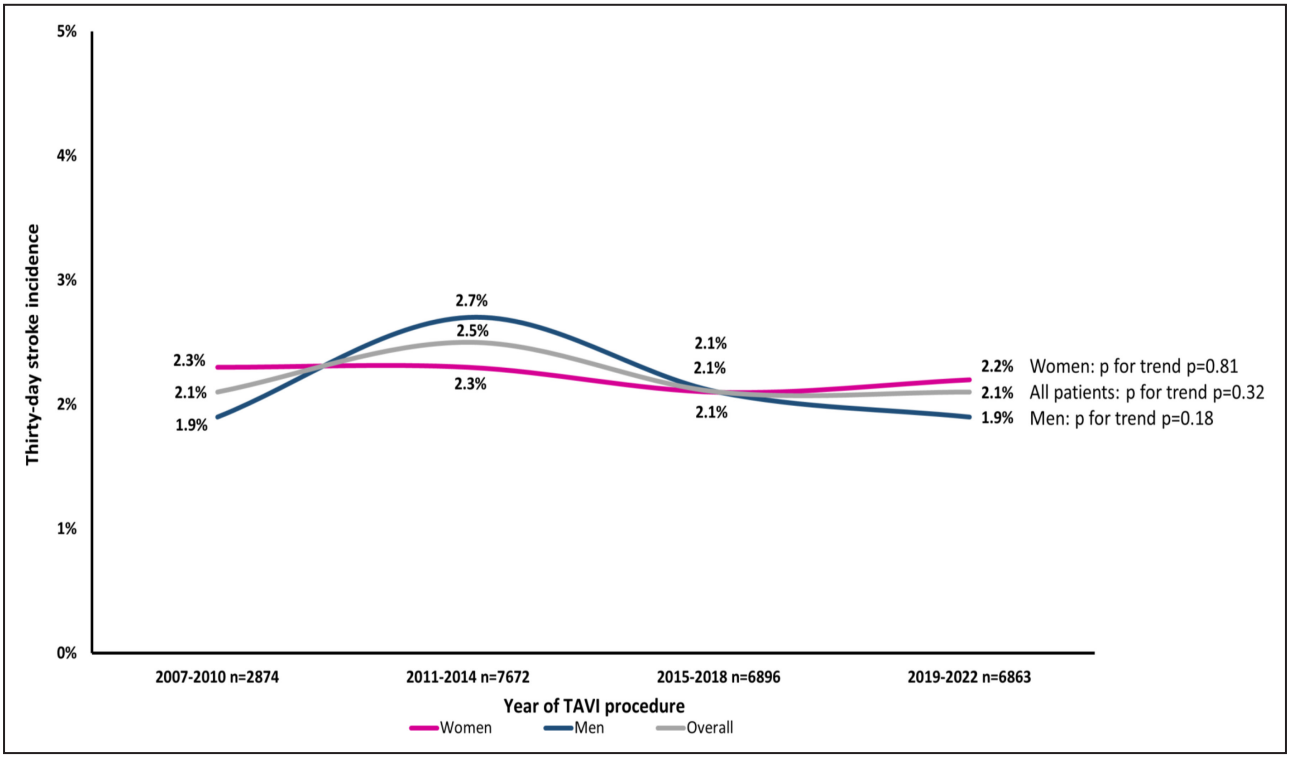

Figure 1. Temporal trends in 30-day stroke incidence according to year of TAVI procedure in women and men.
TAVI indicates transcatheter aortic valve implantation.

Predictors for Stroke

Independent predictors for acute stroke were: age ≥80 years (OR, 1.49 [95% CI, 1.04–2.15]; *P*=0.03), mean aortic valve gradient (OR, 1.01 per mm Hg [95% CI, 1.00–1.02]; *P*=0.01), and body mass index (BMI) (OR, 0.95 per kg/m^2 [95% CI, 0.93–0.99]; *P*=0.01). The Akaike information criterion for this model was 1660.76.

Risk factors for 30-day stroke were: age ≥80 years (OR, 1.26 [95% CI, 1.01–1.57]; *P*=0.04) and previous cerebrovascular events (OR, 1.98 [95% CI, 1.54–2.54]; *P*<0.001). The Akaike information criterion was 31.22.

