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Incidence, Predictive Factors, and Effect of Delirium After Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES The purpose of this study was to investigate the incidence, predictive factors, and effect of post-operative delirium (POD) among patients treated by transcatheter aortic valve replacement (TAVR).

BACKGROUND Patients undergoing operations that involve valve replacement appear at higher risk of POD than patients subjected to coronary artery bypass surgery alone. In patients with severe aortic stenosis undergoing TAVR, little is known regarding the potential impact of POD on the clinical outcomes.

METHODS A retrospective observational cohort study of 268 consecutive patients who underwent TAVR at our institute was conducted. Delirium was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorder, 4th Edition criteria. The primary outcome of this study was the presence of in-hospital POD after TAVR.

RESULTS The incidence of POD after TAVR was 13.4% (n = 36). Of these cases, 18 were associated with post-procedural complications, including major vascular complications/bleeding (n = 4), stroke (n = 3), acute kidney injury (n = 3), atrial fibrillation (n = 4), and infectious disease (n = 4). POD was most frequently diagnosed on the second day after TAVR (interquartile range [IQR]: 1 to 5 days) and was associated with prolonged in-hospital stay regardless of complications (in uncomplicated TAVR: 6 days [IQR: 5 to 10 days] vs. 5 days [IQR: 4 to 5 days]; $p < 0.001$; and in complicated TAVR: 9 days [IQR: 8 to 15 days] vs. 6 days [IQR: 5 to 9 days]; $p < 0.001$). Predictors of POD were nontransfemoral (transapical/transaortic) access (odds ratio [OR]: 7.74; 95% confidence interval [CI]: 3.26 to 18.1), current smoking (OR: 3.99; 95% CI: 1.25 to 12.8), carotid artery disease (OR: 3.88; 95% CI: 1.50 to 10.1), atrial fibrillation (OR: 2.74; 95% CI: 1.17 to 6.37), and age (OR: 1.08; 95% CI: 1.00 to 1.17, per year increase). After a median follow-up of 16 months (IQR: 6 to 27 months), POD remained an independent predictor of mortality in patients undergoing transfemoral TAVR compared with the nontransfemoral TAVR (hazard ratio: 2.81; 95% CI: 1.16 to 6.83 vs. hazard ratio: 0.43; 95% CI: 0.10 to 1.76), adjusted for possible confounders in a time-dependent Cox-regression model (i.e., age, sex, Logistic EuroSCORE and the occurrence of complications).

CONCLUSIONS POD after TAVR has an incidence of around 13% and occurs early in the post-operative course. Nontransfemoral access is strongly associated with the occurrence of POD. Patients who develop POD show prolonged in-hospital stay and impaired long-term survival. (J Am Coll Cardiol Intv 2016;9:160–8) © 2016 by the American College of Cardiology Foundation.

Delirium is an acute organic brain syndrome that often complicates the post-operative course of cardiac surgery (1,2). The incidence of post-operative delirium (POD) after cardiac surgery ranges between 8% and 31% (3–7), increasing with age to 25% to 52% in patients age ≥60 years (8–10) and 31% to 66% in patients age ≥70 years (11–13). Differences in study design and diagnostic criteria are likely responsible for the variance in the reported incidence of POD, as delirium is a clinical diagnosis easily overlooked. A hallmark of delirium is the acute onset and fluctuating course of symptoms related to cognitive dysfunction, including decreased consciousness, inattention, disorientation, and impaired memory (1). Depending on the presence of psychomotor disturbances, delirium can be classified as either hyperactive, hypoactive, or mixed (14). The etiology of delirium involves a complex

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interaction among predisposing factors (e.g., advanced age, pre-existing cognitive impairment, and previous stroke) and precipitating factors (e.g., surgery, medication changes, and hospitalization) (1).

Although mostly transient, delirium is not a benign cognitive disorder. After cardiac surgery, delirium prolongs mechanical ventilation time (14,15) and intensive care unit and hospital stay (7,15-17), and is associated with sepsis (18) and increased perioperative mortality (13,15). Furthermore, it negatively affects early functional and cognitive performance (6,19,20) and is related to increased mortality for up to 10 years (6,17,21). Moreover, delirium in general is linked to an elevated risk of dementia (22) and dramatically accelerates cognitive decline in Alzheimer disease (23). Whether delirium itself can induce dementia remains controversial, although there is evidence supporting this theory (24).

