Evolution of Cognitive Function After Transcatheter Aortic Valve Implantation

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Background—This study aimed to assess the evolution of cognitive function after transcatheter aortic valve implantation (TAVI). Previous smaller studies reported conflicting results on the evolution of cognitive function after TAVI.

Methods and Results—In this prospective cohort, cognitive function was measured in 229 patients ≥70 years using the Mini Mental State Examination before and 6 months after TAVI. Cognitive deterioration or improvement was defined as change of ≥3 points decrease or increase in the Mini Mental State Examination score between baseline and follow-up. Cognitive deterioration was found in 29 patients (12.7%). Predictive analysis using logistic regression did not identify any statistically significant predictor of cognitive deterioration. A review of individual medical records in 8 patients with a major Mini Mental State Examination score decrease of ≥5 points revealed specific causes in 6 cases (postinterventional delirium in 2; postinterventional stroke, progressive renal failure, progressive heart failure, or combination of preexisting cerebrovascular disease and mild cognitive impairment in 1 each). Among 48 patients with impaired baseline cognition (Mini Mental State Examination score <26 points), 18 patients (37.5%) cognitively improved. The preinterventional aortic valve area was lower in patients who cognitively improved (median aortic valve area 0.60 cm^2) as compared with patients who did not improve (median aortic valve area 0.70 cm^2; P=0.01).

Conclusions—This is the first study providing evidence that TAVI results in cognitive improvement among patients who had impaired preprocedural cognitive function, possibly related to hemodynamic improvement in patients with severe aortic stenosis. Our results confirm that some patients experience cognitive deterioration after TAVI. **(*Circ Cardiovasc Interv*. 2016;9:e003590. DOI: 10.1161/CIRCINTERVENTIONS.116.003590.)**

Key Words: aortic valve stenosis ■ cognition ■ geriatric assessment ■ heart failure ■ transcatheter aortic valve replacement

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement in patients with severe aortic stenosis and high surgical risk.[1–7] Consequently, most patients undergoing TAVI are old and have multiple comorbidities.[1–9] In these patients, functional aspects, especially cognitive function, are highly relevant.[8–11] In a previous analysis, we showed that patients with impaired cognitive function before TAVI have an ≈3-fold increased risk of mortality at 1-year follow-up as compared with those with normal cognitive function and that cognitive impairment is also associated with increased morbidity as well as with disability and reduced quality of life after TAVI.[8,9]

Data on evolution of cognitive function after TAVI is sparse. Only 4 small studies reported on evolution of cognitive function in TAVI patients.[12–15] In the largest one, Ghanem et al[12] evaluated the cognitive trajectory in 111 TAVI patients and found that cognitive function was preserved in the great majority throughout the first 2 years after TAVI. Cognitive deterioration was found in only 9% of the patients.[12] Results of the other 3 smaller studies were inconclusive, with 2 reporting mild deterioration and 1 reporting improvement of cognitive function after TAVI.[13–15] The small numbers of patients in all of these studies resulted in a limited statistical power for the analysis of clinical predictors for cognitive change after TAVI in all these studies. We investigated the evolution of cognitive function in a large cohort of patients undergoing TAVI and assessed potential predictors for cognitive deterioration or improvement.

Methods

Study Population

Consecutive patients ≥70 years with symptomatic severe aortic stenosis and referred for TAVI evaluation to Bern University Hospital,

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WHAT IS KNOWN

- In patients undergoing transcatheter aortic valve implantation (TAVI) cognitive function before and after the intervention is highly relevant.
- Previous smaller studies reported conflicting results on the evolution of cognitive function after TAVI. In the largest one investigating 111 patients, cognitive deterioration was found in only 9% of the patients.

WHAT THE STUDY ADDS

- This study confirms that some patients (12.7%) experience cognitive deterioration after TAVI.
- This study provides evidence that TAVI may result in cognitive improvement among patients who had impaired preprocedural cognitive function.
- The cognitive improvement in these patients is possibly related to hemodynamic improvement in patients with severe aortic stenosis.

Switzerland, between September 1, 2009, and December 31, 2012, were eligible for this prospective cohort study. An interdisciplinary team of interventional cardiologists and cardiac surgeons reviewed the individual cases to decide on treatment selection (TAVI, surgical aortic valve replacement, or medical treatment). The consensus was based on several parameters, including anatomic characteristics of the aortic root, vascular access site specifications, the estimated perioperative risk using the logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) and the Society of Thoracic Surgeons score, underlying comorbidities, and the general clinical condition. The following patients were excluded: (1) patients with a treatment other than TAVI (ie, surgical aortic valve replacement or medical treatment); (2) patients in whom TAVI was performed as emergency procedure; and (3) patients who were unable to comply with the scheduled prospective follow-up evaluation. All other patients were asked for study participation. If they provided written informed consent, baseline cognitive testing was performed. Of the patients who received the baseline cognitive testing, we also excluded patients awaiting a TAVI procedure after December 31, 2012, and those in whom the time between baseline cognitive testing and TAVI was >3 months. The final study population consisted of all patients in whom TAVI and baseline cognitive testing was performed during the study period. TAVI was performed according to current standards.[6] The transcatheter aortic valve was introduced transfemorally whenever feasible according to measurements based on a computed tomography scan. Either a Medtronic CoreValve (Medtronic Inc, Minneapolis, MN) or an Edwards Sapien XT bioprosthesis (Edwards Lifesciences, Irvine, CA) was implanted. Patients who received TAVI using the femoral access route received conscious sedation only. This study complies with the Declaration of Helsinki and was approved by the local ethics committee. All patients provided written informed consent.

Measurements

General Evaluation

All participating patients received extensive cardiological and geriatric baseline evaluation. Data from patient history included New York Heart Association functional class, medication, cardiovascular risk factors, prior cardiovascular events and further comorbidities, and years spent for education. Study-specific physical examination included weight, height, and blood pressure. Left ventricular ejection fraction, aortic valve area (AVA), and transvalvular mean gradient were measured with transthoracic or transesophageal echocardiography. All patients underwent cardiac catheterization to provide information on the presence of coronary artery disease, on right heart filling pressures, and on cardiac output. All patients received geriatric evaluation using the Timed Get Up and Go Test for gait function,[16] the Mini Nutritional Assessment for nutritional status,[17] and the Basic Activities of Daily Living for autonomy.[18] In addition, relevant periprocedural information (TAVI access route, postintervention complications according to Valve Academic Research Consortium criteria,[19] and length of in-hospital stay) were recorded in all patients.

Cognitive Testing

Cognitive testing was performed using the Mini Mental State Examination (MMSE).[20] For the purpose of this analysis, the MMSE instrument was dichotomized at a standard cutoff point, which was defined a priori according to current literature: a global score ≥26 points was considered normal and a score <26 points was considered impaired.[21] Testing was conducted face-to-face by specially trained medical personnel. Baseline testing was performed before TAVI, but no longer than 3 months before TAVI. For follow-up cognitive testing, patients were invited 6 months after TAVI. Follow-up cognitive testing was usually done between sixth and ninth month after TAVI, but a maximum range between day 160 and day 300 after TAVI was allowed. To determine relevant cognitive deterioration or improvement between follow-up and baseline, we calculated the MMSE score difference between follow-up and baseline and used the baseline standard deviation rounded to the next integer as cutoff point.[12] We used 2 different cutoffs for the definition of change in MMSE. For the statistical analyses, we used a cutoff of ≥3 points to define relevant change (deterioration or improvement). For medical record review, we used a cutoff of ≥5 points to define a major change in cognitive function, according to test–retest reliability evaluations of MMSE score changes.[22,23]

Medical Record Review

We reviewed individual medical records of patients with a major cognitive deterioration or improvement between baseline and follow-up to search for potential reasons of the major change.

