Geriatrics Gerontology International

DOI: 10.1111/ggi.14064

ORIGINAL ARTICLE

EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Delirium, functional decline and quality of life after transcatheter aortic valve implantation: An explorative study

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Received: 5 April 2020
Revised: 8 September 2020
Accepted: 1 October 2020

Aim: Transcatheter aortic valve implantation (TAVI) has become an important treatment option for older patients with severe aortic stenosis. However, not all patients benefit from this procedure in terms of functional outcome and quality of life. This complicates patient selection and shared decision-making. Postoperative delirium might negatively affect patient outcomes after TAVI. We therefore studied the potential relationship between postoperative delirium and functional outcome, and how this impacts quality of life after TAVI.

Methods: This was a prospective cohort study of 91 consecutive patients undergoing TAVI between 2015 and 2017 at an academic medical center. All patients underwent a Comprehensive Geriatric Assessment before TAVI. Delirium symptoms were assessed daily during hospitalization. Follow up was carried out between 6 and 12 months postprocedure. The primary outcome was functional decline or death at follow up. Secondarily, we measured quality of life at follow up.

Results: The incidence of postoperative delirium was 15.4%. In total, 38.5% of patients experienced functional decline, and 11.0% died during a median follow-up period of 7 months. Delirium resulted in a fourfold increased odds of the combined outcome of functional decline or death. Quality of life was lower in patients that experienced this outcome.

Conclusion: In a cohort of TAVI patients, functional decline or death was a frequent outcome in the first year postprocedure. Postoperative delirium increased the odds for this outcome substantially. This suggests that delirium risk should be an important factor to consider in shared decision-making for TAVI patients. **Geriatr Gerontol Int 2020; 20: 1202–1207**.

Keywords: activities of daily living, cardiovascular surgery, delirium, quality of life, transcatheter aortic valve implantation.

Introduction

Degenerative valvular aortic stenosis is a common medical condition of older age. Severe symptomatic aortic stenosis has a poor prognosis if left untreated, with an annual mortality rate of up to 50%.[1,2] For many patients, a conventional surgical aortic valve replacement is not suitable due to high surgical risk. With the introduction of the transcatheter aortic valve implantation (TAVI), a less invasive therapeutic option became available for high-risk patients that reduces mortality similar to surgical aortic valve replacement.[3] More recently, older patients with intermediate surgical risk, and sometimes even with low risk, are also considered for TAVI.[4,5]

Selecting patients who will benefit from this procedure is a topic of debate. The Society of Thoracic Surgeons score and the European System for Cardiac Operative Risk Evaluation, which are used for patients undergoing conventional cardiac surgery, have proven to be less accurate in predicting mortality for patients being considered for TAVI.[6] Also, for older patients, survival is often not the most important health outcome, and many regard "remaining independent" equally or more important.[7] However, previous research has shown that a subgroup of patients does not benefit from TAVI in terms of functional improvement or quality of life.[8,9]

Up to 44% of TAVI patients experience postoperative delirium.[10] Previous research suggests that delirium might result in a higher chance of functional decline in the first year after TAVI.[11,12] How postoperative delirium and functional outcome influence quality of life in TAVI patients is unknown. This is vital information for cardiologists, geriatricians and patients to make an informed decision.

We therefore aimed to study a potential relationship between postoperative delirium and functional outcome within the first year after the procedure, and how this reflects on quality of life after TAVI, to improve patient selection and shared decision-making for older TAVI patients.

Methods

Study design and population

We carried out an observational prospective cohort study between July 2015 and December 2017. We included consecutive patients

who underwent elective TAVI at a university teaching and tertiary hospital in the Netherlands, and were able and willing to participate in a follow-up visit after 6–12 months. There were no exclusion criteria. All patients were evaluated by a multidisciplinary heart team comprising invasive cardiologists, imaging cardiologists and cardiothoracic surgeons, as well as a geriatrician to establish the indication and suitability for TAVI. Permission was granted by the local Medical Ethics Committee.