Independent predictors for stroke between 30 days and 1 year were: age ≥80 years (OR, 1.50 [95% CI, 1.09–2.07]; *P*=0.01), previous cerebrovascular

Table 2. Clinical Outcomes in Patients With and Without 30-Day Stroke Following Transcatheter Aortic Valve Implantation

Outcome	Stroke at 30 d (n=534)	No stroke at 30 d (n=23 771)	Odds ratio (95% CI)	*P* value
Procedural				
Surgical bailout	5 (1.0%)	124 (0.5%)	1.8 (0.7–4.5)	0.19
Mortality	10 (1.9%)	290 (1.2%)	1.6 (0.8–3.0)	0.16
Paravalvular leakage ≥ moderate	1 (25.0%)	81 (23.6%)	1.1 (0.1–10.5)	0.95
Postprocedural mean gradient, mm Hg	9.3±2.9	10.0±4.9	…	0.82
30 d				
Mortality	96 (20.3%)	960 (4.7%)	5.1 (4.1–6.5)	<0.001
Major bleeding	50 (9.5%)	1495 (6.5%)	1.5 (1.1–2.0)	0.005
Myocardial infarction	7 (1.5%)	200 (1.1%)	1.5 (0.7–3.1)	0.33
New-onset atrial fibrillation	18 (6.1%)	697 (5.8%)	1.0 (0.6–1.7)	0.85
Permanent pacemaker implantation	39 (18.3%)	1613 (17.5%)	1.1 (0.7–1.5)	0.76
1 y				
Mortality	146 (44.1%)	2074 (15.0%)	4.5 (3.6–5.6)	<0.001

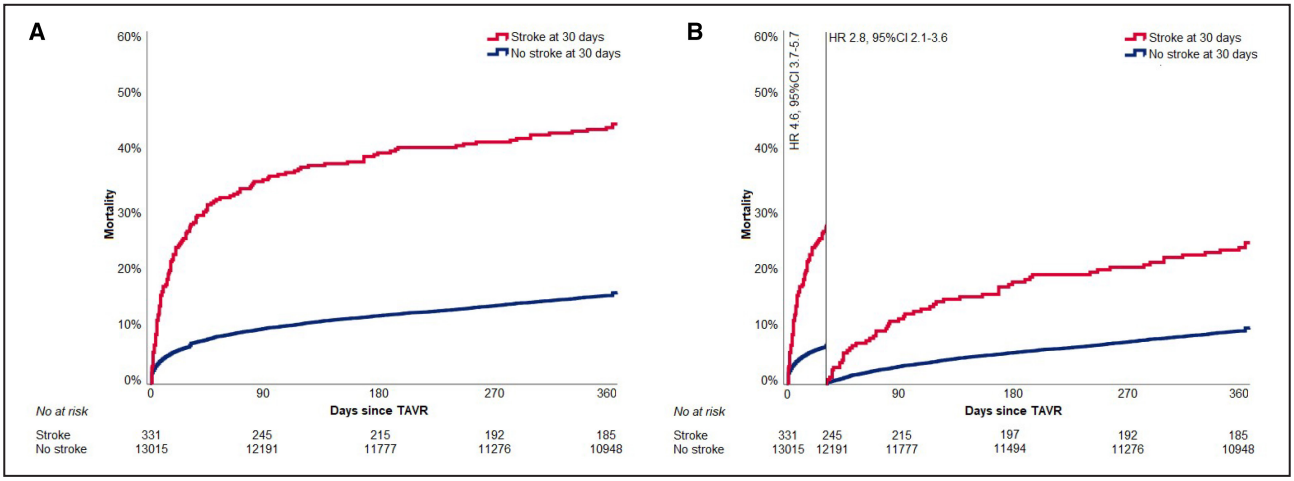

Figure 2. Time to mortality curves for patients with and without 30-day stroke after transfemoral TAVR.
A, Time to mortality curves for patients with and without 30-day stroke after transfemoral TAVR. **B**, Time to mortality curves with landmark at 30 days for patients with and without 30-day stroke and surviving the initial postprocedural period after transfemoral TAVR. One-year follow-up was available in 58.1% of patients. HR indicates hazard ratio; and TAVR, transcatheter aortic valve replacement.

events (OR, 1.55 [95% CI, 1.05–2.28]; *P*=0.03), and renal failure (OR, 1.62 [95% CI, 1.02–2.56]; *P*=0.04). The Akaike information criterion for this model was 41.55.