Statistical Analysis

We described baseline characteristics using frequencies (n) and percentages (%), median and interquartile range. Changes in cognition after TAVI were based on differences of follow-up and baseline MMSE scores of ≥3 points to define a relevant change. We compared baseline characteristics of patients, who cognitively deteriorated or improved, in bivariable analyses. Cognitive deterioration was analyzed for all patients and cognitive improvement in the subgroup of patients with impaired baseline cognition. Group differences were assessed by a chi-squared test for categorical variables and a Wilcoxon rank-sum test for continuous variables. Change differences were assessed by a paired Wilcoxon signed-rank test. P values <0.05 were considered statistically significant.

We used multivariable logistic regression models to investigate predictors for cognitive function. As dependent variable, we used cognitive deterioration. Because of the small sample size of patients with impaired cognitive function, multivariable models were fitted only for cognitive deterioration. Baseline characteristics used as independent variables were selected based on an a priori analysis plan. Continuous variables were modeled as quadratic functions. Nonlinearity was tested by Wald statistics.[24] Estimates from continuous variables were reported as a comparison of the 25th or 75th percentile versus the 50th percentile (median). We used unadjusted models and models adjusted for age, sex, and additionally baseline MMSE. We report both adjusted models (ie, adjusted for age and sex, as well as adjusted for age, sex, and baseline MMSE) because adjustment for baseline cognitive function may substantially alter coefficient estimates of predictor variables in regression models.[25] To address potential selection bias, we used a multiple imputation approach using chained equations.[26,27] The imputation model consisted of baseline and follow-up information, including lifestyle, psychosocial, and socioeconomic variables to make the missing at random assumption more plausible[28] (for a list of all variables included in the imputation model, see Table I in

the Data Supplement). We built 25 complete data sets and reported the pooled estimate results using Rubin's rule.[26] We calculated imputed estimates from the population surviving 6-month follow-up (N=248) and in addition from the total enrolled population (ie, imputed results based on patients who did and did not survive; N=279). Estimates from the predictive analyses were reported as odds ratio with 95% confidence interval. Finally, as a sensitivity analysis, we conducted an analysis with the difference of follow-up and baseline MMSE score as a continuous dependent variable. Because a clinically relevant cognitive deterioration is assumed for MMSE differences of ≤−3 points, we used a censored Gaussian regression model with censored MMSE differences >−3 points to assess clinically relevant cognitive deterioration and report differences in MMSE with 95% confidence interval.[29] All data were analyzed with Stata 13.1 (StataCorp LP, College Station, TX) or R version 3.1.1 (2013; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Population

Figure shows the study flow chart. Of 509 patients ≥70 years referred for TAVI evaluation, 279 patients actually received elective TAVI procedure and met all inclusion criteria for study enrollment. Among the 279 enrolled patients, 31 patients (11.1%) died within 6 months after TAVI. Of the 248 surviving patients, 19 patients (7.7%) did not receive testing because of logistic reasons or patient refusals, and for 229 patients, cognitive testing at follow-up was available.

Table 1 shows the baseline characteristics of the 3 groups of patients: surviving patients who underwent cognitive follow-up testing (N=229), surviving patients who did not receive cognitive follow-up testing (N=19), and patients who died (N=31) over the 6-month follow-up period. Mean age was 83.4±5.5 years (maximum range 71.6–93.2 years) for the surviving patients who underwent cognitive follow-up testing. In this subgroup, the transfemoral access was used in the majority of patients (93.0%); only a minority (7.0%) received the transapical access. Table 1 shows that the subgroup of surviving people with missing cognitive outcome (N=19) had a somewhat worse health status as compared with people with available follow-up information (N=229; eg, difference in logistic EuroSCORE).

Changes in Cognition After TAVI

The median MMSE global score did not change between baseline (median 27.0 points [interquartile range 2.0, range 15–30]) and follow-up (median 27.0 points [interquartile range 3.0, range 16–30]; *P*=0.59) in the study population. There were, however, considerable individual variations: 29 of 229 patients (12.7%) in the study population had relevant deterioration in the MMSE score (3 or more points decrease). Among the subgroup of 48 patients with impaired baseline cognition, 18 patients (37.5%) cognitively improved and only 6 (12.5%) further deteriorated. Detailed information with individual plots and subgroup data based on baseline MMSE are depicted in Figures I and II and Table II in the Data Supplement.

Differences in Baseline Characteristics According to Development of Cognition

There were no significant differences of baseline characteristics between patients who did and who did not cognitively deteriorate (Table III in the Data Supplement) among patients surviving at 6 months. In patients who cognitively improved, the baseline AVA was significantly lower as compared with the baseline AVA of patients in whom cognitive function did not improve at 6-month follow-up (median AVA 0.60 versus 0.70 cm^2; *P*=0.01; Table 2), but no statistically significant differences were found for the other baseline parameters.

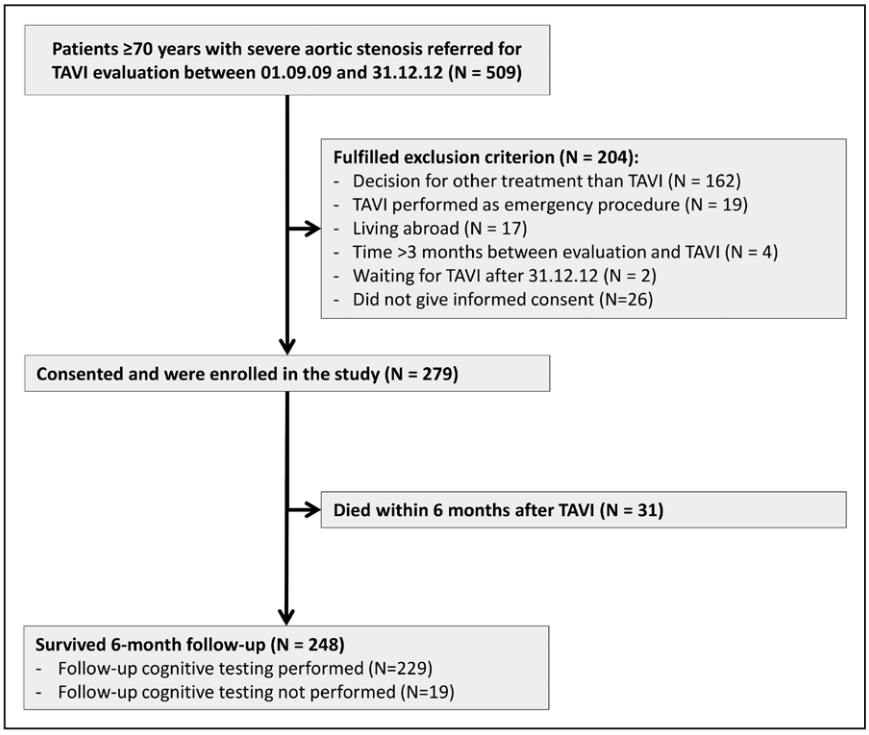

Figure. Flow chart. TAVI indicates transcatheter aortic valve implantation.

