Geriatric assessment in the prediction of delirium and long-term survival after transcatheter aortic valve implantation

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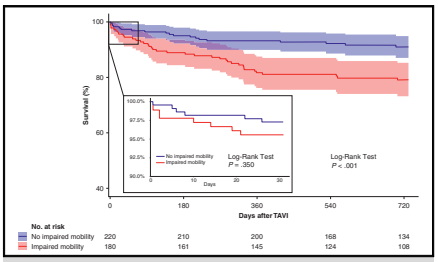
ABSTRACT

Objectives: Transcatheter aortic valve implantation (TAVI) has emerged as the preferred management strategy for elderly patients with severe symptomatic aortic valve stenosis. These patients are often at high risk of postoperative delirium (POD), which is associated with morbidity and mortality. Since POD may be prevented in a considerable part of these patients, identification of patients at risk is essential. The aim of current study was to identify geriatric assessment tools associated with delirium after TAVI, and long-term mortality.

Methods: Consecutive patients were preoperatively assessed by a geriatrician between 2012 and 2017. Geriatric assessment tools consisted of cognitive, functional, mobility, and nutritional tests. POD was prospectively assessed during hospitalization after TAVI. Mortality tracking was performed by consulting municipal registries.

Results: A total of 511 patients were included. Median age was 80 [76-84] years, 44.8% (n = 229) were male, and 14.1% (n = 72) had a history of POD. Delirium was observed in 66 (12.9%) patients. Impaired mobility was the strongest geriatric assessment tool associated with POD (adjusted odds ratio, 2.1 [1.1-4.2], $P = .028$) and 2-year mortality (adjusted hazard ratio, 2.5 [1.4-4.5], $P = .003$). Two-year survival was reduced with more than 10% in patients with impaired mobility before TAVI (79.4% vs 91.4%, $P = .013$).

Conclusions: This study shows that impaired mobility is currently the best single predictor for POD and 2-year mortality in high-risk patients undergoing TAVI. Prospective multicenter studies are needed to optimize and to further explore the facilitation of routine use of POD predictors in TAVI pathways of care, and subsequent preventive interventions. (J Thorac Cardiovasc Surg 2021;161:2095-102)



Short- and long-term survival of patients with or without impaired mobility before TAVI.

CENTRAL MESSAGE

Impaired mobility is the best predictor for both delirium and long-term survival after TAVI.

PERSPECTIVE

Delirium is frequently observed after TAVI and can comprise a burden of downstream complications, costs, and mortality. In many patients, delirium can be prevented. Identification of patients at risk for delirium is essential. This study identified the best geriatric assessments to predict delirium and survival after TAVI and corroborates the improvement of identification of frail TAVI patients.

See Commentaries on pages 2103, 2105, and 2106.

Transcatheter aortic valve implantation (TAVI) has emerged as the preferred management strategy for patients with severe symptomatic aortic valve stenosis. Given the extension of TAVI treatment to low-risk patients, the number of TAVI candidates will further increase.[1-3]

Postoperative delirium (POD) may occur in up to 45% of patients undergoing TAVI[4] and is associated with a burden of downstream complications, mortality, and costs.[5,6] Recently, we showed in a large cohort of patients undergoing TAVI that POD was the strongest independent

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The Departments of Cardiology and Cardiothoracic Surgery at Radboud University Medical Center, with which the authors are affiliated, have received an unrestricted grant from Medtronic.

Received for publication July 19, 2019; revisions received Jan 7, 2020; accepted for publication Feb 14, 2020.

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0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2020.02.076

Abbreviations and Acronyms

BADL = Basic Activities of Daily Living
GA = general anesthesia
HR = hazard ratio
IADL = Instrumental Activities of Daily Living
LACS = local anesthesia/conscious sedation
MMSE = Mini Mental State Exam
OR = odds ratio
POD = postoperative delirium
TAVI = transcatheter aortic valve implantation
TUG = Timed Up and Go

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predictor of long-term mortality and that it was associated with an absolute reduction of survival of 10% in 5 years.[7] Data on the identification of patients at risk for POD after TAVI are scarce.