Cerebrovascular Events in Patients With Nontransfemoral Access

We performed sensitivity analyses in the complete cohort including all patients undergoing TAVI with all

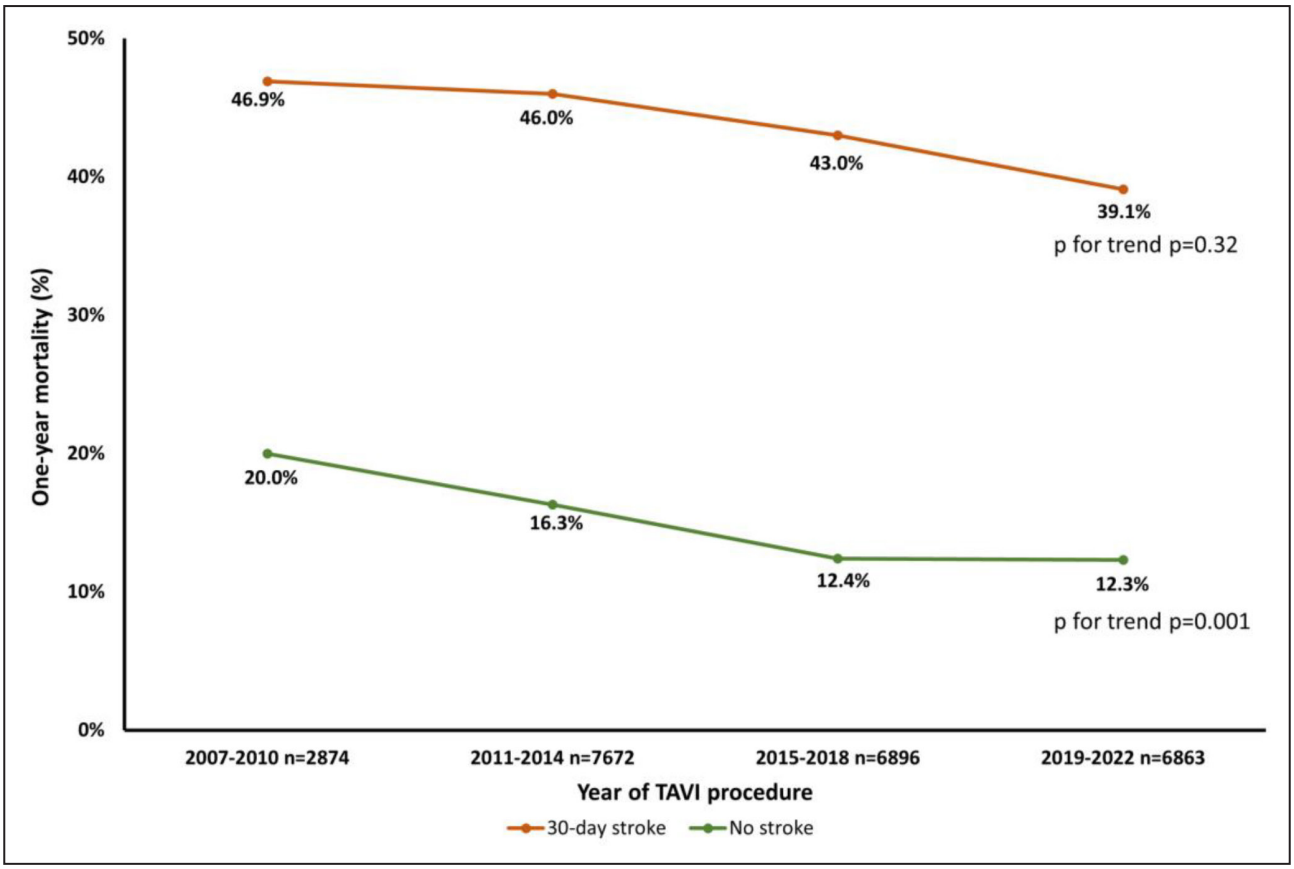

Figure 3. Temporal trends in 1-year mortality in patients with stroke and without stroke.
TAVI indicates transcatheter aortic valve implantation.