Table 1. Characteristics of Patients With Available Follow-Up Cognitive Testing (N=229), Patients With Missing Follow-Up Cognitive Testing (N=19), and Patients Who Died Within 6 Months After Enrollment (N=31)

Characteristic	Surviving Patients, Follow-Up Cognitive Testing Performed (N=229)	Surviving Patients, Follow-Up Cognitive Testing Not Performed (N=19)	Patients Who Died Within 6 mo (N=31)
Age, y, median (IQR)	83.4 (5.5)	83.2 (5.9)	84.5 (7.0)
Female sex, n (%)	128 (55.9)	12 (63.2)	21 (67.7)
Education, ≤9 y of education, n (%)	73 (31.9)	7 (36.8)	15 (48.4)
BMI, kg/m^2, median (IQR)	25.6 (5.5)	24.2 (3.5)	24.7 (5.1)
Comorbidities			
Hypertension, n (%)	209 (91.3)	17 (89.5)	25 (80.7)
Dyslipidemia, n (%)	152 (66.4)	16 (84.2)	20 (64.5)
Diabetes mellitus, n (%)	53 (23.1)	9 (47.4)	8 (25.8)
CAD, n (%)	138 (60.3)	17 (89.5)	23 (74.2)
Previous MI, n (%)	25 (10.9)	6 (31.6)	3 (9.7)
Atrial fibrillation, n (%)	68 (29.7)	8 (42.1)	13 (41.9)
Previous stroke, n (%)	25 (10.9)	2 (10.5)	3 (9.7)
Previous syncope, n (%)	35 (15.3)	5 (26.3)	5 (16.1)
PAD, n (%)	28 (12.2)	5 (26.3)	3 (9.7)
COPD, n (%)	31 (13.5)	3 (15.8)	7 (22.6)
Symptoms at baseline			
NYHA III/IV, n (%)	160 (69.9)	9 (47.4)	10 (32.3)
Angina CCS 3/4, n (%)	31 (13.5)	3 (15.8)	2 (6.4)
Echocardiography and laboratory measurements at baseline			
Systolic BP, mm Hg, median (IQR)	132.0 (31.0)	128.0 (24.0)	124.0 (42.5)
Diastolic BP, mm Hg, median (IQR)	69.0 (19.0)	62.0 (11.5)	65.0 (20.0)
LVEF, %, median (IQR)	60.0 (19.0)	40.0 (23.5)	50.0 (17.5)
Mean gradient aortic valve, mm Hg, median (IQR)	41.0 (21.2)	40.0 (21.0)	42.0 (23.0)
AVA, cm^2, median (IQR)	0.64 (0.30)	0.50 (0.38)	0.62 (0.27)
Creatinine, μmol/L, median (IQR)	90.0 (40.0)	81.0 (25.0)	92.0 (53.0)
Medication at baseline			
Betablocker, n (%)	115 (50.2)	11 (57.9)	19 (61.3)
ACEI/ARB, n (%)	140 (61.1)	7 (36.8)	13 (41.9)
Diuretics, n (%)	163 (71.2)	16 (84.2)	5 (16.1)
Calcium antagonist, n (%)	50 (21.8)	6 (31.6)	2 (6.4)
Risk scores at baseline			
Logistic EuroSCORE, %, median (IQR)	17.6 (15.8)	28.9 (15.1)	29.9 (21.7)
STS score, %, median (IQR)	5.5 (3.7)	6.8 (6.1)	6.9 (3.5)
Geriatric assessment at baseline			
MMSE <26 points, n (%)	48 (21.0)	3 (15.8)	12 (38.7)
TUG ≥20 s, n (%)	59 (26.9)	8 (47.1)	13 (54.2)
MNA <12 points, n (%)	96 (42.3)	10 (52.6)	19 (61.3)
BADL ≥1 activity with limitation, n (%)	54 (23.6)	5 (26.3)	13 (41.9)
Procedural and periprocedural characteristics			
Transfemoral access route, n (%)	213 (93.0)	17 (89.5)	26 (83.9)

(*Continued*)

Table 1. Continued

Characteristic	Surviving Patients, Follow-Up Cognitive Testing Performed (N=229)	Surviving Patients, Follow-Up Cognitive Testing Not Performed (N=19)	Patients Who Died Within 6 mo (N=31)
Length of in-hospital stay, days, median (IQR)	7.0 (3.0)	7.0 (3.0)	7.0 (4.5)
Stroke or myocardial infarction within 30 days based on VARC criteria, n (%)	7 (3.1)	0 (0.0)	8 (25.8)

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVA, aortic valve area; BADL, Basic Activities of Daily Living; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; NYHA, New York Heart Association functional class; PAD, peripheral artery disease; SD, standard deviation; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation; TUG, Timed Get Up and Go Test; and VARC, Valve Academic Research Consortium.

Predictive Analysis

Table 3 shows the results of the multivariable predictive analysis for cognitive deterioration for the 6-month surviving population using multiple imputation. No statistically significant predictor of cognitive deterioration was found in unadjusted and adjusted analyses in the imputed analysis of the total surviving sample at 6-month follow-up (N=249). Alternate analyses (imputation based on the enrolled population, including

Table 2. Characteristics of Patients Who Did and Did Not Cognitively Improve From Baseline to 6-Month Follow-Up After TAVI, Among Patients With Impaired Cognitive Function at Baseline (Baseline MMSE<26, N=48)

Characteristic	Cognitive Improvement (N=18)	No Cognitive Improvement (N=30)	*P* Value (Bivariable Analyses)
Age, y, median (IQR)	82.9 (10.5)	83.8 (6.3)	0.42
Female sex, n (%)	10 (55.6)	12 (40.0)	0.45
BMI, kg/m^2, median (IQR)	25.0 (3.3)	26.3 (3.7)	0.22
Systolic BP, mm Hg, median (IQR)	131.5 (25.8)	136.5 (35.5)	0.86
Diastolic BP, mm Hg, median (IQR)	70.0 (25.0)	75.5 (19.5)	0.69
Hypertension, n (%)	16 (88.9)	27 (90.0)	>0.999
Diabetes mellitus, n (%)	4 (22.2)	5 (16.7)	0.92
Atrial fibrillation, n (%)	7 (38.9)	12 (40.0)	>0.999
Previous stroke, n (%)	4 (22.2)	2 (6.7)	0.26
NYHA III/IV, n (%)	15 (83.3)	21 (70.0)	0.49
Betablocker, n (%)	9 (50.0)	13 (43.3)	0.88
ACEI/ARB, n (%)	12 (66.7)	15 (50.0)	0.41
LVEF, %, median (IQR)	57.0 (10.0)	60.0 (18.8)	0.47
Mean gradient aortic valve, mm Hg, median (IQR)	34.0 (16.5)	41.5 (17.0)	0.64
AVA, cm^2, median (IQR)	0.60 (0.20)	0.70 (0.34)	0.01
Creatinine, μmol/L, median (IQR)	94.0 (62.2)	90.5 (38.0)	0.19
TUG ≥20 s, n/N (%)*	8/17 (47.1)	11/30 (36.7)	0.70
MNA <12 points, n (%)	9 (50.0)	16 (53.3)	>0.999
BADL ≥1 activity with limitation, n (%)	8 (44.4)	13 (43.3)	>0.999
≤9 y spent for education, n (%)	7 (38.9)	15 (50.0)	0.65
Transfemoral access route for TAVI, n (%)	17 (94.4)	30 (100.0)	0.79
Length of in-hospital stay, days, median (IQR)	6.0 (4.0)	6.0 (3.0)	0.59
Stroke or myocardial infarction within 30 days based on VARC criteria, n (%)	0 (0.0)	2 (6.7)	0.71

