Transcatheter Aortic Valve Replacement

Cognitive Trajectory After Transcatheter Aortic Valve Implantation

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Background—Transcatheter aortic valve implantation (TAVI) is known to be associated with silent cerebral injury, which could contribute to cognitive impairment. Considering its increasing use, thorough longitudinal investigation of cognitive trajectory after TAVI is pivotal.

Methods and Results—Repeatable battery for the assessment of neuropsychological status was performed before (E1), 3 days (E2), 3 months (E3), 1 (E4) year, and 2 years (E5) after TAVI. Baseline characteristics, procedural data, imaging parameters of brain injury (diffusion-weighted MRI), and the use of conceivable neuroprotective approaches were investigated for their effect on cognitive function. Cognitive performance was investigated in 111 patients (mean log EuroSCORE, 30±13%). Global cognitive function (repeatable battery for the assessment of neuropsychological status total score) increased transiently at E2 (P=0.02) and was comparable with baseline levels at E3, E4, and E5. Six patients (5.4%) demonstrated early cognitive decline. Persistence and late onset were seen infrequently (n=3, 2.7% and n=4, 3.6%, respectively). Hence, early cognitive decline was ruled out in 105 patients (94.6%), and a majority of patients (91%) demonstrated sustained cognitive performance throughout all investigated time points. Interestingly, only patient age (P=0.012), but not prior cerebrovascular events, cognitive status, direct TAVI, cerebral embolism in diffusion-weighted MRI, or the use of a cerebral embolic protection device was found to be independently associated with cognitive decline, linking higher age to cognitive impairment along the first 2 years after TAVI.

Conclusions—Long-term cognitive performance was preserved in the great majority (91%) of patients throughout the first 2 years after TAVI, despite the high intrinsic risk for cognitive deterioration.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00883285.

Key Words: cognition ■ dementia ■ injury ■ intracranial embolism ■ mild cognitive impairment ■ stroke ■ TAVR

Transcatheter aortic valve implantation (TAVI) emerged as a valid therapeutic option in patients with aortic stenosis at prohibitive and high surgical risk. Recent studies demonstrated that TAVI is associated with a high incidence (73%–84%) of silent cerebral embolism as detected by diffusion-weighted MRI (DW-MRI). Fortunately, embolic events were neither associated with focal neurological deficits nor with crude cognitive function in short-term follow-up. Previous observational and interventional studies investigated the association of silent cerebral embolism and cognitive performance. On the one hand, the effect of cerebral embolism on cognitive performance in patients undergoing cardiac surgery is still controversially discussed. On the other hand, observational investigations in elderly individuals and patients with atrial fibrillation demonstrated that silent embolic events are associated with cognitive impairment. With that said, silence should be considered as a relative term coined for the absence of apparent focal neurological deficits in adherence to current recommendations. Hence, it is conceivable that the onset, the duration, and the degree of nonfocal cognitive changes

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WHAT IS KNOWN

- Transcatheter aortic valve implantation (TAVI) is frequently associated with imaging changes suggestive of silent cerebral embolic events.
- Patients with TAVI could be at increased intrinsic risk for long-term cognitive deterioration as reported after diverse cardiovascular procedures (eg, aortic valve replacement).

WHAT THE STUDY ADDS

- This study prospectively assessed the incidence, course, and potential risk factors of cognitive decline after TAVI using a comprehensive repeatable neuropsychological test battery.
- The majority of patients (91%) in this series did not experience cognitive decline at any time for ≤2 years after TAVI.
- Higher patient age but neither silent cerebral embolism nor the use of a dedicated embolic protection device affected cognitive trajectory after TAVI.

might have been underestimated. The assessment of cognitive trajectory in patients undergoing TAVI is of medical, social, and economic impact because cognitive decline (CD) is known to be associated with increased morbidity and mortality.11

An important question that has not yet received sufficient attention relates to the long-term time course of cognitive performance after TAVI using a sensitive and comprehensive repeatable neuropsychological test battery. This is of central role in view of the association of CD and vascular dementia on the one hand, and the method’s progressive movement towards patients at lower risk on the other hand. Cerebral embolism should be considered as a conceivable contributor of CD. Recently, Kahlert et al12 isolated the 2 major sources of procedural microemboli during TAVI: balloon valvuloplasty and positioning of the prosthesis. Hence, 2 recent procedural strategies could be of neuroprotective nature: first, the direct TAVI approach without valvuloplasty and rapid pacing,13 and second, the use of a dedicated cerebral embolic protection device.14,15

The aims of this study were characterization of cognitive trajectory for ≤2 years after TAVI and investigation of potentially underlying mechanisms.

Methods

All patients scheduled for TAVI between October 2009 and December 2010 were screened for inclusion. Indication was in concordance with the recent consensus statement.16 Inclusion and exclusion criteria are depicted in Methods in the online-only Data Supplement. The study protocol was approved by the local institutional review board and followed the Declaration of Helsinki guidelines. Written informed consent was obtained from all patients.