Baseline assessments

At baseline, patients were evaluated at the geriatric outpatient clinic by a comprehensive geriatric assessment (CGA), to optimize patient selection and the perioperative trajectory. During this CGA, information regarding demographic data, social status, current health status, comorbidities, medication use, laboratory results, cognitive and functional status was gathered. We used the Charlson Comorbidity Index to list comorbidities.[13] Cognitive screening was carried out with the Mini-Mental State Examination.[14] Patients were asked if they experienced a previous delirium. For functional status, two different questionnaires were used. During the first year of the study, the Groningen Activity Restriction Scale (GARS-4) was used.[15] This scale comprises 11 items regarding activities of daily living (ADL) and seven items regarding instrumental activities of daily living (iADL). Each item is scored on four levels: independent without difficulty,[1] independent with some difficulty,[2] independent with much difficulty[3] or dependent.[4] This scale can be recoded into a dichotomous outcome: independent (level 1–3) or dependent (level 4), which is how it was used in the present analysis (thus named GARS-2). During the rest of the study period the 15-item modified Katz Index of Activities of Daily Living (Katz-ADL 15) was used.[16] This scale consists of eight ADL and seven iADL items, scored as dependent or independent. Functional dependency was scored as the number of items in which the participant was dependent, on either the GARS-2 or Katz-ADL 15.

Assessments during hospitalization

A team of experienced geriatric nurses and geriatricians assessed delirium daily during weekdays using the criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.[17] Non-pharmacological measures to prevent delirium were implemented according to the hospital protocol for all patients with an increased delirium risk, as assessed during the CGA. Delirium was treated according to the hospital protocol. Perioperative complications were recorded according to the Valve Academic Research Consortium-2 consensus document.[18]

Follow-up assessment of functional status and quality of life

All patients had several follow-up visits at the cardiology department planned during the first year postprocedure. They were called in advance to ask if they were willing to participate in a geriatric follow-up measurement at one of these appointments, preferably at 6 months postprocedure. Functional status was assessed using the Katz-ADL15 or GARS-2, depending on which scale was used at baseline. Functional decline was defined as an increase of at least 1 point on the Katz-ADL 15 or GARS-2 at follow up compared with baseline. Patients who died before follow up could take place were also included in the analysis, resulting in the combined outcome of functional decline or death as the primary outcome of interest.

Health-related quality of life was measured using the EuroQuol-5D (EQ-5D). The EQ-5D consists of five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), which are scored on three levels: (i) no problems; (ii) some problems; or (iii) extreme problems. A single index value was generated by aggregating and weighting the five domains, using de Dutch EQ-5D tariff.[19] The resulting score ranges from <0 (0 is a health state equivalent to death, negative values are valued as "worse than death") to 1 (perfect health). The EQ-5D visual analog scale (VAS), ranging from 0 to 100 (higher score indicating better health) was used to measure patients' perceived general health status.

Statistical analysis

SPSS version 23.0 (IBM Corporation, Armonk, NY, USA) was used for data analysis. Differences in baseline characteristics and postoperative outcomes between participants with and without delirium were assessed using *t*-tests, χ^2-tests or Mann–Whitney *U*-tests.

A logistic regression was carried out with the combined outcome variable of functional decline or death as the dependent variable, and delirium as the independent variable. To assess the possible causal association between delirium and the combined outcome variable, we used the method of directed acyclic graphs (DAG) to establish confounders of this causal pathway.[20] A DAG is a graph using unidirectional arrows to represent known causal effects between variables (on the basis of prior knowledge). The arrows between variables form paths. Depending on the direction of the arrows, different types of paths are formed, which in turn identify which variable is a confounder, collider or mediator of the causal pathway of interest. Based on our DAG, age, baseline functional dependence and Mini-Mental State Examination, the number of comorbidities and perioperative complications were identified as confounders, and were thus added as covariates to our model (Fig. SS1).