POD may be preventable in more than 50% of patients and can often be effectively treated with non-pharmacologic treatments.[8,9] In geriatric populations, frailty and cognitive impairment are known risk factors for POD. Assessment of underlying measures such as daily functioning, mobility, and cognition therefore may have relevant added value in the prediction of POD after TAVI procedures.

Routine multidimensional geriatric frailty assessment is currently recommended in TAVI pathways.[10-12] It provides the clinician a good overall estimation of a patient's vulnerability and resilience and can serve as a prognostic tool in the work-up of TAVI candidates. Nevertheless, advised tests are time-consuming and, so far, it is unclear which assessments are most indicative predictors of POD and long-term mortality in this population.

Since 2012, our center incorporated geriatric assessment in the work-up for TAVI. In the present study, we aimed to identify geriatric assessment tools that predict the occurrence of POD and long-term mortality after TAVI.

METHODS

In this single-center study, we included all consecutive patients in whom geriatric assessment was performed before TAVI at the Radboud University Medical Centre (Nijmegen, The Netherlands) between April 2012 and December 2017. Patients were referred to our center for a complete cardiac and comprehensive geriatric assessment. Treatment allocation to either TAVI, surgical aortic valve replacement, or conservative treatment was performed by a dedicated heart team according to the current guidelines.[13] General anesthesia was used in all patients; additional procedural details have been described in previous publications.[7,14]

Geriatric Assessment

Geriatric assessment consisted of patient history, (hetero)anamnesis, medication review, and the following geriatric assessment instruments: Mini Mental State Exam (MMSE),[15] Basic Activities of Daily Living (BADL), and Instrumental Activities of Daily Living (IADL),[16] Gait speed and/or Timed Up and Go (TUG) test,[17] and Mini Nutritional Assessment[18] or serum albumin assessment. Cut-off values for the geriatric assessment measures were based on previous literature.[12,19,20] Mobility was impaired in case of gait speed $\leq$0.83 m/s or TUG $\geq$20 seconds.

Outcome Measures

The occurrence of POD was prospectively assessed 3 times a day as part of routine postoperative care after TAVI by means of the *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria.[21] Based on these criteria, postoperative delirium was defined as an acute and fluctuating disturbance of consciousness with reduced ability to focus, maintain, or shift attention, accompanied by change in cognition and perceptual disturbances secondary to a general medical condition. State-of-the-art management of POD was guided by a geriatric team and consisted of both pharmacologic and non-pharmacologic treatments such as improvement of orientation, motivation for early mobilization, promotion of sleep, and the provision of vision- and hearing adaptations.[22]

Mortality tracking on all patients was performed on November 23, 2018, by consulting the Central Bureau for Statistics (The Hague, The Netherlands). Median follow-up at that time was 1052 [646-1528] days. All data were collected in an electronic data-capturing system. Missing data or extreme values were excluded from analysis. Overall, the percentage of missing values was 2.3% (312/13,286 values). Current analysis was approved by the institution's ethics committee and complies with the Declaration of Helsinki.

Statistical Analysis

Baseline characteristics are presented as numbers and percentages. Continuous variables are expressed as mean and standard deviation if normally distributed or as median and interquartile range if skewed. Logistic regression analysis was performed to identify predictors of POD occurrence and Cox regression analysis to identify predictors of long-term mortality after TAVI. To identify predictors, first candidate variables were selected and then introduced in a backward elimination procedure to create a parsimonious model with most relevant predictors. Candidate variables were selected based on the following: (1) P value $<.05$ in univariable analysis and; (2) previous knowledge irrespective of their P value in univariable analysis. Based on previous knowledge, age, body mass index, previous delirium, and aortic valve area <0.75 were selected for POD occurrence and male sex, creatinine, chronic obstructive pulmonary disease, and permanent atrial fibrillation were selected for long-term mortality after TAVI.[7] Univariable analysis was performed for the geriatric assessment instruments with cut-offs based on previous literature.