Study Design

Baseline examinations (E1) were performed before TAVI. After careful investigation of medical history, the mortality risk was estimated by both the logistic EuroSCORE and the risk score of the Society of Thoracic Surgeons (Society of Thoracic Surgeons score: mortality). Twelve-lead surface ECG, serological and hematological analyses, transthoracic and tranesophageal echocardiography, color-coded duplex sonography of the extracranial carotid arteries, ventriculography, and coronary angiography were conducted.1 Clinical examinations according to the National Institutes of Health Stroke Scale (NIHSS) were performed. Furthermore, the repeatable battery for the assessment of neuropsychological status (RBANS) was conducted by a trained neuropsychological research fellow. The RBANS is a neuropsychological testing battery with parallel forms, which is suited for the repeated assessment of cognition in elderly subjects. This test battery has been used in many clinical trials and observational studies.17 The RBANS contains 12 subtests measuring language, attention, visual and constructional skills, immediate memory, and delayed memory. RBANS test scores are transformed into age-, sex- and education-corrected standardized index scores for the 6 cognitive functions assessed and are also integrated into a total score (mean=100; SD=15). A postprocedural decline (at E2) of >1 SD compared with a subject’s score before TAVI (E1) was defined as CD.18 Counterbalanced alternate forms were used to minimize practice effects to allow for repetitive monitoring in short intervals. The widely used but possibly less sensitive mini-mental state examination of general cognitive function was administered to allow comparisons with other studies. We additionally assessed frailty,19 quality of life,20 instrumental activities of daily living,21 and mood22 using the following validated scores and questionnaires: The Edmonton frail scale scores of ≤3 and >7 indicate a lower (odds ratio, 0.3) and excessive risk (odds ratio, 5.0) of having a complication after surgery, respectively.19 The health-related short form allows the assessment of mental and physical health–related status on a scale ranging from 0 to 100.20 The Lawton instrumental activities of daily living score displays function in daily activities, with higher values reflecting better function; a value >52 has previously been used to determine independent lifestyle.21 The geriatric depression score is a 30-item report, which displays patient mood on a scale ranging from 0 to 30, with a value <10 reflecting lack of depressive symptoms.22 The occurrence of systemic inflammatory response syndrome (SIRS) was defined as fulfilling ≥2 of the following 4 criteria: body temperature <36.0°C or >38.0°C, heart rate >90 bpm, respiratory rate >20 breaths/min, or PaO₂ <32 mm Hg, leukocyte count >12 or <4 (10⁹/L) 1, 6, 24, 48, or 72 hours (E2) after TAVI.23 Preprocedural cerebral DW-MRI was performed the day before TAVI. First, postprocedural investigations (E2) were performed 3 days after TAVI and encompassed clinical status, NIHSS, RBANS, mini-mental state examination, and cerebral DW-MRI. All investigations, except DW-MRI, were repeated at E3, E4, and E5.

MRI of the Brain

Cerebral MRI was performed using a 1.5-T whole body system (Intera; Philips Medical Systems, Best, The Netherlands). Detailed imaging protocols and method of data analysis are presented in Methods in the online-only Data Supplement.

Transfemoral Aortic Valve Implantation and Neuroprotective Approaches

TAVI was performed in spontaneously breathing patients in deep sedation using midazolam, propofol, and fentanyl. Details are described in the online-only Data Supplement. In a subset of patients, balloon valvuloplasty before TAVI, rapid ventricular pacing, and postdilatation were omitted at the discretion of the operator. This approach has been described recently and was abbreviated as direct TAVI.13 In a further subset of patients, TAVI was performed with cerebral embolic protection using a dedicated filter device (Montage; Claret Medical Inc, USA).14

Statistical Analyses

Continuous variables are presented as mean±SD if normally distributed and as median (interquartile range) if not normally distributed. Categorical variables are given as frequencies and percentages and were compared by χ² statistics or Fisher exact test. Continuous variables were tested for differences by means of a 2-sided, unpaired
Table 1. Patient Baseline and Procedural Characteristics

<table>
<thead>
<tr>
<th>Clinical Data at E1</th>
<th>Included Patients</th>
<th>Excluded Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>111</td>
<td>14</td>
<td>...</td>
</tr>
<tr>
<td>Age, years±SD</td>
<td>80±6</td>
<td>81±7</td>
<td>0.83</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>60 (54)</td>
<td>6 (43)</td>
<td>0.57</td>
</tr>
<tr>
<td>Body mass index, kg/m²±SD</td>
<td>26.0±5.3</td>
<td>26.8±7.5</td>
<td>0.41</td>
</tr>
<tr>
<td>Log EuroSCORE, %±SD</td>
<td>24.3±14.7</td>
<td>31.7±12.7</td>
<td>0.07</td>
</tr>
<tr>
<td>STS score: mortality, %±SD</td>
<td>8.5±5.4</td>
<td>10.5±4.6</td>
<td>0.24</td>
</tr>
<tr>
<td>STS score: permanent stroke, %±SD</td>
<td>3.1±1.5</td>
<td>3.6±1.2</td>
<td>0.54</td>
</tr>
<tr>
<td>Peak-to-peak gradient, mm Hg±SD</td>
<td>51±24</td>
<td>47±15</td>
<td>0.47</td>
</tr>
<tr>
<td>Ejection fraction, %±SD</td>
<td>51±15</td>
<td>48±16</td>
<td>0.67</td>
</tr>
<tr>
<td>NYHA class±SD</td>
<td>3.0±0.5</td>
<td>3.3±1.5</td>
<td>0.12</td>
</tr>
<tr>
<td>Instrumental activities of daily living score</td>
<td>46.9±9.7</td>
<td>44.8±12.9</td>
<td>0.52</td>
</tr>
<tr>
<td>Edmonton frailty score</td>
<td>6.3±2.5</td>
<td>7.2±2.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Geriatric depression score</td>
<td>2.5±2.3</td>
<td>1.7±1.8</td>
<td>0.39</td>
</tr>
<tr>
<td>Quality of life SF12: physical</td>
<td>30.4±11.1</td>
<td>32.3±16.6</td>
<td>0.82</td>
</tr>
<tr>
<td>Quality of life SF12: mental</td>
<td>57.6±8.8</td>
<td>58.5±9.5</td>
<td>0.57</td>
</tr>
<tr>
<td>RBANS total score</td>
<td>25.4±3.4</td>
<td>23.8±3.4</td>
<td>0.06</td>
</tr>
<tr>
<td>Mini-mental state examination score</td>
<td>30 (27)</td>
<td>7 (50)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Comorbidities