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVA, aortic valve area; BADL, Basic Activities of Daily Living; BMI, body mass index; BP, blood pressure; IQR, interquartile range; LVEF, left ventricular ejection fraction; MMSE, Mini Mental State Examination; MNA, Mini Nutritional Assessment; NYHA, New York Heart Association functional class; TAVI, transcatheter aortic valve implantation; TUG, Timed Get Up and Go Test; and VARC, Valve Academic Research Consortium.

*Because of missing information on some measurements, number with characteristic (n) and number with available information (N) are provided.

Table 3. Predictors of Cognitive Deterioration of Surviving Patients at 6-Month Follow-Up After TAVI (N=248), Using Multivariable Logistic Regression Analyses and Multiple Imputation*

	Cognitive Deterioration					
	Unadjusted		Adjusted†		Adjusted‡	
Predictor	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Baseline MMSE (<26 vs ≥26 points)	0.95 (0.38, 2.40)	0.91	0.87 (0.34, 2.26)	0.78	§	§
NYHA class (III/IV vs I/II)	0.97 (0.42, 2.25)	0.94	0.99 (0.42, 2.32)	0.99	0.99 (0.43, 2.34)	0.99
AVA		0.99		0.98		0.99
Median (0.64 cm^2)	Reference		Reference		Reference	
25th percentile (0.50 cm^2)	0.98 (0.72, 1.35)		1.00 (0.72, 1.40)		1.01 (0.72, 1.41)	
75th percentile (0.80 cm^2)	1.02 (0.71, 1.47)		1.00 (0.68, 1.46)		0.99 (0.68, 1.46)	
TUG (≥20 vs <20 s)	1.56 (0.72, 3.38)	0.26	1.55 (0.71, 3.38)	0.27	1.60 (0.73, 3.53)	0.24
BADL (≥1 vs no activity with limitation)	1.08 (0.45, 2.43)	0.87	1.07 (0.45, 2.55)	0.88	1.12 (0.46, 2.74)	0.81
Transfemoral access route (yes vs no)	1.13 (0.26, 4.97)	0.87	1.14 (0.26, 5.09)	0.86	1.18 (0.26, 5.27)	0.84
Length of in-hospital stay after TAVI		0.25		0.20		0.21
Median (7 days)	Reference		Reference		Reference	
25th percentile (5 days)	0.64 (0.35, 1.15)		0.62 (0.34, 1.11)		0.62 (0.34, 1.11)	
75th percentile (8 days)	1.25 (0.93, 1.68)		1.27 (0.95, 1.70)		1.27 (0.95, 1.70)	

AVA indicates aortic valve area; BADL, Basic Activities of Daily Living; CI, confidence interval; MMSE, Mini Mental State Examination; NYHA, New York Heart Association functional class; OR, odds ratio; TAVI, transcatheter aortic valve implantation; and TUG, Timed Get Up and Go Test.

*For list of variables used in multiple imputation, see Table I in the Data Supplement.

†Models adjusted for age and sex.

‡Models adjusted for age, sex, and MMSE (<26 vs ≥26 points).

§Estimated ORs with MMSE (<26 vs ≥26 points) adjustment are 0.87 (95% CI 0.33, 2.27) for predictor NYHA class; 0.88 (95% CI 0.34, 2.28) for predictor AVA; 0.79 (95% CI 0.30, 2.09) for predictor TUG; 0.84 (95% CI 0.31, 2.26) for predictor BADL; 0.86 (95% CI 0.33, 2.25) for predictor transfemoral access route; and 0.96 (95% CI 0.37, 2.51) for predictor length of in-hospital stay after TAVI.

people who did not survive, analysis without imputation based on the population with available data on cognitive function at 6-month follow-up alone) revealed the same results (Tables IV and V in the Data Supplement). Similarly, the analysis with cognitive function as a continuous dependent variable, instead of a dichotomous variable, did not show any statistically significant predictors of cognitive deterioration (Table VI in the Data Supplement).

Medical Record Review

Eight (27.6%) among the 29 patients with a ≥3-point decline in the global MMSE score experienced a major decline of ≥5 points. A presumable cause of the cognitive deterioration was found in 6 (75%) of these 8 patients. Two patients had postinterventional delirium after the TAVI procedure, 1 patient had a cerebral embolic event after TAVI, 1 patient had progressive renal failure after TAVI, 1 patient had symptomatic heart failure, despite successful TAVI, and 1 patient had a combination of preexisting cerebrovascular disease and mild cognitive impairment before TAVI. An increase of 5 or more points in the MMSE global score was observed in 9 patients. None of these patients had a postinterventional complication.

Discussion

This prospective evaluation of cognitive trajectories in a large cohort of TAVI patients adds important information to the current knowledge in this field. The median MMSE global score at baseline was 27 points, with a minimum at 15 points. As compared with the MMSE score distribution in the general population, only few of the study participants had moderately to severely impaired baseline cognition.[30] We, therefore, conclude that patients with severely impaired cognition because of dementia are not referred for TAVI evaluation. Overall, cognitive function was preserved over 6 months after TAVI, despite high patient's age with elevated intrinsic risk of cognitive deterioration. However, there are considerable individual variations in cognitive changes between pre- and postinterventional conditions.

Ghanem et al[12] found that 9% of patients experience cognitive deterioration after TAVI. We found a similar proportion of patients with cognitive deterioration (12.7%). From the clinician's perspective, it would be important to know preinterventional predictors for cognitive deterioration after the intervention. Our study did not reveal such predictors, although we performed a thorough baseline evaluation in all patients. In this regard, our study is in agreement with the study by Ghanem et al.[12] That study did not find any risk factors for cognitive decline except increasing patient's age, which often is a surrogate for other unmeasured factors. Presumably, both studies did not reveal preinterventional predictors of cognitive deterioration because deterioration is associated with different postinterventional complications. One important and preventable complication is postinterventional delirium, which is a known cause of persistent cognitive deterioration

after interventions or critical illness.[31,32] Though we did not systematically assess patients for postinterventional delirium, our medical record review found postinterventional delirium in a quarter of patients with marked cognitive deterioration. Postinterventional delirium seems to be an important target for the prevention of cognitive deterioration. As a research implication, future studies should systematically assess patients for postinterventional delirium and, in addition, use imaging to detect embolic lesions or supra-aortic vascular disease as potential factors causing cognitive deterioration.