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Nonpharmacological strategies have shown effectiveness in the prevention of delirium in surgical patients, reducing the incidence by 30% to 40%, resulting in less morbidity, shorter length of stay, and reduced medical costs (25). Knowledge of the predictive factors of POD is crucial to identify patients who are at increased risk, and most likely to benefit from preventive measures and intensified post-operative monitoring. Numerous predictors of POD after cardiac surgery have been identified, of which higher age (3-5,7,11,15,26), cognitive impairment (3,4,7,8,10,13), active depression (4,7,10,14), atrial fibrillation (4,5,7), and cardiopulmonary bypass time (3,5,13,14) are most consistently reported.

Patients undergoing operations that involve valve replacement appear at higher risk of POD than patients subjected to coronary artery bypass surgery alone (8,27-29). Nowadays, transcatheter aortic valve replacement (TAVR) is used as an alternative to surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis (AS) who are deemed to be inoperable or at high surgical risk (30). Characterized by advanced age, frailty, and extensive comorbidities, patients undergoing TAVR seem particularly prone to develop POD. Despite the potential effect of delirium on outcomes and the vulnerability of typical candidates for the procedure, little is known regarding POD after TAVR. By means of this retrospective, descriptive study, we sought to investigate the incidence, predictive factors, and effect of POD among patients treated with TAVR.

TABLE 1 Diagnostic Criteria for Delirium According to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

I	Disturbance of consciousness (i.e., reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention).
II	A change in cognition (such as memory deficit, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.
III	The disturbance is developed over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
IV	Delirium is caused by the direct physiological consequences of a general medical condition (further criteria for specific forms of delirium caused by substance intoxication or withdrawal).

ABBREVIATIONS AND ACRONYMS

POD = post-operative delirium

TAVR = transcatheter aortic valve replacement

METHODS

This is a retrospective single-center study. All patients who underwent TAVR for severe native AS

TABLE 2 Baseline Clinical Characteristics of the Total Study Population

	Overall (n = 268)	Delirium		p Value
		Yes (n = 36)	No (n = 232)	
Age, yrs	80 ± 7	82 ± 5	80 ± 8	0.094
Male	123 (46)	17 (47)	106 (46)	0.864
BMI, kg/m^2	26 ± 4	26 ± 4	26 ± 4	0.830
BSA, m^2	1.83 ± 0.20	1.79 ± 0.18	1.84 ± 0.20	0.443
Logistic EuroSCORE	18 ± 9	20 ± 10	17 ± 9	0.814
NYHA functional class III-IV	154 (60)	24 (69)	130 (58)	0.238
Recent decompensation	50 (19)	11 (31)	39 (17)	0.050
Diabetes mellitus	82 (31)	11 (31)	71 (31)	0.995
Dialyses	4 (2)	2 (6)	2 (1)	0.088
Hypertension	154 (58)	26 (72)	128 (55)	0.054
Dyslipidemia	88 (33)	15 (42)	73 (32)	0.225
Smoking status				
Never smoker	180 (67)	19 (53)	161 (69)	0.048
Prior smoker	62 (23)	9 (25)	53 (23)	0.775
Current smoker	26 (10)	8 (22)	18 (8)	0.013
COPD	57 (21)	8 (22)	49 (21)	0.881
Estimated GFR, ml/min	57 ± 22	51 ± 24	58 ± 21	0.571
Syncope	36 (14)	6 (17)	30 (13)	0.439
Carotid artery disease*	33 (12)	12 (33)	21 (9)	0.000
Prior stroke	35 (13)	5 (14)	30 (13)	0.795
Peripheral artery disease	62 (23)	18 (50)	44 (19)	0.000
Coronary artery disease	144 (54)	20 (56)	124 (53)	0.813
Prior myocardial infarction	49 (18)	9 (25)	40 (17)	0.262
Prior PCI	109 (41)	15 (42)	94 (41)	0.896
Prior CABG	49 (18)	6 (17)	43 (19)	0.787
Prior BAV	8 (3)	0	8 (3)	0.603
Atrial fibrillation	92 (34)	17 (47)	75 (32)	0.080
Prior pacemaker implantation	21 (8)	2 (6)	19 (8)	0.749
Pulmonary hypertension	12 (5)	2 (6)	10 (4)	0.667
Active malignancy	16 (6)	1 (3)	15 (7)	0.704
Liver disease	5 (2)	1 (3)	4 (2)	0.517
Frailty	63 (24)	9 (25)	54 (23)	0.820

Values are mean ± SD or n (%). *Prior or planned carotid artery intervention and/or ≥50% diameter stenosis of the common carotid artery evaluated by computed tomography angiography or Duplex investigation.