- Hypertension, n (%) | 109 (98) | 14 (100) | 1.00
- Diabetes mellitus, n (%) | 35 (31) | 5 (36) | 0.77
- Smoking, n (%) | 20 (18) | 5 (36) | 0.15
- Dyslipidemia, n (%) | 90 (81) | 13 (93) | 0.46
- Creatinine, mg/dL±SD | 1.4±0.8 | 1.5±0.7 | 0.71
- Glomerular filtration rate, ml/min±SD | 50±18 | 47±11 | 0.80
- Hemodialysis, n (%) | 5 (7) | 1 (7) | 0.52
- Atrial fibrillation or flutter, n (%) | 41 (37) | 7 (50) | 0.39
- CHADS, score±SD | 2.6±0.9 | 3.1±1.3 | 0.10
- Prior stroke or TIA, n (%) | 18 (16) | 4 (29) | 0.27
- PVD, n (%) | 39 (35) | 5 (36) | 1.00
- Aortic atheroma ≥4 mm, n (%) | 40 (36) | 5 (36) | 1.00
- Coronary artery disease, n (%) | 71 (63) | 8 (58) | 0.77
- Prior myocardial infarction, n (%) | 14 (13) | 4 (29) | 0.12
- Prior PCI, n (%) | 39 (35) | 5 (36) | 1.00
- Prior CABG, n (%) | 15 (13) | 2 (14) | 1.00

Procedural characteristics

- Procedure time, min±SD | 97±44 | 110±59 | 0.08
- Direct TAVI without predilatation, n (%) | 39 (35) | 2 (14) | 0.14
- Cerebral embolic protection device, n (%) | 20 (18) | 0 (0) | 0.12
- CoreValve 23/26/29/31 mm, n | 2/21/50/22 | 0/2/6/1 | 0.0/0.0/0.0/0.9
- Edwards-Sapien 23/26 mm, n | 8/8 | 1/3 | 0.9/0.9
- Postdilatation, n (%) | 27 (24) | 4 (28) | 0.75
- Rapid pacing runs, n±SD | 1.3±1.1 | 2.1±1.8 | 0.06

Table 1. Continued

<table>
<thead>
<tr>
<th>Clinical Data at E1</th>
<th>Included Patients</th>
<th>Excluded Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postprocedural characteristics at E2</td>
<td></td>
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<td></td>
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</tbody>
</table>
| SIRS (%) | 36 (32) | 14 (100) | 0.0001
| Minor bleeding, n (%) | 25 (22) | 2 (14) | 0.73
| Major bleeding, n (%) | 6 (5) | 3 (21) | 0.06
| Stroke, n (%) | 0 (0) | 1 (7) | 0.11
| Lack of embolic events in DW-MRI, n (%) | 20 (18) | NA | NA

CABG indicates coronary artery bypass grafting; CHAD, congestive heart failure, hypertension, age, diabetes, stroke; DW-MRI, diffusion-weighted MRI; IQR, interquartile range; NA, not applicable; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RBANS, repeatable battery for the assessment of neuropsychological status; SIRS, systemic inflammatory response syndrome; TAVI, transcatheter aortic valve implantation; and TIA, transient ischemic attack.

Student t test for comparison between groups and with a 2-sided, paired Student t test for intragroup comparison. Nonparametric testing (Mann–Whitney test) was performed where indicated (eg, CD subgroup). Longitudinal data were compared by means of multivariate ANOVA adjusted for age, sex, risk factors of CD, and baseline RBANS. Longitudinal mixed-effects modeling was performed (using a longitudinal growth curve modeling approach), if applicable. A value of *p*<0.05 was considered statistically significant. Analyses were conducted with SPSS Statistics version 17.0.0 (SPSS Inc, Chicago, IL) and Mplus Version 7 (Muthén & Muthén).