A Kaplan–Meier survival curve was created for the strongest independent geriatric assessment measure to illustrate 2-year survival. Statistical comparison between both curves was performed using the log-rank test. All tests were 2-tailed, and a P value of $< .05$ was considered statistically significant. Analyses were performed using IBM SPSS Statistics software (version 25.0.0.1; IBM Corp, Armonk, NY) and illustrated with GraphPad Prism (version 5.03; GraphPad Software Inc, San Diego, Calif).

RESULTS

Between November 2012 and December 2017, a total of 559 patients were found eligible to undergo TAVI in the

TABLE 1. Baseline characteristics of patients undergoing TAVI

Baseline assessment	(n = 511)
Age, y	80 [76-84]
Male	44.8 (229)
BMI, kg/m^2	26.7 [24.0-30.5]
Logistic EuroSCORE I	13.1 [8.9-21.3]
NYHA functional class III-IV	73.8 (377)
Diabetes mellitus	32.7 (167)
Creatinine, mg/dL	1.0 [0.8-1.3]
COPD	24.3 (124)
Coronary artery disease	59.7 (305)
Permanent atrial fibrillation	22.5 (115)
Previous stroke or TIA	22.3 (114)
Peripheral artery disease	35.4 (181)
Use of walking aid	37.0 (189)
Psychoactive drug use*	23.9 (122)
History of delirium†	14.1 (72)
LVEF, %	55 [45-60]
Aortic valve area, cm^2	0.75 [0.60-0.90]

Data are presented as median [interquartile range] or % (n). *BMI*, Body mass index; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *NYHA*, New York Heart Association; *COPD*, chronic obstructive pulmonary disease; *TIA*, transient ischemic attack; *LVEF*, left ventricular ejection fraction. *Psychoactive drug use, use of benzodiazepine, antidepressants, or antipsychotic medication. †History of delirium was obtained by means of chart review and preoperative outpatient clinic patient and family reports.

Radboud University Medical Center in Nijmegen, The Netherlands. Preoperative multidimensional geriatric risk assessment was performed in 511 (91.4%) patients, who were all included in the current study. The baseline characteristics are shown in Table 1. Median age was 80 [76-84] years and 44.8% were male. The prevalence of comorbid illnesses was high. A walking aid was used by 189 (37.0%) patients and 72 (14.1%) patients had a history of postoperative delirium. All TAVI procedures were performed with patients under general anesthesia (GA) with the axillary artery as predominant access used (71.4%) (Table E1).

TABLE 2. Geriatric assessment measures

Frailty assessment	Instrument with used cut-off	n (%)
Cognition	MMSE <27 points	139 (30.5)
BADL	Barthel ≤19 points	234 (47.2)
IADL	Lawton ≤6 points	172 (36.1)
Malnutrition	Albumin* < 3.5 OR MNA < 12 points	118 (26.0)
Anemia	Hemoglobin* ♂ < 13.0 g/dL OR ♀ < 12.0 g/dL	236 (46.2)
Impaired mobility	Gait speed ≤0.83 m/s OR TUG ≥20 s	180 (35.2)

Patients in whom tests were performed: MMSE (n = 455), BADL (n = 496), IADL (n = 477), gait speed (n = 397), TUG (n = 268), albumin (n = 65), MNA (n = 441), hemoglobin (n = 511). *MMSE*, Mini Mental State Examination; *BADL*, Basic Activities of Daily Living; *IADL*, Instrumental Activities of Daily Living; *MNA*, Mini Nutritional Assessment; *TUG*, Timed Up and Go. *Albumin and hemoglobin cut-offs were based on previous literature.[12]

Vulnerability for POD, as indicated by an abnormal test result on one of the geriatric assessment instruments, was diagnosed in 26.0% of all patients (Table 2). Cognition, measured by means of the MMSE, was impaired in 30.5% of patients. Basic activities and instrumental activities of daily living were impaired in 47.2% (BADL, n = 234) and 36.1% (IADL, n = 172), respectively. Signs of malnutrition were found in 118 (26.0%) patients and anemia, assessed on the day before TAVI, was present in 236 (46.2%) patients. Impaired mobility, based on either slow gait speed (≤0.83 m/s) or TUG ≥20 seconds, was seen in 180 (35.2%) patients.