BAV = balloon aortic valvuloplasty; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

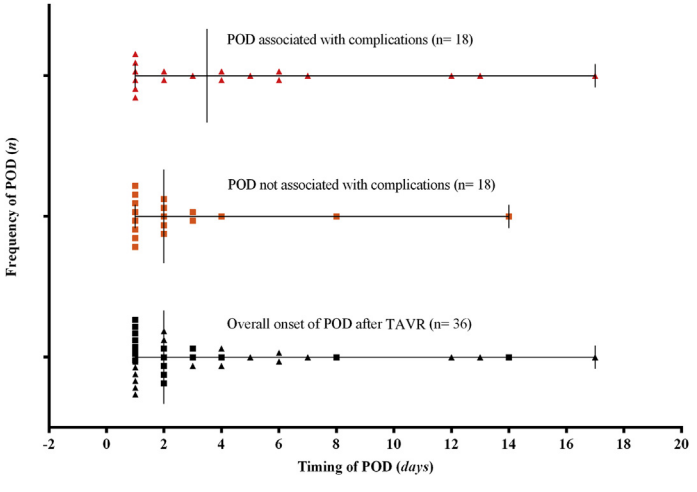
TABLE 3 Procedural Features

	Overall (n = 268)	Delirium		p Value
		Yes (n = 36)	No (n = 232)	
Procedural approach				0.000
TF	228 (85)	18 (50)	210 (91)	0.000
TF with general anesthesia	12 (5)	0	12 (6)	0.379
Nontransfemoral access*	40 (15)	18 (50)	22 (10)	0.000
General anesthesia	52 (19)	18 (50)	34 (15)	0.000
Balloon-expandable valve	174 (65)	27 (75)	147 (63)	0.173
Post-dilation	55 (21)	4 (11)	51 (22)	0.133
Conversion to surgery	1 (0.4)	0	1 (0.4)	1.000
Intraprocedural death	1 (0.4)	0	1 (0.4)	1.000
Radiation, mGy	683 (390–1,021)	701 (408–975)	694 (392–1,165)	0.244
Contrast volume, ml	159 ± 51	159 ± 59	160 ± 50	0.847
Procedural time, min	124 (112–145)	140 (122–159)	124 (110–144)	0.014
Interventional time, min	85 (73–105)	90 (76–110)	85 (74–104)	0.330

Values are n (%), median (interquartile range), or mean ± SD. *Transapical/transaortic.
TF = transfemoral approach.

at the University Medical Center Utrecht were identified in our institutional database and included in the study. Eligibility for TAVR was discussed by the heart team and required the consensus of at least 1 interventional cardiologist and 1 cardiac surgeon. Motivations to refuse SAVR in patients were high operative risk (as assessed by logistic EuroSCORE-I ≥15%) or the presence of contraindications to cardiac surgery (e.g., porcelain aorta, frailty, or patent grafts in proximity of the sternum). Frailty was subjectively measured before allocating TAVR by an interventional cardiologist and/or cardiothoracic surgeon on the basis of the informal "eyeball test" (including cognition function, physical weakness, and walk speed). Patients previously diagnosed with pre-cognitive impairment were excluded. All patients gave informed consent for the procedure, and due to the retrospective nature of the study design, ethics committee approval was waived.

FIGURE 1 Time to Onset of POD After Transcatheter Aortic Valve Replacement



POD = post-operative delirium; TAVR = transcatheter aortic valve replacement.

STUDY ENDPOINTS. The primary outcome of this study was the presence of delirium on any day during the in-hospital stay after TAVR. In case of suspected delirium observed by the nurse or attending physician, a delirium observational score (DOS) was used for further assessment. The DOS combines an assessment of the patient's level of consciousness with an evaluation of mental status, inattention, and disorganized thinking. When scoring ≥3 points, a trained geriatrician was consulted to establish or exclude the diagnosis of delirium on the basis of Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria (Table 1). If the diagnosis of delirium was established, a standardized work-up to exclude precipitating factors was set up (31). Other clinical outcomes were adjudicated in compliance with the Valve Academic Research Consortium 2 criteria (32). Vascular complications were documented for all procedural "access sites," defined as any location traversed by a guidewire, a catheter, or a sheath during the procedure, including arteries, veins, left ventricular apex, and the aorta. Post-discharge survival status was established by contacting the Municipal Civil Registries.