Results

Patients

Baseline examinations were performed in 125 patients. Postprocedural cognitive assessment at E2 was not feasible in 14 patients because of postprocedural complications (respiratory failure caused by pneumonia or septic shock or multiorgan failure [n=7], major vascular complication [n=4], emergent conversion to open heart surgery [n=1], procedural stroke [NIHSS=9; modified Rankin scale=4; n=1], and procedural death [n=1]). All patients with pneumonia and vascular complications were mechanically ventilated at E2. These patients demonstrated higher burden of comorbidities and were at higher surgical risk (EuroSCORE: 24.3±14.7 versus 31.7±12.6; *P*=0.07). Therefore, 111 patients constituted the study population. Minimal and maximal follow-up periods were 12 (n=111) and 24 months (n=42), respectively. The baseline characteristics are summarized in Table 1.

Neurological and Cognitive Performance

All patients demonstrated normal focal neurological function before TAVI (NIHSS=0). One ischemic stroke occurred 8 months after TAVI (NIHSS=6; modified Rankin scale=1). All other patients (n=110, 99.1%) had no cerebrovascular events during follow-up period and demonstrated normal focal neurological function at E2, E3, E4, and E5. Thirty-five patients (31.5%) died during the follow-up period (Figure 1).

Before TAVI, the cognitive performance of patients was low on average (mean RBANS total score at E1, 82.9±14.6; *P*<0.05). Longitudinal data were compared by means of multivariate ANOVA adjusted for age, sex, risk factors of CD, and baseline RBANS. Longitudinal mixed-effects modeling was performed (using a longitudinal growth curve modeling approach), if applicable. A value of *p*<0.05 was considered statistically significant. Analyses were conducted with SPSS Statistics version 17.0.0 (SPSS Inc, Chicago, IL) and Mplus Version 7 (Muthén & Muthén).
age-, sex- and education-adjusted norms at baseline and were considered as a subgroup with mild cognitive impairment (MCI; mean RBANS total score at E1, 65.5±8.0). Despite the high-risk profile of the investigated old patients, early post-procedural testing (E2) demonstrated incident CD in only 6 patients (5.4%), reflected by a significantly lower RBANS total score at E2 (60.0±11.3; \( P < 0.001 \)). Patients experiencing early postprocedural CD revealed similar preprocedural cognitive performance (Table 2). In 3 patients, early CD persisted during the follow-up period (2.7%). Late onset of CD (at E3, E4, or E5) was apparent in 4 patients (3.6%; Figure 3). The domain that was affected most frequently was visual and constructional skills (n=4, 100%). Patients with CD further experienced significant deficits in language (n=2, 50%) and attention (n=2, 50%), as well as in delayed (n=2, 50%) and immediate memory (n=1, 25%). The RBANS total scores before and after TAVI were closely associated, pointed out by high correlation coefficients at E2 (\( r = 0.86 \); confidence interval, 0.79–0.89), E3 (\( r = 0.87 \); confidence interval, 0.81–0.91), and E4 (\( r = 0.875 \); confidence interval, 0.82–0.91), respectively. These relationships indicate stable trajectory of cognitive performance, independent of the baseline level. None of the 105 patients without early CD (94.6%) demonstrated significant decline in >1 of the 5 domains during follow-up. Individual data of global cognitive function are shown in Figure 3, indicating CD (dots below −1 SD) as rare event at all time points. Longitudinal data of mean values of global and regional cognitive performance are depicted in Figure 4, demonstrating stable cognitive performance throughout the follow-up period. In all, significant CD throughout the first 2 years after TAVI could be ruled out in the majority of patients (91%).

Potential Risk Factors for Cognitive Dysfunction

To elucidate the underlying mechanism of CD after TAVI, conceivable risk factors of CD were examined: (1) baseline characteristics (eg, previous stroke, cognitive performance...
Table 2. Clinical Data at E1

<table>
<thead>
<tr>
<th></th>
<th>CD at E1</th>
<th>CD at E2</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>105</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Age, years±SD</td>
<td>80±6</td>
<td>84±5</td>
<td>0.19</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>58 (54)</td>
<td>4 (67)</td>
<td>0.88</td>
</tr>
<tr>
<td>Body mass index, kg/m²±SD</td>
<td>25.8±5.5</td>
<td>27.5±3.4</td>
<td>0.54</td>
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<td>Log EuroSCORE, %±SD</td>
<td>24.2±14.8</td>
<td>29.6±9.2</td>
<td>0.50</td>
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<tr>
<td>STS score: mortality, %±SD</td>
<td>8.5±5.4</td>
<td>8.8±3.3</td>
<td>0.93</td>
</tr>
<tr>
<td>STS score: permanent stroke, %±SD</td>
<td>3.0±1.5</td>
<td>4.2±1.3</td>
<td>0.34</td>
</tr>
<tr>
<td>Peak-to-peak gradient, mm Hg</td>
<td>51±24</td>
<td>47±21</td>
<td>0.69</td>
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<td>Ejection fraction, %</td>
<td>51±15</td>
<td>54±12</td>
<td>0.49</td>
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<td>NYHA class±SD</td>
<td>46.9±9.7</td>
<td>47.7±6.5</td>
<td>0.91</td>
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<td>Instrumental activities of daily living score</td>
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<td></td>
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</tr>
<tr>
<td>Geriatric depression score</td>
<td>6.5±2.5</td>
<td>6.1±0.8</td>
<td>0.90</td>
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<td>Quality of life SF12: physical</td>
<td>33.6±11.0</td>
<td>23.9±5.8</td>
<td>0.16</td>
</tr>
<tr>
<td>Quality of life SF12: mental</td>
<td>56.8±8.7</td>
<td>60.8±9.8</td>
<td>0.43</td>
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<tr>
<td>RBANS total score</td>
<td>82.7±14.7</td>
<td>87.0±13.7</td>
<td>0.46</td>
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<tr>
<td>Mini-mental state examination score</td>
<td>25.4±3.3</td>
<td>25.1±3.8</td>
<td>0.58</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>30 (27)</td>
<td>0 (0)</td>
<td>0.57</td>
</tr>
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Table 2. Continued