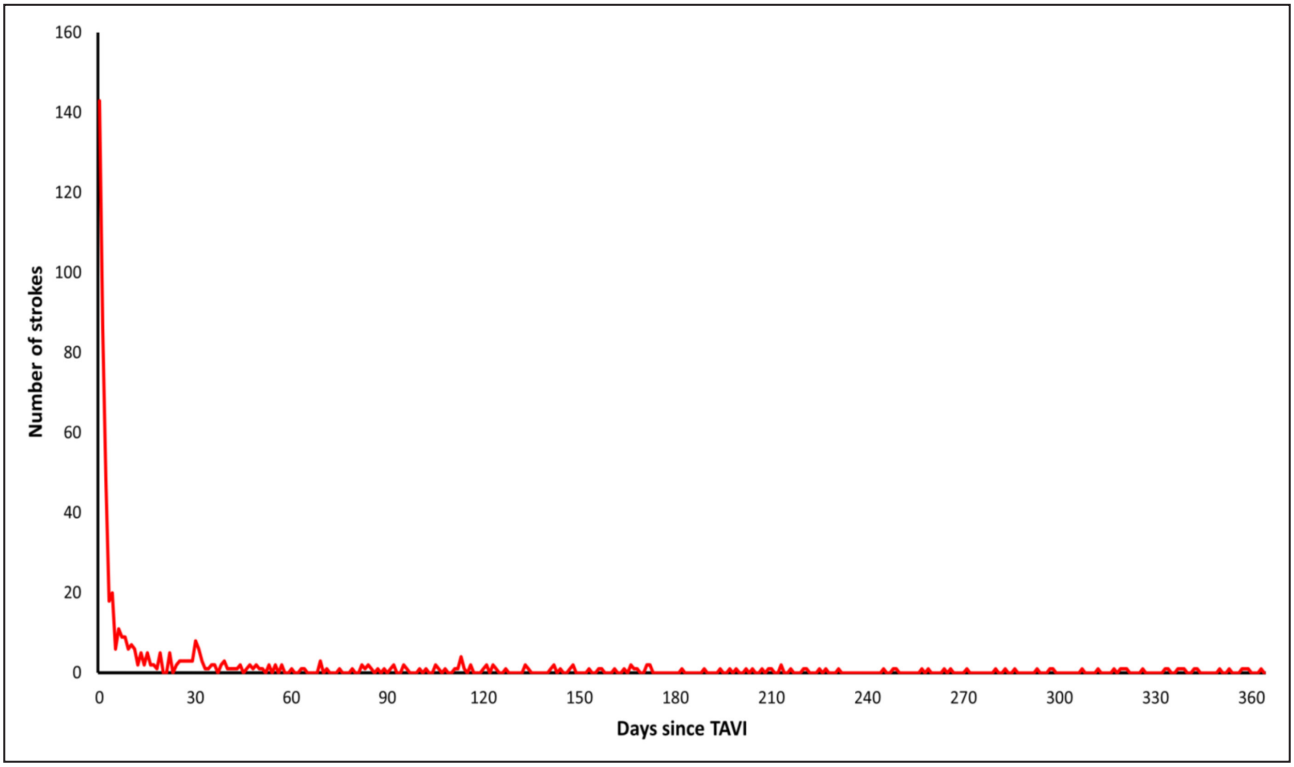

Figure 4. Timing of cerebrovascular events during the first year after TAVI.
TAVI indicates transcatheter aortic valve implantation.

accesses (n=25 754). Here, 30-day stroke incidence was 2.2%, and 1-year stroke was 7.0%.