We found cognitive improvement for 37.5% of our study participants with impaired baseline cognition. Orvin et al[15] recently reported cognitive improvement in patients undergoing TAVI, but the study was conducted in a small and highly selected subgroup of 36 of 130 patients undergoing TAVI. Therefore, our study is the first adequately powered study to provide evidence that TAVI results in cognitive improvement among patients who had impaired preprocedural cognitive function. Our analyses also suggest that patients with low AVA are particularly prone to cognitive improvement after TAVI because of the hemodynamic improvement after successful intervention. As a research implication, future confirmatory studies should also measure hemodynamics to evaluate the correlations between hemodynamic and cognitive improvement.

Some limitations need to be mentioned. First, the present findings originate from a single center. Therefore, confirmation in an independent sample is important to document generalizability of our findings. Second, even if our study presents cognitive trajectories for the largest cohort to date, the sample was still too small to investigate all potentially relevant predictors of a change in cognition. This particularly applies to the subgroup of patients with impaired baseline cognition; this subgroup was too small to perform a multivariate predictive analysis for cognitive improvement. Third, we used the MMSE for the evaluation of cognition. Although the MMSE tests a variety of important cognitive domains, it does not cover all cognitive domains. In particular, executive and visuo-spatial orientation are, to some extent, underrepresented in the MMSE. Findings might, therefore, be somewhat different if other instruments are used. However, previous research confirmed good performance of the MMSE to measure change of cognitive function over time.[23] Fourth, cognitive function data at 6-month follow-up was missing in a minority (7.7%) of surviving people, and preintervention health status of people with missing information was somewhat worse. Extensive confirmatory analyses did not reveal evidence for bias resulting from missing data. Fifth, we did not measure hemodynamic improvement. Therefore, our finding that cognitive improvement was better in patients with low preinterventional AVA and, therefore, was possibly related to hemodynamic improvement after TAVI, is preliminary and should be confirmed in further studies. Finally, it is well known that using the continuity equation for evaluating the AVA has the general limitation of a certain operator and image quality dependence. However, continuity equation valve area calculations have been well validated in clinical and experimental studies, and AVA is considered a reliable parameter for predicting clinical outcomes and for appropriate clinical decision-making. Also, we used a consistent evaluation of AVA according to a standardized protocol by trained personnel and experienced echocardiographic specialists according to current recommendations.[33]

This study has several important clinical implications. First, TAVI is able to improve cognition and should not be withheld in patients with symptomatic severe aortic stenosis and preprocedural cognitive impairment. Second, preprocedural TAVI evaluation should include systematic assessment of cognitive function to detect patients at highest risk for postinterventional delirium because this is has been shown to be a preventable cause of persistent cognitive deterioration.[34–36] Third, routine cognitive assessment for early detection of postprocedural delirium is important to initiate appropriate treatment already in the early postinterventional phase. Finally, patients with cognitive deterioration should be identified quickly to ensure early appropriate geriatric interventions. For example, these patients should receive appropriate geriatric interventions ensuring drug adherence because they are at the greatest risk for not taking prescribed drugs after TAVI.

The present study, in conclusion, revealed that individual cognitive function varies considerably after TAVI. It also showed that cognitive deterioration is often caused by postinterventional complications; delirium, in particular, seems to play an important role. Furthermore, this study suggests that a relevant proportion of patients with impaired baseline cognition have good prospects to improve owing to TAVI. Therefore, TAVI should not be withheld in patients with impaired preprocedural cognition.

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Disclosures

None.

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Evolution of Cognitive Function After Transcatheter Aortic Valve Implantation