<table>
<thead>
<tr>
<th></th>
<th>CD at E1</th>
<th>CD at E2</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Postdilatation, n (%)</td>
<td>26 (24)</td>
<td>1 (25)</td>
<td>1.00</td>
</tr>
<tr>
<td>Rapid pacing runs, n±SD</td>
<td>1.3±1.1</td>
<td>1.0±1.0</td>
<td>0.80</td>
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<tr>
<td>Postprocedural characteristics at E2</td>
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</tr>
<tr>
<td>SIRS (%)</td>
<td>33 (31)</td>
<td>3 (50)</td>
<td>0.38</td>
</tr>
<tr>
<td>Minor bleeding, n (%)</td>
<td>24 (23)</td>
<td>1 (17)</td>
<td>1.00</td>
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<tr>
<td>Major bleeding, n (%)</td>
<td>5 (5)</td>
<td>1 (17)</td>
<td>0.29</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Lack of embolic events in DW-MRI, n (%)</td>
<td>20 (18)</td>
<td>...</td>
<td>NA</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; CHAD, congestive heart failure, hypertension, age, diabetes, stroke; DW-MRI, diffusion-weighted MRI; IQR, interquartile range; NA, not applicable; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RBANS, repeatable battery for the assessment of neuropsychological status; SIRS, systemic inflammatory response syndrome; TAVI, transcatheter aortic valve implantation; and TIA, transient ischemic attack.

before TAVI), (2) the use of procedural characteristics (eg, direct TAVI or the use of a dedicated cerebral protection device), and (3) postprocedural complications with hemodynamic or embolic compromise of cerebral blood flow (eg, bleeding complications, aortic regurgitation, SIRS, and cerebral embolic events in DW-MRI at E2).

Patient Characteristics

Patient baseline data were dichotomized for the occurrence of early CD and compared in univariate fashion. Interestingly, previous stroke and other conceivable risk factors of CD were distributed without significant differences (Table 2). Furthermore, the preprocedural mean total RBANS score did not significantly differ in patients with and without early postprocedural CD. Patients with terminal renal failure requiring hemodialysis were at increased risk for CD. Ultimately, as an intraprocedural predictor of CD, procedure duration as an indicator for technical challenge and complexity was significantly higher in patients with CD.

Mild Cognitive Impairment

MCI was present in 30 patients (27%) before TAVI, of which all remained without early CD after TAVI. Conversely, patients with impaired cognitive function demonstrated transient improvement of cognitive performance early after TAVI (Figure 5). Hence, patients with an underlying MCI had similar outcome with respect to cognitive performance ≤24 months after TAVI.

Vascular Complications

Vascular complications are known to be associated with adverse outcome. Most likely, this complication is aggravated by its periprocedural hemodynamic deterioration caused by bleeding and concomitant SIRS, which is known to be associated with increased morbidity and mortality. Bleeding events were not associated with CD. Patients with CD revealed slightly but statistically nonsignificant higher incidence of SIRS during the first
2 days after TAVI. Both patients with transient CD demonstrated SIRS followed by pneumonia and sepsis during hospitalization. SIRS and consecutive nonembolic hemodynamic deterioration seem to be a contributor of cognitive impairment after TAVI.

Cerebral Embolism

Embolization of solid material during TAVI could be discussed as a potential mechanism of early CD after cardiovascular procedures. However, its relationship to CD remains elusive. Baseline characteristics of patients undergoing standard TAVI procedure, direct TAVI, or TAVI with a cerebral protection device were without significant differences (data not shown). Fifty-six patients (50.4%) completed the imaging protocol, and cerebral embolization was performed in 36 patients (64%). Patients could not undergo DW-MRI at E2 because of the necessity of permanent pacemaker implantation (n=34, 30%), logistical reasons (n=14, 12.6%), hemodynamic instability (n=5, 4.5%), and new onset of claustrophobia (n=2, 1.8%). We, therefore, compared trajectories of patients with and without signs of cerebral embolization in DW-MRI (Figure 5). Thirty-six patients demonstrated new embolic events (range, 1–10; median, 4), with a median total volume of 0.7 mL (range, 0.1–3.6 mL), whereas cerebral embolism was ruled out in a subset of 20 patients. Cognitive trajectory in this particular subgroup is of pivotal interest because most recent neuroprotective approaches aim to reduce the surrogate parameters, presuming the most optimal case to be a cerebral embolic burden of zero. Interestingly, this subgroup without any embolic events presented comparable cognitive trajectory compared with patients with embolization or patients without imaging protocol (Figure 5). Interestingly, patient age was found to be the only covariate significantly associated with longitudinal decline of RBANS total score during the follow-up period (P=0.012), linking higher age to more CD after TAVI. Hence, the age of the patient but neither the absence of silent cerebral embolism nor the use of a dedicated embolic protection device affected cognitive trajectory in this observational study.