DISCUSSION

Main Results

In 24 305 patients undergoing transfemoral TAVI between 2007 and 2022, 30-day stroke incidence was 2.2% in the first 30 days after TAVI. Thirty-day stroke rates did not decrease during the study period and were consistent through STS-PROM risk categories. Although mortality decreased in the total cohort, 1-year mortality rates in patients with 30-day stroke remained stable and high at ≈44%.

Risk factors for acute stroke were older age, higher mean aortic valve gradient, and lower BMI. Independent predictors for stroke after the acute period were higher age, previous cerebrovascular events, and renal failure.

Stroke Incidence

Thirty-day stroke incidence was consistent at ≈2.2% and did not decline during the study period, in line with previous studies.[8,14–16] Moreover, 30-day stroke incidence did not decrease in patients who had lower surgical risk scores. This is in contrast with the consecutive PARTNER (Placement of Aortic Transcatheter Valve Trial) and CoreValve randomized trials, which found decreasing rates of cerebrovascular events in subsequent studies with lower surgical-risk patients.[4,5] However, patients included in randomized controlled trials are in general more selected and may therefore not be representative of the general TAVI population. A recent analysis from the Transcatheter Valve Therapy registry found a modest decline in stroke incidence: from 2.7% in 2012 to 2.3% in 2019. However, the percentage of patients treated with a transfemoral approach dramatically increased during this period, from 57% to 93%.[7]

Despite lower-risk patients, improved valve design, and growing operator experience, stroke rates did not decline over the years. To reduce cerebrovascular event rates, various anticoagulation and antiplatelet strategies have been evaluated.[17–19]

The GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) trial randomized 1644 patients without an indication for oral anticoagulation to either rivaroxaban with aspirin (plus 3 months clopidogrel) or aspirin only (plus 3 months clopidogrel). The trial was halted prematurely due to higher bleeding and death rates in the rivaroxaban group, whereas there was no difference in cerebrovascular event rates.[19]

The ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic

and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis) trial stratum 2 randomized 1049 patients without an indication for anticoagulation to apixaban or standard of care (single or dual antiplatelet therapy). There were no differences in the combined primary end point of death, stroke, major bleeding, systemic embolism, cardiac or valve thrombosis.[17]

POPular TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic-Valve Implantation) trial randomized 690 patients without an indication for anticoagulation to aspirin plus 3 months clopidogrel or aspirin only. Aspirin only was superior for reduction of bleeding, but there was no difference in cerebrovascular event rates between treatment groups.[18]

Cerebral protection devices were developed to prevent cerebrovascular events by periprocedural capturing (or deflection) of emboli. These devices capture debris in up to 99% of patients.[20,21] The PROTECTED-TAVR (Stroke Protection with Sentinel During Transcatheter Aortic Valve Replacement) study randomized 3000 patients to TAVI with versus without cerebral protection. There was no reduction in clinical stroke, but rates of disabling stroke were lower. However, this finding should be interpreted with caution, because disabling stroke was 1 of 15 secondary end points for which the study was not powered.[16]

In summary, more intensive anticoagulation resulted in higher bleeding risk without a benefit on cerebrovascular event rates. Also, routine use of cerebral protection devices did not reduce overall cerebrovascular event rates.

In the current study, major bleeding incidence in patients with stroke was higher than in patients without stroke, which may be explained by hemorrhagic strokes or as a result of stroke therapy with thrombolysis or thrombectomy. Alternatively, frail patients are at increased risk for both bleeding and thromboembolic events.

Prediction of Cerebrovascular Events

Identification of patients at high risk for periprocedural cerebrovascular events remains challenging. Previously developed stroke prediction models in patients undergoing TAVI were not accurate.[22,23] In the current cohort, acute stroke was associated with older age and higher mean aortic valve gradient. These factors may both serve as indicators of a higher calcification burden in the aorta and aortic valve. More severe atherosclerosis has been associated with increased cerebral embolization during TAVI.[24,25] Interestingly, higher BMI was protective for acute stroke. In previous studies, an obesity paradox was observed in patients undergoing TAVI: higher BMI was associated with better clinical outcomes, whereas lower BMI may be a frailty indicator.[26]