Postoperative Delirium

Delirium after TAVI was observed in 66 (12.9%) patients. During TAVI, 3 patients had to undergo conversion to surgical aortic valve replacement. All 3 patients developed delirium after TAVI (Table E1). Patients with delirium more often experienced stroke (7.6% 1.3%, $P = .008$) and new onset of atrial fibrillation (12.1% vs 4.9%, $P = .042$) and had significantly longer hospital stay durations (7 days vs 5 days, $P < .001$) as compared with patients without delirium (Table E2).

With regards to the geriatric assessment before TAVI, all geriatric assessment measures, except for anemia, were univariately associated with POD (Table 3). Impaired mobility had the greatest odds ratio (OR, 2.2 [1.2-3.9], $P = .008$) followed by MMSE <27 points (OR, 2.1 [1.2-3.6], $P = .008$). Independent predictors of postoperative delirium were impaired mobility (adjusted OR, 2.1 [1.1-4.2], $P = .028$) and IADL (Lawton) ≤6 points (adjusted OR, 1.9 [1.0-3.6], $P = .048$) (Table 3).

Mortality

In-hospital mortality occurred in 15 (2.9%) patients and increased to 19 (3.7%) patients in 30 days after TAVI. At 1 year, 65 (12.7%) patients were deceased. Two-year mortality was 15.3% (n = 78). Impaired mobility (hazard ratio [HR], 2.5 [1.4-4.4], $P = .001$), malnutrition (HR, 2.3 [1.4-3.7], $P = .001$), and impaired BADL (HR, 1.9 [1.2-2.9], $P = .008$) were significantly associated with 2-year mortality (Table 4). Impaired mobility was the strongest independent geriatric assessment predicting long-term 2-year mortality when adjusted for known baseline risk factors of mortality (adjusted HR, 2.5 [1.4-4.5], $P = .003$). Malnutrition was the second-best independent predictor of 2-year mortality (adjusted HR,

TABLE 3. Geriatric assessment measures and their association with delirium after TAVI

	Postoperative delirium			
	Univariable		Multivariable	
	OR [95% CI]	*P* value	aOR [95% CI]	*P* value
MMSE <27 points	2.1 [1.2-3.6]	**.008**	1.2 [0.6-2.3]	.637
BADL (Barthel) ≤19 points	2.0 [1.1-3.3]	**.014**	1.8 [0.9-3.7]	.096
IADL (Lawton) ≤6 points	1.8 [1.1-3.1]	**.028**	1.9 [1.0-3.6]	**.048**
Malnutrition	1.8 [1.0-3.2]	**.035**	1.3 [0.6-2.7]	.461
Anemia	1.0 [0.6-1.6]	.899	–	
Impaired mobility	2.2 [1.2-3.9]	**.008**	2.1 [1.1-4.2]	**.028**

Univariable and multivariable logistic regression analyzes of frailty assessment instruments and their association with postoperative delirium. Details of analyzes are shown in Tables E3 and E4. Statistically significant *P* values are shown in bold. The covariates in the multivariable model were adjusted for age, body mass index, previous delirium and aortic valve area <0.75. *TAVI*, Transcatheter aortic valve implantation; *OR*, odds ratio; *CI*, confidence interval; *aOR*, adjusted odds ratio; *MMSE*, Mini Mental State Examination; *BADL*, Basic Activities of Daily Living; *IADL*, Instrumental Activities of Daily Living.

2.3 [1.3-4.0], $P = .004$) (Table 4). Short- and long-term survival of patients with or without impaired mobility are illustrated in Figure 1. Although both curves diverge after TAVI, short-term survival curves did not significantly differ between patients with or without baseline impaired mobility (respectively 95.6% vs 97.3%, $P = .350$). However, Kaplan–Meier calculated long-term survival was significantly lower in patients with impaired baseline mobility; at 1 year 81.7% versus 93.2% ($P < .001$) and 2 years 79.4% versus 91.4% ($P = .013$, overall curve comparison by log rank $P < .001$).