Discussion

This is the first study to investigate the cognitive trajectory throughout the first 2 years after TAVI. This trial adds several new insights. First, despite the high age of the subjects and the expectedly high incidence of new embolic events, there was no indication of general CD after TAVI. Marked CD remains rather uncommon throughout the first 2 years after TAVI. Second, patient factors (such as initial cognitive status or lack of cerebral embolism) and the nonuse of conceivably neuroprotective measures were not associated with CD. In contrast, procedural duration as a measure of technical complexity and nonembolic hemodynamic deterioration seem to be associated with CD. However, the exact pathophysiological mechanism of CD after TAVI remains elusive.

Neurological and Cognitive Performance

We observed 2 strokes (1.6%) in our study population, 1 of which was periprocedural. In 6 patients (5.4%), early CD was obtained, 3 of which revealed a transient course with recovery of cognitive function during follow-up. We chose deterioration of the RBANS total score >1 SD as the cutoff criterion for CD based on previous studies and the retest variability of the
In all patients with transient early CD, the underlying cause was incipient sepsis caused by pneumonia. Unfortunately, patients with persistent early CD dropped out of the imaging protocol because of the necessity of permanent pacemaker implantation, precluding mechanistic insights. Previous reports demonstrate a high risk of transient and persistent CD in patients undergoing surgical aortic valve replacement (≤50%). However, the reports on the rate of CD after cardiac surgery vary considerably depending on how the deficit is defined, cognitive tests performed, timing of test administration, and composition of the population investigated. Nevertheless, it is generally recognized that short-term changes in cognitive performance do occur frequently early after surgery and typically encompass domains such as attention, memory, and psychomotor speed. Recent data investigated cognitive trajectories ≤3 months using the mini-mental state examination as a test. However, the sensitivity of the mini-mental state examination is low and does not allow repetitive testing for the analysis of postprocedural CD. Although 35 patients died during the study, we conclude the low incidence of CD because 9 of them were followed up once and 26 patients underwent thorough testing at least twice at E2, E3, and E4 before death, respectively. In all, 101 of 111 patients demonstrated no CD at any time after TA VI (91%).

**Potential Risk Factors for Early Cognitive Dysfunction**

The high risk of CD after conventional valve replacement is of clinical relevance because of its association with increased morbidity and mortality. Reversibility of CD could be dependent not only on the trigger (eg, incipient sepsis), but also on the patient’s age and risk factors. Previous studies demonstrated irreversible deficits in the older patient group (mean age, 68 years) and reversible changes in the younger patient group (age, 52 years). Hence, risk stratification with respect to neuropsychological outcome could be a major challenge in aged patients undergoing TA VI. Our further analyses aimed at the investigation of conceivable risk factors, potential triggers, and plausible mechanisms of early CD.

**Patient Characteristics**

Previous studies demonstrated higher Society of Thoracic Surgeons score to be associated with higher risk of focal neurological deficit. Furthermore, it is known that patients with previous stroke have an increased risk of a cerebrovascular event after cardiac surgery. Similar results have been presented for patients undergoing TA VI. However, silent and subtle neuropsychological impairment has not yet been investigated for risk factors. The present study revealed a slightly but nonsignificantly higher Society of Thoracic Surgeons score in patients with early CD. Notably, previous cerebrovascular events were not predictive of early CD.

**Preexisting Mild Cognitive Impairment**

Mild cognitive impairment is an established risk factor and prerequisite of manifestation of vascular dementia. Objective knowledge on preprocedural cognitive function and early postprocedural CE could be of clinical value in patient selection and procedural neuroprotective approaches because we know...
that cerebral white matter lesions and subclinical microembolic events are a potential mechanism of CD and manifestation of vascular dementia. This is the first data set reporting on the incidence of MCI to be as high as 30% in real-world patients undergoing TA VI. This subset of patients with a low baseline value would have required a deterioration of RBANS score <50 points, which is an extremely low value. But it remains elusive whether the lower the baseline value is, the more stable it is, which could be a first explanation for the good outcome of the MCI subgroup. Interestingly, patients with low cognitive function at baseline tend to transiently improve cognitive performance. It remains speculative whether improved hemodynamics after TA VI contributed to this remarkable finding.

Procedural Complications
It is a well-known fact that vascular complications are crucial factors of procedural morbidity and mortality. In addition, global hemodynamic deterioration caused by SIRS occurs in ≤40% early after TAVI and is a strong predictor of adverse outcome. Besides bleeding complications, we proposed infection, uremia, and aortic regurgitation as causal mechanisms of SIRS and hemodynamic deterioration. Affection of cerebral perfusion and alteration of cognitive performance are known sequelae of SIRS and can cause early CD. In this cohort, we found no significant association of nonembolic hemodynamic deterioration and CD.