Results

Patient recruitment and baseline data

During the study period, 100 consecutive patients were eligible to participate in the study. One patient had an incomplete functional assessment at baseline, five patients declined follow up, two patients were not able to participate in follow up due to poor condition and one patient was lost to follow up, resulting in 91 patients that were included in the present study. During a median follow-up period of 7 months (interquartile range [IQR] 6.0–10.0 months), 35 patients experienced functional decline (38.5%) and 10 patients died (11.0%; Fig. 1).

The baseline characteristics of the 91 included patients are described in Table 1, subdivided by delirium status. As shown by the European System for Cardiac Operative Risk Evaluation, 18.7% had low, 56.0% had intermediate and 25.3% had high surgical risk. During hospitalization, 14 patients (15.4%) experienced delirium. Patients with delirium more often had experienced prior delirium, had a lower Mini-Mental State Examination score and had poorer kidney function at baseline than patients without delirium. They also appeared to have a lower baseline functional status, but the difference was not statistically significant.

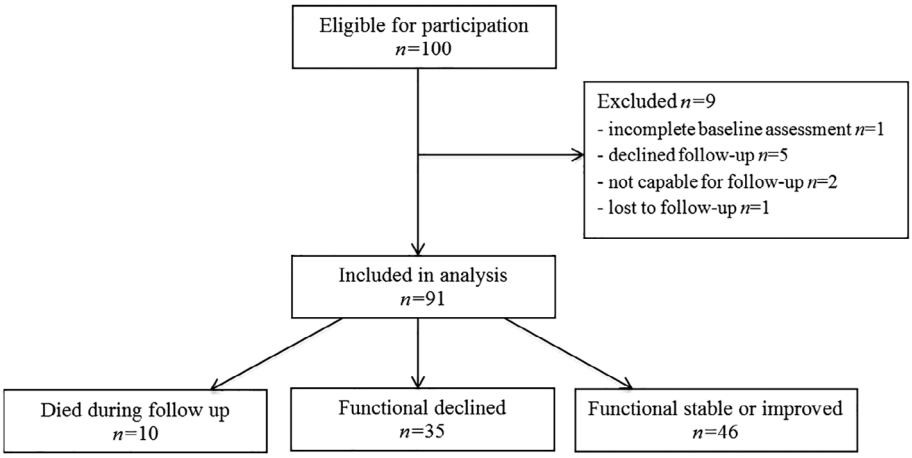

Figure 1 Enrollment and follow up of patients.

Procedural and postprocedural outcomes

All but one patient received general anesthesia. The access route for TAVI was transfemoral in 75 (82.4%) patients. Patients with delirium more often had a non-transfemoral approach than patients without delirium, but this difference was not statistically significant (46.7% and 13.0%, respectively, P = 0.07). Table 2 shows the procedural and postprocedural outcomes of patients with and without delirium. The number of Valve Academic Research Consortium-2 complications and in-hospital mortality were comparable between groups. During the median follow-up period of 7 months, death and functional decline were more frequent in patients with delirium (28.6% and 50.0%, respectively), than in patients without delirium (7.8% and 36.4%, respectively), although the latter difference between groups was not statistically significant. The combined outcome of functional decline or death occurred in 45 patients, and was more frequent in patients with delirium, than in patients without (78.6% *vs* 44.2%).

Functional decline or death and the association with delirium

In multivariate analysis, postoperative delirium was associated with an increased odds of functional decline or death (odds ratio 4.75, 95% confidence interval 1.10–20.43). All other covariates showed no significant association with the outcome (Table 3).

Quality of life and the association with functional decline

Results of the EQ-5D were available for the 81 patients that survived until the follow-up visit. For the entire cohort, the median EQ-5D index was 0.81 (IQR 0.65–0.89) and the mean EQ VAS was 70.0 (IQR 60.0–75.0). When comparing EQ-5D scores of patients with and without functional decline, both the index score and VAS were lower in patients with functional decline than patients without functional decline (Table 4). On the individual EQ-5D items, patients with functional decline had lower scores on the items "mobility" and "self-care"(Table 4).