IMPLANTATION PROCEDURE. Patients were admitted 1 day before the procedure at our institution (if they were not already admitted because of clinical instability). Valve implantation was performed per the transfemoral, transapical, or transaortic approach, in order of our institutional preference, depending on the presence of suitable access sites. Common access techniques were used. All transfemoral procedures involved a fully percutaneous technique. Conscious sedation was the default anesthetic method in transfemoral procedures; in nontransfemoral TAVR, general anesthesia was instituted. For the transfemoral approach, conscious sedation was established by intravenous infusion of the sedative propofol and the analgesic remifentanil. Sedation was assessed according to the Ramsay sedation scale and was maintained between 3 and 5. Local anesthesia of the access sites was performed by lidocaine infiltration. After the procedure, transfemoral patients were transferred directly to the ward, avoiding any intensive care stay (including the coronary care unit). Nontransfemoral patients stayed for at least 1 night in the intensive care unit,

followed by the surgical medium care unit and thereafter the ward.

STATISTICAL ANALYSIS. Categorical variables are expressed as frequencies and percentages and were compared with the chi-square or Fisher exact test. Continuous variables are expressed as mean and SD if normally distributed or as median (interquartile range [IQR]) if skewed and compared with the Student *t* test or its nonparametric equivalents, respectively.

Univariable variables with p values <0.10 were entered in the backward stepwise multivariable logistic regression to identify the pre-procedural risk factors of POD. Collinearity diagnostics were evaluated for all variables considered for multivariable analysis. In case of multicollinearity, the variable with the higher odds ratio (OR) was incorporated into the model. The association between POD and mortality was analyzed using Kaplan-Meier survival estimates and the log-rank test. To isolate the association of POD with all-cause mortality, a Cox regression model was developed including possible confounders (i.e., age, sex, any post-procedural complication, and logistic EuroSCORE). The proportional hazards assumption was tested for each variable by visual inspection of the log-minus-log plots. Nonproportionality was accounted for by incorporation of time-dependent covariates. Results are reported as ORs or hazard ratios (HRs), where appropriate, with 95% confidence intervals (CIs). All tests were 2-tailed, and a p value <0.05 was considered statistically significant. All statistical analyses were carried out using the IBM Statistical Package for Social Science for Windows, version 21.0 (IBM Corp., Armonk, New York) and GraphPad Prism, version 6 (GraphPad Software, La Jolla, California).

RESULTS

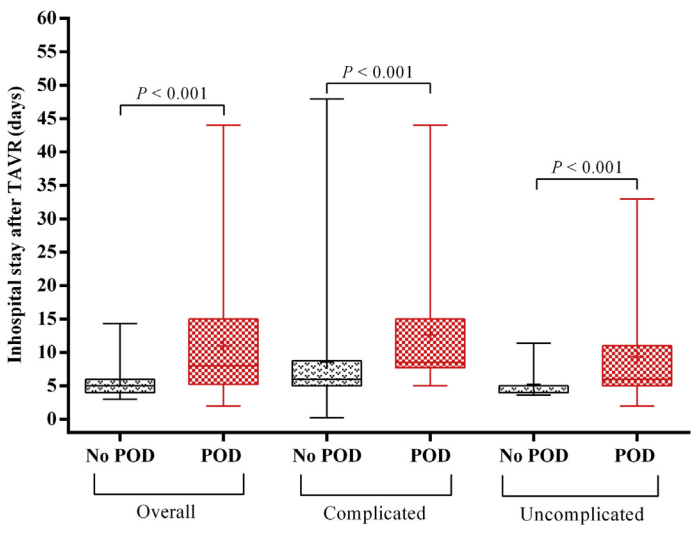
Between November 2011 and December 2014, 270 patients underwent TAVR because of severe symptomatic AS at the University Medical Center Utrecht. Two patients (0.7%) were excluded because of known Alzheimer disease, leaving 268 patients for further analysis. There were no cases of delirium observed before the procedure. The overall incidence of POD diagnosed in accordance with DSM-IV criteria was 13.4% (n = 36). Baseline characteristics and procedural and hospital outcomes of the study population stratified according to the occurrence of POD are summarized in Tables 2 to 4. Pre-operatively, the POD versus non-POD groups differed significantly in the rates of carotid disease (33% vs. 9%; p < 0.001), peripheral artery disease (50% vs. 9%; p < 0.001), and current smoking habit (22% vs. 18%; p = 0.013). Regarding procedural features, patients who developed POD more frequently underwent nontransfemoral procedures (50% vs. 10%; p < 0.001), more frequently received general anesthesia (50% vs. 15%; p < 0.001), and underwent longer procedures (140 min vs. 124 min; p = 0.014). Concerning clinical outcomes, stroke (8% vs. 1%; p = 0.034), cardiac tamponade (11% vs. 2%; p = 0.013), post-operative atrial fibrillation (11% vs. 0%; p < 0.001), infectious disease (11% vs. 0.4%; p = 0.001), and acute kidney injury (8% vs. 2%; p = 0.053) were more prevalent in the POD group. Of the 36 POD cases, 18 were associated with at least 1 post-procedural complication,