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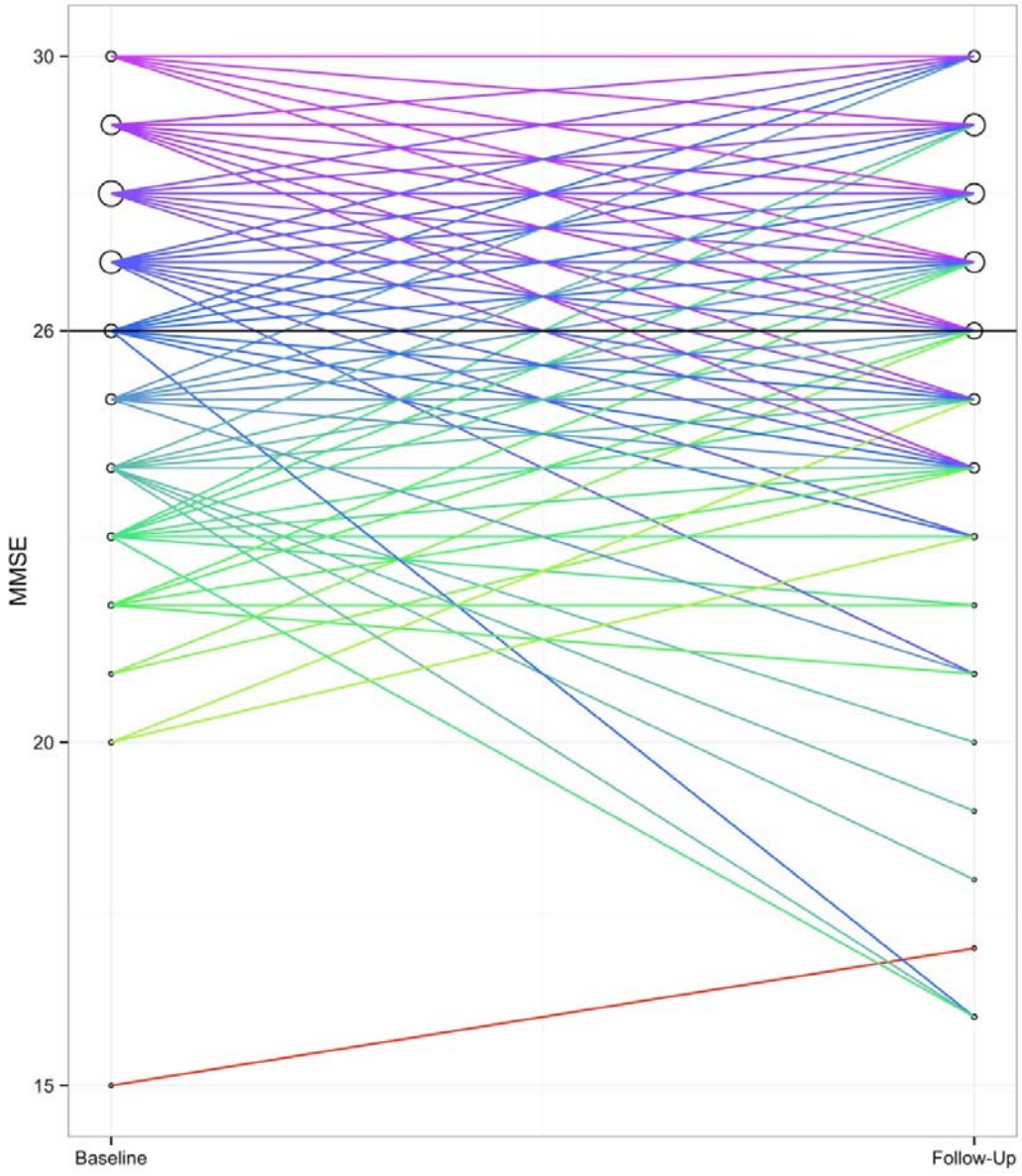
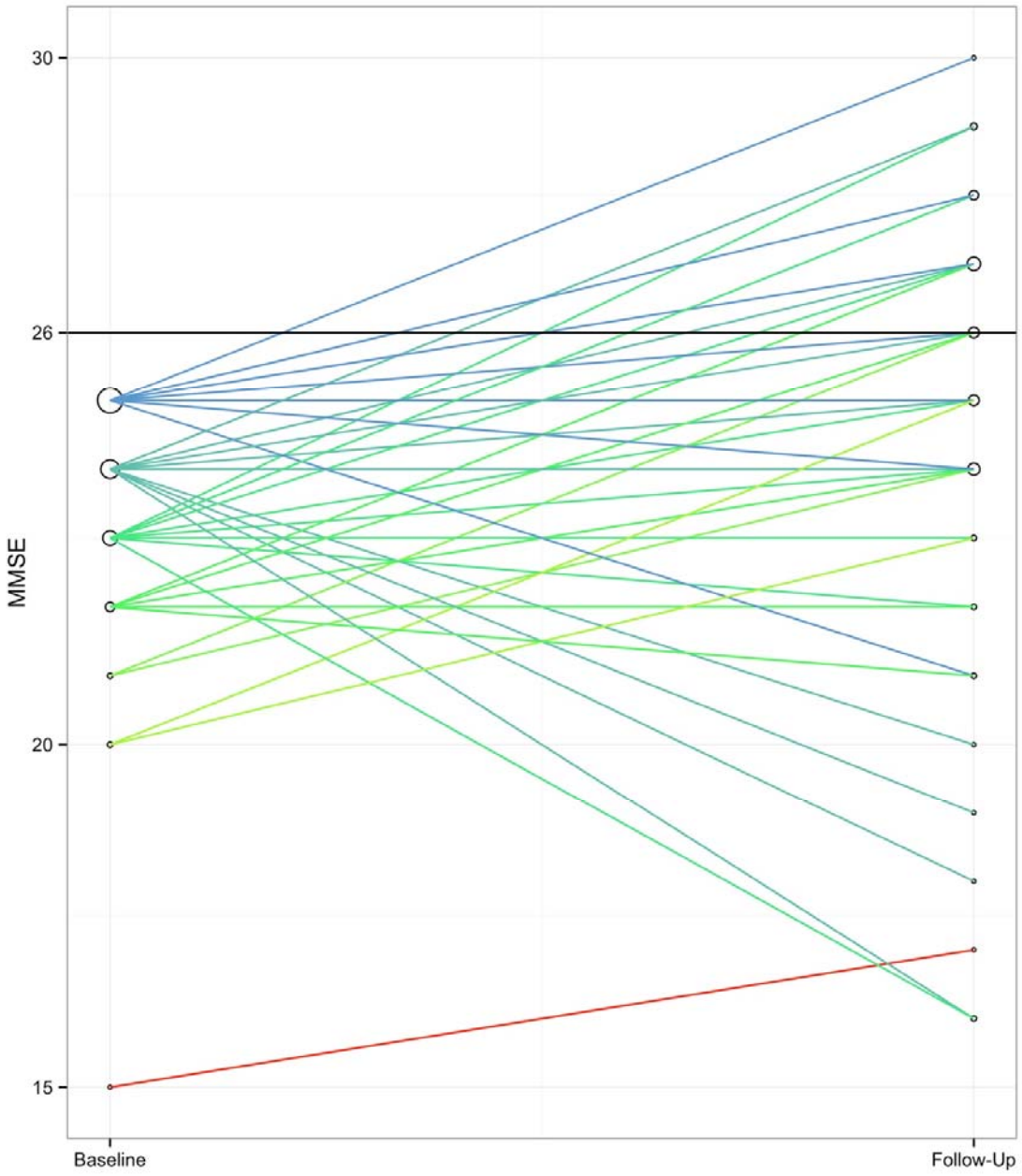
Supplemental Material

Supplementary Figure 1. Change plot of MMSE in population with available follow-up cognitive function over time (N=229).*



* Circles are indicating number of persons per MMSE category with the size proportional to the number of persons. Color shades gradually changing from higher baseline MMSE to lower baseline MMSE.

Supplementary Figure 2. Change plot of MMSE over time in subgroup of patients with base-line MMSE<26 (N=48).*



* Circles are indicating number of persons per MMSE category with the size proportional to the number of persons. Color shades gradually changing from higher baseline MMSE to lower baseline MMSE.

Supplementary Table 1: Variables used in multiple imputation model for enrolled study population (N=279) and survived 6-month follow-up population (N=248).

	Time point	Imputed	Missing values	
Characteristic			Enrolled population (N=279) n (%)	Survived population (N=2 n (%)
Personal				
Gender	Baseline	No	0	0
Age	Baseline	No	0	0
Body Mass Index	Baseline	No	0	0
Highest completed education	Baseline	Yes	4 (1.4)	3 (1.2)
Self-perceived health	Baseline	Yes	4 (1.4)	0
Self-perceived health	Follow-up	Yes	31 (11.1)	0
Socio-economic				
Swiss area based socioeconomic position*	Baseline	Yes	1 (0.4)	0
Psycho-social				
Social Network: Friends	Baseline	Yes	3 (1.1)	3 (1.2)
Social Network: Family	Baseline	Yes	2 (0.7)	2 (0.8)
Social Network: Emotional	Baseline	Yes	2 (0.7)	2 (0.8)
Depression Score	Baseline	No	0	0
Depression Score	Follow-up	Yes	37 (13.3)	6 (7.7)
Lifestyle				
Current smoker	Baseline	Yes	26 (9.3)	24 (9.7)
Multidimensional Geriatric Assessment				
Mini Mental State Examination	Baseline	No	0	0
Mini Mental State Examination	Follow-up	Yes	50 (17.9)	19 (7.7)
Nutritional Assessment	Baseline	Yes	2 (0.7)	2 (0.8)
Nutritional Assessment	Follow-up	Yes	31 (11.1)	0
Basic Activities of Daily Living	Baseline	No	0	0

Basic Activities of Daily Living	Follow-up	Yes	31 (11.1)	0
Instrumental Activities of Daily Living	Baseline	Yes	1 (0.4)	0
Instrumental Activities of Daily Living	Follow-up	Yes	38 (13.6)	7 (2.5)
Timed Up and Go Test	Baseline	Yes	19 (6.8)	12 (4.8)
Timed Up and Go Test	Follow-up	Yes	49 (17.6)	18 (6.5)
Ability to walk 200 meters	Baseline	No	0	0
Ability to walk 200 meters	Follow-up	Yes	31 (11.1)	0
Cardiologic information				
Dyspnea NYHA Class	Baseline	No	0	0
AVA	Baseline	Yes	6 (2.2)	5 (2.0)
Diabetes mellitus	Baseline	No	0	0
Hypertension	Baseline	No	0	0
Dyslipidemia	Baseline	No	0	0
COPD	Baseline	No	0	0
Cerebrovascular accident	Baseline	No	0	0
Previous pacemaker implantation	Baseline	No	0	0
Coronary artery disease	Baseline	No	0	0
History of myocardial infarction	Baseline	No	0	0
Peripheral artery disease	Baseline	No	0	0
Stable angina pectoris	Baseline	No	0	0
Syncope	Baseline	No	0	0
Creatinine level	Baseline	No	0	0
Logistic EuroSCORE	Baseline	No	0	0
STS Score	Baseline	No	0	0
Aspirin	Baseline	No	0	0
Betablocker	Baseline	No	0	0
ACE inhibitor	Baseline	No	0	0
Transfemoral route access	Baseline	No	0	0
VARC Myocardial infarction	Follow-up	No	0	0
VARC Stroke	Follow-up	No	0	0