Table 1 Baseline characteristics of patients with and without delirium

Variable	Delirium (n = 14)	No delirium (n = 77)	P-value
Age (mean ± SD)	83.6 ± 4.0	80.4. ± 6.1	0.06
Male, *n* (%)	7 (50.0)	30 (39.0)	0.44
Living at home, *n* (%)	11 (78.6)	68 (89.5)	0.25
No or only primary education, *n* (%)	7 (50.0)	29 (38.6)	0.43
No. iADL dependencies, median (IQR)	4.0 (0.75–7.5)	2.0 (0.0–4.5)	0.17
Subjective memory complaints, *n* (%)	7 (50.0)	23 (29.9)	0.15
Data missing	0	1	
Prior delirium, *n* (%)	7 (50.0)	10 (13.0)	<0.001
MMSE, median (IQR)	27.0 (24.8–28.2)	28.0 (27.0–29.0)	0.05
Data missing	0	1	
Charlson Comorbidity Index, median (IQR)	2.0 (1.0–2.5)	2.0 (1.0–3.0)	0.98
No. prescriptions, median (IQR)	9.5 (6.8–12.5)	8.0 (5.5–11.0)	0.27
Logistic EuroSCORE I, median (IQR)	19.0 (12.9–22.3)	15.0 (10.0–19.0)	0.12
Left ventricular ejection fraction in %, median (IQR)	47.5 (40.0–55.0)	55.0 (45.0–55.0)	0.64
Atrial fibrillation (%)	6 (42.9)	27 (35.1)	0.58
eGFR, mean mL/min/1.73 m^2 (SD)	57.7 (17.2)	47.1 (8.2)	0.03
Hb, mean mmol/L (SD)	7.8 (0.8)	8.1 (1.1)	0.38

ADL, activities of daily living; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; iADL, instrumental activities of daily living; IQR, interquartile range; MMSE, Mini-Mental State Examination; SD, standard deviation.

Table 2 Procedural and postprocedural outcomes of patients with and without delirium

Variable	Delirium (n = 14)	No delirium (n = 77)	P-value
Complications, n (%)			
Myocardial infarction	0 (0)	0 (0)	n.a.
Stroke	0 (0)	2 (2.6)	0.54
Bleeding	4 (28.6)	24 (31.2)	0.85
Vascular	2 (14.3)	12 (15.6)	0.77
Acute kidney injury	1 (7.1)	4 (5.2)	0.77
Need for a pacemaker	0 (0)	10 (13.0)	0.15
Length of hospital stay in days, median (IQR)	7.5 (6.8–15.0)	7.0 (6.0–8.0)	0.05
Functional decline[†]	7 (50.0)	28 (36.4)	0.07
Data missing[‡]	4	6	
Mortality			
In hospital	1 (4.1)	3 (3.9)	0.59
During follow up	4 (28.6)	6 (7.8)	0.02
Functional decline or death	11 (78.6)	34 (44.2)	0.02

[†]Increase of at least one point on the 15-item modified Katz Index of Activities of Daily Living or Groningen Activity Restriction Scale at follow up compared with baseline.

[‡]All cases are missing due to death at the time of measurement.

IQR, interquartile range.

Discussion

In this observational study of 91 consecutive TAVI patients, we found that postoperative delirium resulted in a fourfold increased odds for functional decline or death in the first year postprocedure. Functional decline occurred in over one-third of patients when measured after a median follow-up period of 7 months, and these patients experienced a lower quality of life than patients with a stable or improved functional status. The present results emphasize that TAVI, although a less invasive treatment option for severe aortic stenosis, still results in a poor functional outcome in a substantial number of patients, and that delirium risk should be an important factor to consider in shared decision-making.