TABLE 4 In-Hospital Clinical Outcome

	Overall (n = 268)	Delirium Yes (n = 36)	Delirium No (n = 232)	p Value
Permanent pacemaker implantation	29 (11)	6 (17)	23 (10)	0.247
Stroke	6 (2)	3 (8)	3 (1)	0.034
Myocardial infarction	3 (1)	1 (3)	2 (1)	0.352
Cardiac tamponade	8 (3)	4 (11)	4 (2)	0.013
Atrium fibrillation	4 (2)	4 (11)	0	0.000
Infection	5 (1.9)	4 (11.1)	1 (0.4)	0.001
Any acute kidney injury	29 (11)	5 (14)	24 (10)	0.563
Acute kidney injury stage II/III	7 (3)	3 (8)	4 (2)	0.053
Major vascular complication	20 (8)	4 (11)	16 (7)	0.323
Bleeding (any)	80 (30)	14 (39)	66 (28)	0.240
Major or life-threatening bleeding	21 (8)	4 (11)	17 (7)	0.500
All-cause mortality	7 (3)	1 (3)	6 (3)	1.000

Values are n (%).

FIGURE 2 Post-Operative In-Hospital Stay



Abbreviations as in Figure 1.

TABLE 5 Baseline and Procedural Predictors for POD in Univariable and Multivariable Analysis

	Univariable	p Value	Multivariable	p Value
Age	1.04 (0.98–1.10)	0.160	1.08 (1.00–1.17)	0.041
Atrial fibrillation	1.87 (0.92–3.81)	0.083	2.74 (1.17–6.37)	0.020
Carotid artery disease	5.02 (2.20–11.5)	0.000	3.88 (1.50–10.1)	0.005
Current smoker	3.39 (1.35–8.53)	0.009	3.99 (1.25–12.8)	0.020
Peripheral artery disease	4.27 (2.06–8.87)	0.000	–	–
Hypertension	2.11 (0.97–4.58)	0.058	–	–
Nontransfemoral access*	9.55 (4.34–21.0)	0.000	7.74 (3.26–18.1)	0.000
General anesthesia	5.82 (2.75–12.3)	0.000	–	–

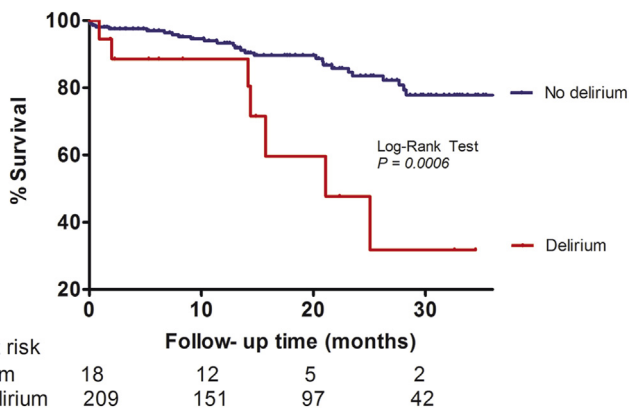
Values are odds ratio (95% confidence interval). *Transapical or transaortic transcatheter aortic valve replacement approach.

including major vascular complications/bleeding (n = 4), stroke (n = 3), acute kidney injury (n = 3), atrial fibrillation (n = 4), and infectious disease (n = 4).