Length of in-hospital stay after TAVI	Follow-up	No	0	0
Attrition				
Follow-up MGA not performed due to death	Follow-up	No	0	0
Follow-up MMSE not performed	Follow-up	No	0	0

* Socio-economic status: Swiss neighbourhood index. Higher scores denote higher levels of socio-economic status (Panczak R, Galobardes B, Voorpostel M, Spoerri A, Zwahlen M, Egger M. A Swiss neighbourhood index of socioeconomic position: development and association with mortality. Journal of Epidemiology & Community Health 2012;66:1129–36. 10.1136/jech-2011-200699).

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Supplementary Table 2: Evolution of cognitive function in subgroups of patients, according to baseline cognitive function.

	MMSE Decline (n=29)	**MMSE Stable (n=176)**	**MMSE Improvement (n=24)**
MMSE Score (points)	n (%)	n (%)	n (%)
≥26	23 (79.3)	152 (86.4)	6 (25.0)
19 to <26	6 (20.7)	23 (13.1%)	18 (75.0)
<19	0 (0.0)	1 (0.6%)	0 (0.0)

Supplementary Table 3. Bivariable comparison of characteristics of surviving patients aged ≥ 70 years with and without cognitive deterioration at 6 months after TAVI (N=229).

Characteristic	***Cognitive deterioration (N = 29)***	***No cognitive deterioration (N = 200)***	***P value***
Age, years, median (IQR)	83.6 (6.3)	83.4 (5.4)	0.77
Female sex, n (%)	15 (51.7)	113 (56.5)	0.78
BMI, kg/m^2, median (IQR)	26.0 (6.2)	25.5 (5.4)	0.84
Systolic BP, mmHg, median (IQR)	131 (20.0)	132.0 (33.8)	0.96
Diastolic BP, mmHg, median (IQR)	71.0 (15.0)	69.0 (20.0)	0.38
Hypertension, n (%)	28 (96.5)	181 (90.5)	0.47
Diabetes, n (%)	6 (20.7)	47 (23.5)	0.92
Atrial fibrillation, n (%)	9 (31.0)	59 (29.5)	>0.999
Previous stroke, n (%)	3 (10.3)	22 (11.0)	>0.999
NYHA III/IV, n (%)	20 (69.0)	140 (70.0)	>0.999
Betablocker, n (%)	10 (34.5)	105 (52.5)	0.11
ACEI/ARB, n (%)	17 (58.6)	123 (61.5)	0.93
LVEF, %, median (IQR)	60.0 (20.0)	60.0 (15.5)	0.58
Mean gradient aortic valve, mmHg, median (IQR)	42.0 (18.0)	41.0 (21.5)	0.90

AVA, cm^2, median (IQR)	0.70 (0.30)	0.64 (0.30)	0.81
Creatinine, µmol/L, median (IQR)	89.0 (48.0)	90.0 (40.0)	0.69
MMSE <26 points, n (%)	6 (20.7)	42 (21.0)	>0.999
TUG ≥20 seconds, n/N* (%)	10/28 (35.7)	49/191 (25.6)	0.37
MNA <12 points, n/N* (%)	14/29 (48.3)	82/198 (41.4)	0.62
BADL ≥1 activity with limitation, n (%)	7 (24.1)	47 (23.5)	>0.999
≤9 years spent for education, n (%)	7 (24.1)	66 (33.0)	0.46
Transfemoral access route for TAVI, n (%)	27 (93.1)	186 (93.0)	0.85
Length of in-hospital stay, days, median (IQR)	6.0 (2.0)	7.0 (3.0)	0.40
Stroke or myocardial infarction within 30 days based on VARC criteria, n (%)	1 (3.5)	6 (3.0)	>0.999

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AVA, aortic valve area; BADL, Basic Activities of Daily Living; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MMSE, Mini Mental State Exam; MNA, Mini Nutritional Assessment; NYHA, New York Heart Association functional class; PAD, peripheral artery disease; SD, standard deviation; TAVI, transcatheter aortic valve implantation; TUG, Timed Get Up and Go Ttest; VARC, Valve Academic Research Consortium.

* Due to missing information on some measurements, number with characteristic (n) and number with available information (N) are provided.

Supplementary Table 4. Predictors of cognitive deterioration, **using available cases for cognitive testing, without imputation (N=229).**

Predictor	**Cognitive deterioration**					
	Unadjusted		***Adjusted****		***Adjusted †***	
	OR (95% CI)	***P value***	***OR (95% CI)***	***P value***	***OR (95% CI)***	***P value***
Baseline MMSE (<26 vs ≥26 points)	0.98 (0.38, 2.57)	0.97	0.91 (0.35, 2.39)	0.85	§	§
NYHA class (III/IV vs. I/II)	0.95 (0.41, 2.21)	0.91	0.98 (0.42, 2.28)	0.95	0.98 (0.42, 2.32)	0.97
AVA		0.96		0.96		0.96
- median (0.64 cm^2)	Reference		Reference		Reference	
- 25th percentile (0.50 cm^2)	0.97 (0.71, 1.32)		0.98 (0.72, 1.33)		0.98 (0.72, 1.33)	
- 75th percentile (0.80 cm^2)	1.02 (0.77, 1.36)		1.01 (0.76, 1.34)		1.01 (0.76, 1.34)	
TUG (≥20 vs. <20 seconds)	1.61 (0.70, 3.72)	0.27	1.60 (0.68, 3.76)	0.28	1.64 (0.69, 3.89)	0.26
BADL (≥1 vs. no activity with limitation)	1.04 (0.42, 2.58)	0.94	1.04 (0.42, 2.60)	0.93	1.07 (0.39, 2.94)	0.89

Transfemoral route access (yes vs. no)	1.02 (0.22, 4.72)	0.98	1.04 (0.22, 4.99)	0.96	1.06 (0.22, 5.13)	0.94
Length of in-hospital stay after TAVI		0.29		0.26		0.27
- median (7 days)	Reference		Reference		Reference	
- 25th percentile (5 days)	0.76 (0.53, 1.10)		0.76 (0.52, 1.10)		0.76 (0.52, 1.10)	
- 75th percentile (8 days)	1.11 (0.95, 1.30)		1.12 (0.95, 1.32)		1.12 (0.95, 1.32)	

Abbreviations: AVA, aortic valve area; BADL, Basic Activities of Daily Living; CI, confidence interval; MMSE, Mini Mental State Exam; NYHA, New York Heart Association functional class; OR, odds ratio; TAVI, transcatheter aortic valve implantation; TUG, Timed Get Up and Go Test.