DISCUSSION

This study in a prospective cohort of elderly patients, in whom multidimensional geriatric risk assessment was performed before TAVI, identified impaired mobility as strongest independent risk assessment tool for both POD and long-term mortality. Overall, patients with impaired mobility had a 2 times greater odds of POD and a more than 10% absolute reduction in 2-year survival.

The present study is the first to describe the predictive value of mobility testing with regards to POD and long-term follow-up in a large cohort of patients undergoing TAVI. Geriatric assessment in regard to POD was studied by Goudzwaard and colleagues[23] in 213 patients undergoing TAVI. They identified the malnutrition screening tool as strongest geriatric assessment predicting POD (OR, 2.9 [1.06-7.81], $P = .04$). Dichotomized gait speed was their strongest independent 1-year mortality/frailty assessment tool (HR, 3.3 [1.25-8.51]).

In line with previous research, performed in a subset of the currently studied patients,[24] impaired mobility was the most prominent marker of the risk for both POD and 2-year mortality. Impaired mobility can be seen as a clinical marker of a patients' vulnerability since it can represent several disturbances, such as impairment in muscle strength, vision, alertness, proprioception, and physical condition. Baseline characteristics of patients with impaired mobility largely differed from patients with normal mobility (Table E5) showing that mobility testing has great

TABLE 4. Geriatric assessment measures and their association with mortality within 2 years after TAVI

	Mortality			
	Univariable		Multivariable	
	HR [95% CI]	*P* value	aHR [95% CI]	*P* value
MMSE <27 points	1.2 [0.7-1.9]	.510	–	
BADL (Barthel) ≤19 points	1.9 [1.2-2.9]	**.008**	1.6 [0.9-2.9]	.133
IADL (Lawton) ≤ 6 points	1.5 [0.9-2.3]	.089	–	
Malnutrition	2.3 [1.4-3.7]	**.001**	2.3 [1.3-4.0]	**.004**
Anemia	1.1 [0.7-1.7]	.640	–	
Impaired mobility	2.5 [1.4-4.4]	**.001**	2.5 [1.4-4.5]	**.003**

Univariable and multivariable Cox Regression analyzes of frailty assessment instruments and their association with mortality within 2 years. Details of analyzes are shown in Tables E3 and E4. Statistically significant *P* values are shown in bold. The covariates in the multivariable model were adjusted for male sex, creatinine, chronic obstructive pulmonary disease, and permanent atrial fibrillation. *HR*, Hazard ratio; *CI*, confidence interval; *aHR*, adjusted hazard ratio; *MMSE*, Mini Mental State Examination; *BADL*, Basic Activities of Daily Living; *IADL*, Instrumental Activities of Daily Living.