We found that a large portion of patients (38.5%) experienced functional decline after TAVI. When measuring functional outcome after TAVI, previous research mostly reported a clinically important improvement in New York Heart Association class, corresponding to fewer limitations in physical activities due to heart failure symptoms.[9] However, given that the estimates of change in these studies often show a lower end of the 95% confidence interval near 0, this indicates that a proportion of patients fail to improve. Measuring the mean change in New York Heart Association class in an entire cohort does not provide information on this latter subgroup, nor on individual domains of functional capacity. A more specific way of evaluating functional status is by measuring individual ADL and iADL limitations. In a cohort of 143 TAVI patients, 22.9% of patients had a trajectory with moderate-to-large functional decline, and 19.4% of patients showed only minimal decline during the first 12 months postprocedure. The remaining 37.1% had full functional recovery after TAVI.[21] This is comparable to the present findings. In another cohort of 106 patients, 20.8% had a decrease of ≥1 point on an ADL scale 6 months after TAVI.[22] In this study of Schoenenberger et al.,[22] iADL activities were not measured, which could explain the lower incidence of functional decline. Including limitations on both ADL and iADL in the definition of functional decline might be more sensitive to detect change.

Table 3 Results from multivariate analysis, effect of delirium on outcome functional decline or death

Factor	P-value	Odds ratio (95%CI)
Delirium	0.04	4.75 (1.10–20.43)
Age	0.24	1.05 (0.97–1.14)
Baseline MMSE	0.48	0.92 (0.74–1.16)
Baseline iADL dependencies[†]	0.59	0.95 (0.79–1.14)
Charlson Comorbidity Index	0.87	0.98 (0.74–1.30)
No. VARC-2 complications[‡]	0.12	2.14 (0.82–5.64)

[†]Number of dependencies on either 15-item modified Katz Index of Activities of Daily Living or Groningen Activity Restriction Scale.

[‡]Myocardial infarction, cerebrovascular event, vascular, hemorrhage, acute kidney injury or need for pacemaker implantation.

CI, confidence interval; iADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; VARC-2, Valve Academic Research Consortium-2.

We found that 15.4% of patients developed delirium, and that patients with delirium had a fourfold increased odds of experiencing functional decline or dying during follow up. Evidence on the association between delirium and functional decline in the TAVI population is scarce and shows inconsistent findings. In a cohort of 110 TAVI patients, 25.5% of patients experienced delirium, and severe delirium was associated with poor ADL and iADL recovery or death after 6 and 12 months, but this was not the case for mild delirium.[12] In a cohort of 63 TAVI patients with a higher delirium incidence of 44%, delirium predicted lower ADL and iADL score 1 month after TAVI, but at 6 months' follow up this was no longer the case.[11] The different findings of this latter study might be explained by the fact that deceased patients were not included in the primary analyses, which could have introduced survival bias. Overall, the present results add to the limited body of evidence that delirium after TAVI is an important predictor of poor functional outcome, including death.

Previous research found that frailty, comorbidity and route of procedure were also associated with poor outcome in TAVI patients.[22–24] We could not replicate these findings. We did not include an overall frailty measure in our model, because it was not part of the CGA before TAVI; and route of procedure was not included, because according to our DAG it was a mediator of the

Table 4 Results on EuroQuol-5D of surviving patients with and without functional decline

Variable		Functional decline (n = 35)	No functional decline (n = 46)	P- value
EQ-5D index, median (IQR)		0.77 (0.43–0.81)	0.81 (0.69–0.89)	0.04
EQ-VAS, median (IQR)		70.0 (60.0–70.0)	70.0 (60.0–80.0)	0.02
Individual items	Level			
Mobility, *n* (%)	No problems	4 (11.4)	16 (34.8)	0.02
	Some problems	31 (88.6)	30 (65.2)	
	Extreme problems	0 (0)	0 (0)	
Self-care, *n* (%)	No problems	22 (62.9)	40 (87.0)	0.02
	Some problems	10 (28.6)	3 (6.5)	
	Extreme problems	3 (8.6)	3 (6.5)	
Usual activities, *n* (%)	No problems	22 (62.9)	31 (67.4)	0.73
	Some problems	10 (28.6)	13 (28.3)	
	Extreme problems	3 (8.6)	2 (4.6)	
Pain/discomfort, *n* (%)	No problems	13 (37.1)	19 (41.3)	0.88
	Some problems	18 (51.4)	21 (45.7)	
	Extreme problems	4 (11.4)	6 (13.0)	
Anxiety/depression, *n* (%)	No problems	25 (71.4)	40 (87.0)	0.08
	Some problems	7 (20.0)	6 (13.0)	
	Extreme problems	3 (8.6)	0 (0)	