Cerebral Embolism
TAVI is known for its association with silent cerebral embolism. Despite the high rate of cerebral embolism, the incidence of early CD is low. Notably, embolism was investigated only in the subset of transportable, stable patients without the need for postprocedural pacing. However, the patient subset without cerebral imaging presented comparable cognitive performance. In a review of 22 cardiac surgery studies, no association of cerebral embolism and CD was found in 15 studies. Only 1 trial using DW-MRI assumed an association. After TAVI, the majority of focal embolic lesions were silent. In a recent study, cerebral microembolism after transapical AVI was not found to be associated with CD for ≤3 months using a broad testing battery. Furthermore, cognitive performance was altered only mildly compared with the surgical valve replacement. In parallel with our data, in the 3 studies that included the assessment of cognitive function, a correlation between cerebral embolism and cognitive function was not found. Although these events are not unequivocally accepted as a contributing mechanism of early CD, various protective approaches aim to reduce embolic burden during cardiovascular procedures. Predilatation was recently demonstrated to be of embolicigenic potential. Recent data of a large multicentric analysis found an association between postdilatation and early stroke. Direct TAVI minimizes alteration of the native valve and could conceivably be neuroprotective because predilatation, hemodynamic deterioration during rapid pacing, and postdilatation can be avoided. However, univariate analysis revealed no significant effect of this approach on cognitive performance after TAVI (RBANS total score at E2, E3, and E4: +1.7, +2.4, and +2.3 (direct) versus +3.3, +0.4, and +0.1 (conventional); P=0.08, P=0.6, and P=0.71, respectively). Also, the use of the Montage embolic protection system revealed no effect on cognitive trajectory. Only higher patient age was associated with CD during the first 2 years after TAVI. Taken together, the long-term cognitive trajectory in most patients undergoing TAVI is neither influenced by the patient nor by procedural characteristics. Our findings should affect the end point definitions and calculations of the required sample sizes of ongoing and future neuroprotective trials.
Limitations
The low event rate and sample size limit the data analysis to univariate statistics. Several patients could not undergo the repetitive imaging protocol, for example, because of the need for permanent pacemaker implantation. Furthermore, patients had to be excluded because of critical condition. Based on the observed low incidence of CD, missing data could have an effect on the risk of type II error. Cognitive performance was not directly compared with healthy octogenarians or patients undergoing surgical or conservative treatment. We, therefore, chose a comprehensive neuropsychological test battery, which allows age-, sex-, and education-based comparisons with healthy individuals. Because surgically and conservatively treated patients are subjected to selection bias, only future randomized studies will be able to compare cognitive trajectory of each treatment strategy. However, our protocol objectified and related individual data to an age-, sex- and education-corrected control group. Functional and morphological follow-ups are ongoing at the time of this report and scheduled ≤4 years. Ultimately, our observational data set does not evaluate the efficacy of a distinct neuroprotective protocol. Especially, the effect of valve deployment mechanism on cognitive performance could be a critical issue but remains elusive. Although these aspects are of clinical relevance, this study was not intended to measure this.

Conclusions
The majority of patients (91%) do not have CD at any time for ≤2 years after TAVI. This study is unique in its prospective examination of the incidence, course, and potential risk factors of CD using a comprehensive repeatable neuropsychological test battery. Future studies need to elucidate the effect of patient selection and postprocedural protocols on the prevention of CD.

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Disclosures
Dr Grube is a proctor for CoreValve/Medtronic. The other authors report no conflicts.

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Cognitive Trajectory After Transcatheter Aortic Valve Implantation
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Supplemental Material

Supplemental methods

Study inclusion criteria were: a) severe, symptomatic aortic stenosis with or without regurgitation and high or excessive peri-operative risk, b) echocardiographic aortic valve annulus diameter >20 and <27 mm, and c) diameter of the ascending aorta <45 mm. Exclusion criteria included contraindications to DW-MRI, e.g. permanent pacemaker implantation, claustrophobia, or hemodynamic instability impeding transport to DW-MRI, hypersensitivity or contraindication to post-interventional dual platelet inhibition; sepsis or active endocarditis; bleeding diathesis or coagulopathy; recent cerebrovascular accident; mitral or tricuspid valvular insufficiency (> grade II); left ventricular or atrial thrombus; previous aortic valve replacement; progressive disease with life expectancy <1 year, and inability to give written informed consent. Furthermore, patients with a non-autarkic lifestyle or a psychiatric disorder were excluded.

Magnetic resonance imaging of the brain

Cerebral MRI was performed using a 1.5 Tesla whole body system (Intera, Philips Medical Systems, Best, The Netherlands). Cranial MRI was performed using a 1.5 Tesla whole body system (Intera, Philips Medical Systems, Best, The Netherlands). Quantitative DW-MRI was performed before and within four days after TAVI. The imaging protocol included transversal and coronal DWI, transversal T2-weighted turbo spin echo (Turbo spin echo (TSE); Repetition time (TR) / Echo time (TE): 4800 / 100 ms) and fluid attenuated inversion recovery (FLAIR; TR/TE 6000/120 ms) sequences. DWI was performed with a spin-echo echo-planar pulse sequence (TE: 78 ms; TR: 2921 ms; echo-planar imaging factor: 77; field of view: 240 mm; matrix: 128 x 256; section thickness: 5 mm; intersection gap: 1 mm; total acquisition time, 21.4 seconds) with diffusion sensitization b-values of 0, 500 and 1000 s/mm². Apparent diffusion coefficient maps were obtained in all cases. Pre-existing brain abnormalities (e.g. microangiopathy, infarctions, or atrophy) and the appearance of new hyperintense lesions in DWI on postoperative scans were evaluated. Diffusion abnormalities consistent with embolic lesions were included in the analysis. Hence, post-interventional new lesions were determined on the DWI images with maximum contrast between lesion and normal tissue signal. Scans were read by two experienced radiologists without knowledge of the timing of the imaging with respect to therapy and blinded to the clinical and neurological status of the patient. In case of discrepancy, a consensus reading was held. For volume quantification of new hyperintense lesions in DW-MRI, the images were magnified fourfold, the area of lesion was manually delineated in each image slice by
region of interest. For image analysis, the commercially available software of the MRI unit was used (Viewforum, Philips Medical Systems, Best, The Netherlands).