Delirium was most frequently diagnosed on day 2 (IQR: 1 to 5 days) after TAVR (Figure 1) and was associated with prolonged in-hospital stay regardless of complications (in uncomplicated TAVR: 6 days [IQR: 5 to 10 days] vs. 5 days [IQR: 4 to 5 days]; p < 0.001; and in complicated TAVR: 9 days [IQR: 8 to 15 days] vs. 6 days [IQR: 5 to 9 days]; p < 0.001) (Figure 2).

Multivariable logistic regression analysis showed that nontransfemoral access (OR: 7.74; 95% CI: 3.26 to 18.10), current smoking (OR: 3.99; 95% CI: 1.25 to 12.80), carotid artery disease (OR: 3.88; 95% CI: 1.50 to 10.10), atrial fibrillation (OR: 2.74; 95% CI: 1.17 to 6.37), and age (OR: 1.08; 95% CI: 1.00 to 1.17) were independent predictors of POD (Table 5). General anesthesia was not incorporated in the model because of multicollinearity with nontransfemoral access.

FIGURE 3 Kaplan-Meier Survival Curves of the Association Between POD After Transfemoral TAVR and Mortality



POD = post-operative delirium; TAVR = transcatheter aortic valve replacement.

After a median follow-up of 16 months (IQR: 6 to 27 months), overall mortality was 18%. Patients who developed POD demonstrated higher mortality in transfemoral TAVR (39% vs. 13%; p = 0.003) but not in nontransfemoral TAVR (33% vs. 36%; p = 0.841). POD remained a significant predictor of mortality in transfemoral TAVR (HR: 2.81; 95% CI: 1.16 to 6.83), but not in nontransfemoral TAVR (HR: 0.43; 95% CI: 0.10 to 1.76), independent of age, sex, logistic EuroSCORE, and the occurrence of complications (Online Table 1, Figures 3 and 4).

DISCUSSION

In the present study, we investigated the incidence, predictors, and effect of POD after TAVR. The incidence of POD (on the basis of DSM-IV criteria) was 13.4% in this cohort. Nontransfemoral TAVR, increased age, carotid artery disease, current smoking habit, and AF were independent predictors of POD. The occurrence of POD was associated with prolonged in-hospital stay regardless of complications and remained an independent predictor of mortality in transfemoral TAVR but not in nontransfemoral TAVR when adjusted for age, sex, logistic EuroSCORE, and the occurrence of complications.

Post-operative delirium is an outcome that certainly deserves attention in TAVR, as the typical target TAVR patient and several procedural aspects of TAVR designate this intervention as “high risk” of being complicated by delirium. Advanced age and significant comorbidities may predispose all TAVR candidates to POD. Moreover, ischemic brain injury, 1 of the mechanisms suspected to cause POD through alteration of cerebral acetylcholine levels (33), is commonly encountered in TAVR. In cardiac surgery, a higher microembolic load (34), elevated biomarkers of brain tissue damage (35), and clinical cerebrovascular events (5,10,26) have been associated with POD. In response to brain injury, increased microglia activity induced by neuroinflammation in the brain has been hypothesized to be 1 of the mechanisms that may contribute to POD (36). Brain injury related to TAVR most often involves (micro)infarctions caused by cerebral embolization of aortic plaque or valve particles dislodged during prosthesis positioning and deployment (37). Rapid ventricular pacing may also contribute to ischemic brain injury by causing episodic hypotension and cerebral hypoperfusion (38).

Data on the incidence of delirium after TAVR are scarce, as the present study is 1 of the first on this topic. A previous small cohort study (including patients treated in 2008 and 2009, n = 122) reported a 12% incidence of POD after transfemoral TAVR and 53%