In addition to highest stroke rates on the day of TAVI, risk for cerebrovascular events is also increased during the first week after TAVI (Figure 4). These subacute strokes may not be directly related to periprocedural emboli. Possibly, these cerebrovascular events might be due to silent (new onset) atrial fibrillation.[27] However, we did not find higher 30-day stroke rates in patients with preexisting or new-onset atrial fibrillation. Moreover, patients are continuously monitored during the first few days, which should enable detection of early new-onset atrial fibrillation. Alternatively, the TAVI procedure itself may enhance thrombin concentrations or platelet activation.[28] However, addition of clopidogrel in the POPular TAVI trial was not associated with lower risk for thromboembolic events.[29]

Risk factors for 30-day and 1-year stroke were older age and previous cerebrovascular events. These 2 risk factors both account for 2 points in the CHA_2DS_2-VASc and are therefore also strong predictors for stroke in patients with atrial fibrillation. Overlapping risk factors (older age and cerebrovascular events) may affirm that risk for cerebrovascular events approximates that of the background population once the bioprosthetic valve is endothelialized.[30] Renal failure is another well-known risk factor for stroke and was associated with increased risk for 1-year stroke in the current cohort. Renal failure has overlapping risk factors with stroke: aging, hypertension, diabetes, dyslipidemia, and obesity. In addition to these traditional cardiovascular risk factors, kidney-specific risk factors increase the risk for stroke through vascular injury and endothelial dysfunction: thrombogenic factors, chronic inflammation, sympathetic nerve overactivity, and hyperhomocysteinemia. In patients with severe renal failure, uremia-related factors even further increase stroke risk.[31]

Self-expanding valves have been previously associated with increased stroke risk.[6,21] However, these were all nonrandomized data. Factors associated with choice for a specific valve type may confound these findings. For example, patients with more severely calcified valves, and thus a potentially higher risk for cerebrovascular events, may be selected for self-expandable devices.

Although cerebrovascular events are relatively frequent, and half of strokes occurred on the day of procedure, there is no evidence-based guidance on optimal therapy for TAVI-related procedural stroke. Mortality in patients with stroke remains high. There was a nonstatistically significant trend to decreasing 1-year mortality over the years, but this may reflect younger and lower-risk patients undergoing TAVI. Future studies should therefore focus on identifying optimal therapy following stroke, because most patients are now treated conservatively.[14,32] Strokes caused by emboli originating from valve tissue, arterial wall, or even foreign material, may not respond to thrombolytic therapy.[20,21] Therefore,

thrombectomy may be the preferred therapy for procedural stroke if anatomically feasible.[14,32] Acute stroke treatment should be further explored in future studies and has the potential to drastically reduce mortality and morbidity.

Limitations

This study represents a global and real-world cohort, reflecting 15 years of TAVI experience. However, the observational design of our study has its inherent limitations. The current cohort was limited to patients with transfemoral access, because 95% of TAVI procedures are nowadays performed through a transfemoral approach.[7] Due to the more invasive nature of nontransfemoral access methods, our results cannot be directly extrapolated to these patients. All patients were treated according to local guidelines, which may have changed over the study period. Cerebral protection devices were used selectively in line with local practice, but use was not routinely captured. Data on cerebrovascular events were site reported, and not all studies had adjudication committees, which may have resulted in inaccuracies in the estimation of stroke incidence. One-year follow-up was not available in all patients, which could have potentially influenced the results of the secondary outcome analysis of 1-year stroke. Detailed information about vascular territory, stroke severity, and stroke treatment were not available. Moreover, potential predictors such as aortic valve calcium score, left ventricular outflow tract calcification, carotid artery stenosis, and prosthesis patient mismatch, were not available for all patients, and their influence on stroke could not be determined.

CONCLUSIONS

In this large global data set of 24 305 patients with aortic valve stenosis undergoing transfemoral TAVI, stroke rates did not decrease between 2007 and 2022. STS-PROM was not a good indicator of stroke risk, and stroke rates remained constant across surgical risk categories. Mortality remains high in patients with stroke during the study period. Our results underscore the need for more research into prevention of cerebrovascular events. In addition to prevention, futures studies should also focus on identifying high-risk patients and treatment strategies for periprocedural stroke.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Tables S1–S4

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