* Models adjusted for age and sex.

† Models adjusted for age, sex and MMSE (<26 vs ≥26 points).

§ Estimated ORs with MMSE (<26 vs ≥26 points) adjustment are: 0.92, 95% CI (0.35, 2.42), for predictor NYHA class; 0.97, 95% CI (0.36, 2.60), for predictor AVA; 0.85, 95% CI (0.31, 2.28), for predictor TUG; 0.90, 95% CI (0.31, 2.62), for predictor BADL; 0.91 (0.35, 2.39) for predictor transfemoral route access; 1.00 (0.38, 2.64), for predictor length of in-hospital stay after TAVI.

Supplementary Table 5. Predictors of cognitive deterioration, **using multiple imputation for enrolled study population, including persons who died from baseline to 6-month follow-up (N=279).**

Predictor	**Cognitive deterioration**					
	Unadjusted		***Adjusted†***		***Adjusted ‡***	
	OR (95% CI)	***P value***	***OR (95% CI)***	***P value***	***OR (95% CI)***	***P value***
Baseline MMSE (<26 vs. ≥26 points)	0.89 (0.34, 2.34)	0.81	0.84 (0.31, 2.27)	0.72	§	§
NYHA class (III/IV vs. I/II)	1.01 (0.46, 2.23)	0.98	1.04 (0.47, 2.30)	0.93	1.04 (0.47, 2.31)	0.92
AVA		0.95		0.95		0.96
- median (0.64 cm^2)	Reference		Reference		Reference	
- 25th percentile (0.50 cm^2)	0.97 (0.71, 1.32)		0.98 (0.71, 1.36)		0.99 (0.72, 1.36)	
- 75th percentile (0.80 cm^2)	1.04 (0.73, 1.48)		1.02 (0.71, 1.47)		1.01 (0.70, 1.46)	
TUG (≥20 vs. <20 seconds)	1.54 (0.76, 3.15)	0.23	1.55 (0.75, 3.19)	0.23	1.61 (0.78, 3.34)	0.20
BADL (≥1 vs. no activity with limitation)	1.07 (0.47, 2.43)	0.87	1.06 (0.47, 2.41)	0.88	1.12 (0.48, 2.63)	0.79

Transfemoral access route (yes vs. no)	0.98 (0.23, 4.12)	0.98	0.98 (0.23, 4.19)	0.98	0.99 (0.23, 4.28)	0.99
Length of in-hospital stay after TAVI - median (7 days) - 25th percentile (5 days) - 75th percentile (8 days)	Reference 0.73 (0.46, 1.17) 1.17 (0.93, 1.48)	0.38	Reference 0.71 (0.45, 1.15) 1.18 (0.93, 1.50)	0.33	Reference 0.72 (0.45, 1.15) 1.18 (0.93, 1.50)	0.34

Abbreviations: AVA, aortic valve area; BADL, Basic Activities of Daily Living; CI, confidence interval; MMSE, Mini Mental State Exam; NYHA, New York Heart Association functional class; OR, odds ratio; TAVI, transcatheter aortic valve implantation; TUG, Timed Get Up and Go Test.

† Models adjusted for age and sex.

‡ Models adjusted for age, sex and MMSE (<26 vs ≥26 points).

§ Estimated ORs with MMSE (<26 vs ≥26 points) adjustment are: 0.83, 95% CI (0.31, 2.27), for predictor NYHA class; 0.85, 95% CI (0.31, 2.29), for predictor AVA; 0.76, 95% CI (0.28, 2.10), for predictor TUG; 0.81, 95% CI (0.29, 2.27), for predictor BADL; 0.84 (0.31, 2.28), for predictor transfemoral access route; 0.85 (0.31, 2.35), for predictor length of in-hospital stay after TAVI.

Supplementary Table 6. Predictors of cognitive deterioration, **with MMSE as a continuous dependent variable, using a censored Gaussian regression model with available cases for cognitive testing (N=229)*.**

Predictor	**Cognitive deterioration**					
	Unadjusted		***Adjusted†***		***Adjusted ‡***	
	Difference (95% CI)	***P value***	***Difference (95% CI)***	***P value***	***Difference (95% CI)***	***P value***
Baseline MMSE (<26 vs. ≥26 points)	-0.51 (-2.60, 1.58)	0.63	-0.42 (-2.57, 1.74)	0.74	§	§
NYHA class (III/IV vs. I/II)	0.41 (-1.47, 2.28)	0.67	0.34 (-1.53, 2.21)	0.72	0.36 (-1.50, 2.23)	0.70
AVA		0.68		0.73		0.69
- median (0.64 cm^2)	Reference		Reference		Reference	
- 25th percentile (0.50 cm^2)	0.14 (-0.55, 0.83)		0.09 (-0.64, 0.82)		0.11 (-0.61, 0.83)	
- 75th percentile (0.80 cm^2)	0.30 (-1.18, 1.78)		0.20 (-1.37, 1.76)		0.23 (-1.32, 1.78)	
TUG (≥20 vs. <20 seconds)	-1.08 (-3.04, 0.88)	0.28	-1.15 (-3.09, 0.79)	0.25	-1.11 (-3.08, 0.85)	0.27
BADL (≥1 vs. no activity with limitation)	0.18 (-1.88, 2.25)	0.86	0.07 (-2.00, 2.14)	0.95	0.15 (-1.94, 2.25)	0.88

Transfemoral route access (yes vs. no)	-0.44 (-3.96, 3.08)	0.81	-0.53 (-4.07, 3.00)	0.77	-0.45 (-4.00, 3.10)	0.80
Length of in-hospital stay after TAVI		0.21		0.20		0.19
- median (7 days)	Reference		Reference		Reference	
- 25th percentile (5 days)	1.09 (-0.61, 2.78)		1.04 (-0.55, 2.63)		1.07 (-0.52, 2.65)	
- 75th percentile (8 days)	-0.54 (-1.39, 0.30)		-0.52 (-1.31, 0.27)		-0.53 (-1.33, 0.26)	

Abbreviations: AVA, aortic valve area; BADL, Basic Activities of Daily Living; CI, confidence interval; MMSE, Mini Mental State Exam; NYHA, New York Heart Association functional class; OR, odds ratio; TAVI, transcatheter aortic valve implantation; TUG, Timed Get Up and Go Test.

* Estimates are differences of follow-up minus baseline MMSE. Censoring was defined at the cutoff value of -3 points (negative values of the difference correspond to a deterioration of MMSE from baseline to follow-up). See Methods section for details.

† Models adjusted for age and sex.

‡ Models adjusted for age, sex and MMSE (<26 vs ≥26 points).

§ Estimated difference in MMSE (<26 vs ≥26 points) adjustment are: -0.44, 95% CI (-2.59, 1.71), for predictor NYHA class; -0.61, 95% CI (-2.50, 1.28), for predictor AVA; -0.25, 95% CI (-2.49, 1.99), for predictor TUG; -0.45, 95% CI (-2.64, 1.75), for predictor BADL; -0.38 (-2.55, 1.79) for predictor transfemoral route access; -0.59, 95% CI (-2.73, 1.55), for predictor length of in-hospital stay after TAVI.