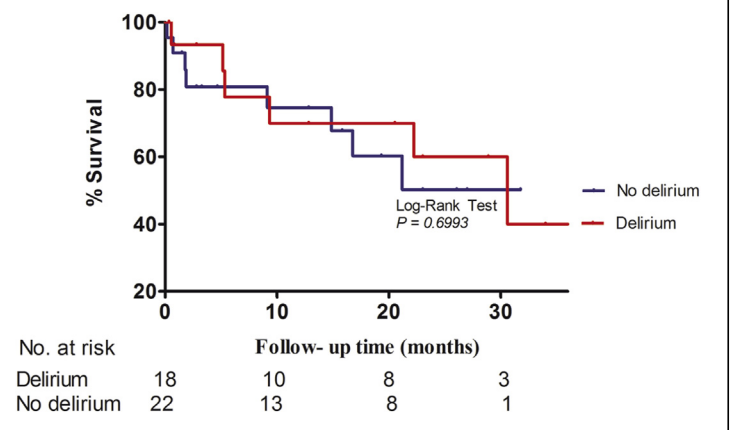
after transapical TAVR (39). This is in line with the 8% and 45% POD rate after transfemoral and nontransfemoral TAVR in our analysis. Despite extensive comorbidities, POD appears to occur substantially less often after transfemoral TAVR (<10%) than after SAVR in elderly patients (31% to 66%), whereas the incidence of POD after nontransfemoral TAVR (~50%) seems to approach that of SAVR (8,12). Recently, a nonrandomized prospective study investigating POD in octogenarians after TAVR and SAVR reported SAVR as a risk factor for POD, with a 22% higher incidence compared with TAVR (12). The reported 44% rate of POD after TAVR in this study is difficult to interpret, however, due to the absence of data on procedural access and the use of a different diagnostic tool (confusion assessment method) for delirium.

Similar to previous data, nontransfemoral access was identified as the strongest predictor of POD in the present analysis (39). A distinct feature of patients with nontransfemoral access is the presence of advanced vascular disease, which may be indicative of coexisting cerebrovascular disease, creating increased potential for intraprocedural cerebral ischemia and POD. Otherwise, nontransfemoral procedures involve a stronger noxious stimulus than transfemoral TAVR, due to the need for general anesthesia, the intensive care stay, and the disorienting effect of the frequent change of environment, and is therefore more likely to precipitate delirium. Nontransfemoral access also comes with post-operative pain, increased opioid use, and post-operative inflammation, all factors capable of triggering POD. Although significantly associated with POD in the univariable analysis, the independent effect of general anesthesia could not be assessed in the present study because of multicollinearity with nontransfemoral TAVR. General anesthesia has been linked to post-operative cognitive dysfunction, as general anesthetics exert an anticholinergic effect and interfere with many neural processes, involving intracellular calcium signaling, receptor functioning, and gene transcription (40). Clinical data on the relevance of anesthetic technique (general anesthesia vs. local anesthesia ± sedation) in provoking delirium are inconclusive. However, considering the many procedural aspects that may promote delirium, it seems implausible that anesthetic technique is solely causative for the higher rate of POD in nontransfemoral TAVR.

All remaining predictors found in this study, including older age (3-5,7,11,15,26), carotid artery disease (5,26,41), atrial fibrillation (4,5,7), and current smoking (42), have been previously related to POD in cardiac surgery. The common denominator of these factors may be their involvement in the causative chain of ischemic brain injury through an association with (cerebral) atherosclerosis or thromboembolism. Older age is also a risk factor of POD due to an age-dependent decrease in neurotransmitter release and overtime accumulation of cerebral tissue damage that aggravate susceptibly to brain dysfunction (1,43). Besides promoting atherosclerosis, active smoking has been hypothesized to contribute to POD by abrupt cessation during hospitalization, because nicotine withdrawal involves acetylcholine disturbances similar to POD (44). Pre-operative AF not only is postulated to predispose to POD by inflicting thromboembolic brain damage, but may additionally provoke periods of hypotension causing cerebral hypoperfusion (45).

Analogous to observations in conventional cardiac surgery, POD after TAVR was related to an adverse outcome in the present analysis, characterized by prolonged in-hospital stay, and, in case of transfemoral TAVR, elevated follow-up mortality. Stratification according to the presence of post-operative complications (other than delirium) demonstrated that POD in itself leads to prolonged hospitalization after TAVR. To what extent increased morbidity and mortality can be truly attributed to POD is difficult to establish (46). Rather than being causally related to adverse events, POD may reflect a patient's decreased resilience against noxious stimuli (i.e., fragility), merely identifying those individuals already predisposed to worse treatment outcomes. Along similar lines, the occurrence of POD after less physically demanding transfemoral procedures may identify extremely frail patients, which may explain the higher mortality rate. Uncertainty regarding the

FIGURE 4 Kaplan-Meier Survival Curves of the Association Between POD After Nontransfemoral TAVR and Mortality



Abbreviations as in Figure 3.