EQ-5D, EuroQuol-5D; IQR, interquartile range; VAS, visual analog scale.

association between delirium and outcome, and not a potential confounder (Fig. SS1). The reason that individual frailty domains, such as cognition, functional dependency and comorbidity, were not significant in our model might be due to selection bias. The present cohort consisted of patients who were evaluated and approved for TAVI by the heart team, and patients who underwent surgical aortic valve replacement or medical treatment were thus excluded. This might have resulted in more homogeneity in these variables and thus no significant association in our model.

Quality of life was satisfactory in the present cohort, although lower scores were found in patients with functional decline. Normal values for Dutch persons of aged ≥75 years on the EQ-5D index and VAS are 0.83 and 72.9, respectively, which are slightly higher than the scores in our cohort.[25] To our knowledge, the association between functional outcome and quality of life has not been studied before in TAVI patients.

There were some limitations to the present study. First, in the study population, all but one patient received general anesthesia. TAVI is a rapidly evolving treatment, and anesthesia is currently more often carried out locally or with sedation instead of general anesthesia.[26] This might have influenced our findings, although existing literature has not identified a clear causal association between type of anesthesia and postoperative delirium or mortality.[27,28] Second, two different instruments were used to measure ADL and iADL. These instruments are similar, although there are differences both with respect to the number of items (Katz-ADL15 consists of 15 items and GARS-2 of 18) and the content of the items. Therefore, a 1-point change on the Katz-15 is not exactly the same as on the GARS-2. Finally, there was a difference in follow-up time between patients. However, the spread in follow-up duration was small (IQR 6.0–10.0 months), so we do not expect that this has impacted the present findings substantially.

A strength of the present study was that this was a real-life cohort with no exclusion criteria, that accurately describes daily clinical practice. Also, a complete CGA was carried out at baseline, and during hospitalization delirium assessment was carried out daily by a specialist team of geriatricians and geriatric nurses, which has resulted in high-quality data. Finally, by using a DAG, we systematically addressed confounding and made a stronger argument for the possible causal association between delirium and functional decline or death, than would have resulted from a statistically based method.

In conclusion, in the present study of 91 TAVI patients, we found that over one-third of patients experienced functional decline, and one out of 10 patients had died after a median follow-up period of 7 months. Delirium was an important risk factor for the combined outcome functional decline or death. Quality of life was lower in patients with functional decline than in patients with a stable functional status or improvement. Delirium risk should be incorporated in the process of shared decision-making, and delirium prevention should remain a top priority in TAVI patients. Future studies that address patients goals for TAVI, and whether or not they were met after treatment, in relation to functional outcome, could further improve decision-making and patient selection.

Acknowledgements

None.

Disclosure statement

The authors declare no conflict of interest.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Directed acyclic graphs (DAG) that were used for the analysis of the possible causal association between delirium and the combined outcome variable functional decline or death (bold arrow). Each arrow represents a causal effect. (a) All possible associations between variables. Continuous arrows form paths that can result in confounding. Dotted arrows form paths that can result in other types of bias (mediation, colliding for example). (b) Only paths that result in confounding and thus identify the variables that were used in the final analysis. For example the variable age has a causal association with both delirium and the combined outcome functional decline or death, and is therefore a confounder.

How to cite this article: Beishuizen SJ, Festen S, Loonstra YE, van der Werf HW, de Rooij SE, van Munster BC. Delirium, functional decline and quality of life after transcatheter aortic valve implantation: An explorative study. Geriatr. Gerontol. Int. 2020;20:1202–1207. https://doi.org/10.1111/ggi.14064