Transfemoral aortic valve implantation and neuroprotective approaches
TAVI was performed in spontaneously breathing patients in deep sedation using midazolam, disoprivane and fentanyl. Firstly, valvuloplasty of the aortic valve was performed with a 20- to 25-mm balloon catheter under rapid right ventricular pacing. After manual crimping of the balloon-expandable valve (Edwards-Sapien, Edwards Inc., USA) onto a delivery balloon catheter or loading of the self-expandable prosthesis (Third-generation CoreValve® revalving system, Medtronic Inc., USA) into the sheathed delivery system, the prosthesis was advanced into the left ventricle with retrograde passage of the aortic valve. After positioning with the use of fluoroscopic and angiographic guidance, the balloon-expandable stent valve was deployed by balloon inflation under rapid right ventricular pacing at 160 to 220 bpm. The CoreValve® was deployed stepwise and under guidance by several small-volume angiograms without rapid pacing. Percutaneous closure system (Prostar XL, Abbott Inc.) was routinely used for the closure of the 18 F arterial access site. During TAVI, the patients received weight-adjusted intravenous heparin to achieve an activated clotting time of 300 – 350 s for the duration of the procedure. Additionally, 500 mg of acetylsalicylic acid (ASS) and 300 mg clopidogrel hydrogen sulfate were administered. Dual antiplatelet treatment was continued with 100 mg of ASS and 75 mg of clopidogrel for six months followed by ASS monotherapy. In a subset of patients, balloon valvuloplasty prior TAVI, rapid ventricular pacing and post-dilatation were omitted at the discretion of the operator. This approach has been described recently and was abbreviated as direct TAVI.¹ In a further subset of patients, TAVI was performed with cerebral embolic protection utilizing a dedicated filter device (Montage, Claret Medical Inc., USA) as described previously.²

Supplemental References

Vývoj kognitivních funkcí po katetrizační náhradě aortální chlopně

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Úvod — Katetrizační náhrada aortální chlopně (TA VI) je spojena s němým poškozením mozku, které může přispívat ke vzniku kognitivní dysfunkce. Vzhledem k narůstajícímu užívání TA VI je zcela zásadní provedení podrobného dlouhodobého výzkumu hodnotícího vývoj kognitivních funkcí po tomto výkonu.

Metody a výsledky — Opakovatelná baterie testů pro vyšetření neuropsychologického stavu (RBANS) byla u pacientů provedena před výkonem (E1) a dále 3 dny (E2), 3 měsíce (E3), 1 rok (E4) a 2 roky (E5) po TA VI. Byl zkoumán vliv vstupních charakteristik, procedurálních dat, výsledků zobrazovacího vyšetření mozku (difuzí váženého zobrazení magnetickou rezonancí) a využití dostupných neuroprotektivních postupů na kognitivní funkce. Kognitivní funkce byly zhodnoceny u 111 pacientů (průměrné logistické EuroSCORE, 30 ± 13 %). Globální parametr kognitivních funkcí (celkové skóre RBANS) přechodně vzrostl při kontrole E2 (p = 0,02) a byl srovnatelný se vstupní hodnotou při kontrole E3, E4 a E5. U šesti pacientů (5,4 %) bylo patrné časné zhoršení kognitivních funkcí. Přetrvávání časného poklesu kognitivních funkcí (n = 3; 2,7 %) a pozdní pokles kognitivních funkcí (n = 4; 3,6 %) byly málo časté. U 105 pacientů (94,6 %) bylo tudíž vyloučeno časné zhoršení kognitivních funkcí a u většiny pacientů (91 %) bylo prokázáno nezměněné udržení kognitivních funkcí při všech kontrolách během studie. Je zajímavé, že pouze věk pacienta (p = 0,012) byl nezávisle spojený s poklesem kognitivních funkcí, což nebylo prokázáno pro anamnézu cerebrovaskulárních příhod, vstupní stav kognitivních funkcí, přímou TA VI, obraz embolizace do mozku při difuzí váženém zobrazení magnetickou rezonancí, nebo použití zařízení pro protekci embolizace do mozku. Vyšší věk má tedy vztah ke zhoršení kognitivních funkcí v prvních dvou letech po TA VI.

Závěry — Úroveň kognitivních funkcí byla dlouhodobě zachována u převážné většiny (91 %) pacientů během prvních dvou let po provedení TA VI navzdory vysokému samostatnému riziku zhoršení kognitivních funkcí v populaci tohoto věku.


Klíčová slova: kognice ■ demence ■ poškození ■ embolizace do mozku ■ lehká kognitivní dysfunkce ■ cévní mozková příhoda ■ TAVI

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