TABLE 6 Adapted Guidelines for Prevention of Delirium in At-Risk Adults From the National Institute for Health and Care Excellence

	Pre-Operative Assessment
1	Avoid moving persons within and between wards or rooms unless absolutely necessary
2	Give a tailored, multicomponent intervention package on the basis of the risk factors for delirium
	Post-Operative Care
3	Reorient the patient at risk by providing appropriate lighting and clear signage, ensuring that a clock (consider providing a 24-h clock in the critical care unit) and a calendar are easily visible
4	Address dehydration and constipation by ensuring adequate fluid intake
5	Assess for hypoxia and optimize oxygen saturation, if necessary, as clinically appropriate
6	Treat infections and avoid unnecessary catheterization
7	Promote mobility
8	Address and assess for pain
9	Carry out a medication review for persons receiving several drugs, taking into account both the type and the number of medications
10	Address poor nutrition by following the advice given in the nutrition support in adults section in the NICE clinical guideline
11	Screen and address sensory impairment by providing hearing and visual aids
12	Promote good sleep patterns

Guidelines adapted from O'Mahony et al. (47).
NICE = National Institute for Health and Care Excellence.

sequence of events also clouds the perception of the true effect of POD; for example, prolonged mechanical ventilation has been reported as both a predictor as well as a consequence of delirium, and the same holds true for cognitive impairment (7,9,14,15). Nevertheless, in view of the magnitude of evidence reporting unfavorable outcomes and increased medical costs in POD, it certainly seems like an entity to be avoided, especially in the elderly.

Primary prevention and early recognition of delirium have demonstrated effectiveness in reducing delirium incidence and falls. Moreover, prevention may decrease the length of in-hospital stay, reduce the need for institutionalization, and ultimately reduce medical costs (1,25). The predictors identified in this study can aid in the identification of TAVR patients who are at higher risk for developing POD and who will benefit most from intensified surveillance and targeted prevention. Although many predisposing and precipitating factors of delirium are nonmodifiable, several nonpharmacological measures can be taken to prevent POD in susceptible patients, as summarized in **Table 6** (47). Specifically, in the TAVR setting, it seems advisable to avoid nontransfemoral access whenever justified. To date, there is no consensus on the efficacy of pharmacological therapy in the prevention and treatment of delirium (1). Whether a reduction of embolic burden by cerebral protection devices may positively affect the rate of POD in TAVR seems speculative considering the multifactorial nature of this cognitive disorder.

STUDY LIMITATIONS. The main limitations of this study are related to its retrospective, single-center design. The retrospective assessment of delirium may have led to underestimation of the incidence of delirium, as symptoms can be subtle, especially in the case of the hypoactive form. Furthermore, we were unable to reliably quantify in retrospect the presence of pre-operative cognitive impairment and active depression, important predictors of POD in cardiac surgery. Finally, the relatively small sample size (transfemoral and nontransfemoral groups) did not allow for exhaustive multivariable analysis to fully isolate the independent effect of delirium on follow-up mortality.

CONCLUSIONS

Despite their apparent susceptibility, only 1 in 8 TAVR patients develops delirium during the post-operative course. The incidence of POD heavily depends on procedural access, with a 5-fold higher rate in nontransfemoral compared with transfemoral TAVR. Besides procedural access, older age; carotid artery disease; current smoking; and pre-operative AF were identified as independent predictors of POD. Post-operative delirium after TAVR was associated with prolonged in-hospital stay and increased all-cause mortality during follow-up. Early recognition and prevention strategies may decrease the incidence of POD and improve outcomes in TAVR patients. Future large prospective studies are needed to confirm these first findings on POD after TAVR.

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PERSPECTIVES

WHAT IS KNOWN? In cardiac surgery, POD complicates the post-operative course with prolonged in-hospital stay and increased long-term mortality. Despite the potential effect of delirium on outcomes after TAVR and the susceptibility of these patients, little is known regarding POD after TAVR.

WHAT IS NEW? The incidence of POD is 13.4% in this cohort, which is 5-fold higher in nontransfemoral TAVR (45% vs. 8%). The baseline independent predictors of POD are nontransfemoral TAVR, age, carotid artery disease, current smoking, and atrial fibrillation. The occurrence of POD was associated with prolonged in-hospital stay regardless of complications, and remained an independent predictor of mortality in a transfemoral TAVR but not in nontransfemoral TAVR when adjusted for age, sex, logistic EuroSCORE, and the occurrence of complications.

WHAT IS NEXT? The predictors identified in this study can aid the identification of TAVR patients who are at higher risk for developing POD and who will benefit most from intensified surveillance and targeted prevention.

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KEY WORDS post-operative delirium, transcatheter aortic valve replacement

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