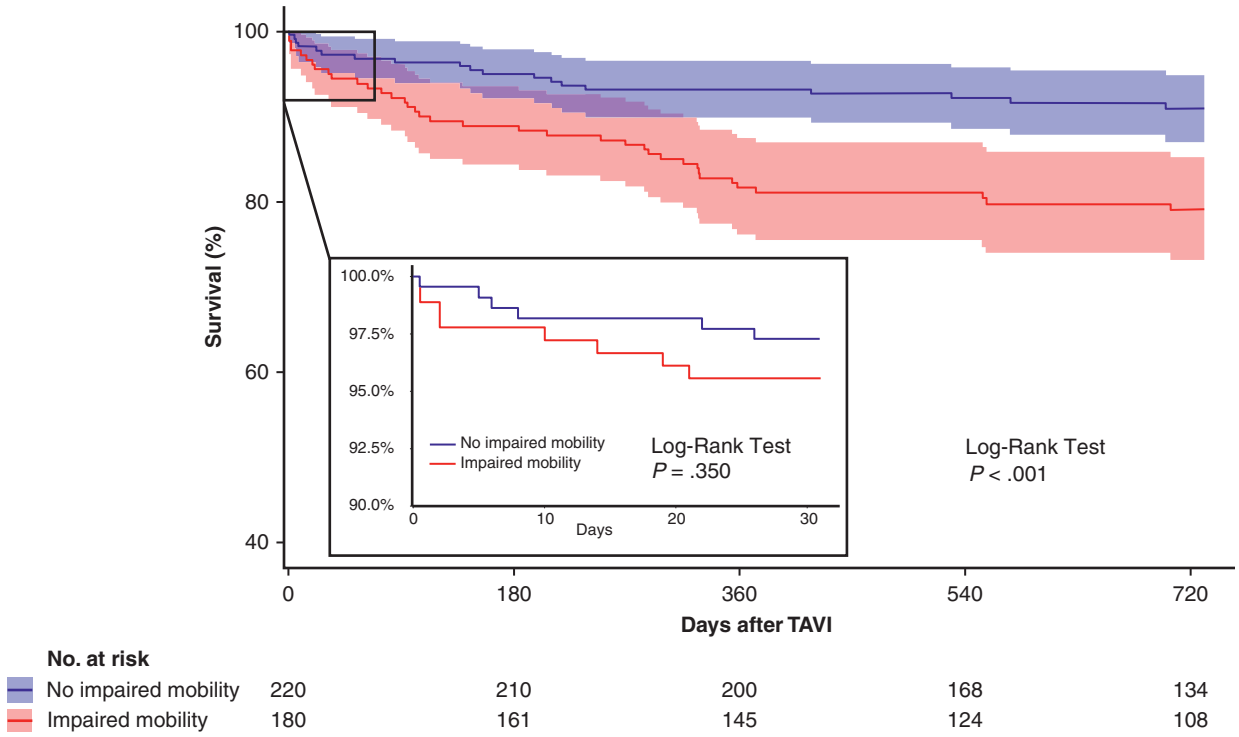

FIGURE 1. Short- and long-term survival in patients with or without impaired mobility prior to TAVI. Shown is the survival of patients with or without impaired mobility before TAVI. Mobility testing was performed as part of frailty assessment and was defined as gait speed ≤0.83 m/s or Timed Up and Go ≥20 seconds. Thirty-day survival is illustrated in the *box* and did not significantly differ between both groups. Severe impairment of survival was observed during long-term follow-up in patients who had impaired mobility before TAVI as compared with patients with no impaired mobility. *TAVI*, Transcatheter aortic valve implantation.

discriminative power. It is a well-known risk stratification tool in elderly adults undergoing TAVI but its use as a stand-alone test has so far being discouraged.[20,25] Alfredsson and colleagues[20] described the association of gait speed with 30-day mortality after TAVI. They proposed 3 different frailty identification walking speed groups: slowest walkers (<0.5 m/s), slow walkers (0.5-0.83 m/s), and normal walkers (>0.83 m/s). Subanalysis in our population were in line with their findings, with higher incidences of delirium and 2-year mortality in patients with lower gait speeds (Table E6).

Limitation in IADL was the second-best predictor, independently associated with POD. A recently published systematic review about POD-predicting factors and models illustrated the scarcity of data.[26] However, although limited IADL has predominantly been associated with mortality in previous studies,[27] in our study it was not independently associated with long-term mortality. As observed in everyday life, IADL tasks (such as preparing meals, doing the household and/or laundry, transportation, and financial management) can be supported or taken over by the patient's social network. It is possible that impairment in IADL is caused by underlying cognitive impairment, which in turn can be the predisposing factor for the development of delirium on the short term. In the long term, the social support could preclude patients from impaired survival.

Regarding long-term survival, malnutrition was the second strongest independent predictor of 2-year mortality. An inadequate feeding state before TAVI has been linked to frailty and impaired short- and long-term prognosis.[7,28,29] Over time, malnutrition can lead to anemia, impaired host immune response, elevated C-reactive protein, lowered body mass index and, importantly, a decrease in muscle mass and strength (sarcopenia), leading to reduced mobility.[30] In the future, attention should be paid to malnourished TAVI candidates, especially when mobility is impaired.

Previous studies on frailty mainly focused on late and often irreversible outcome. The FRAILTY-AVR (Frailty in Older Adults Undergoing Aortic Valve Replacement) study prospectively compared different frailty scales in 374 surgical and 646 transcatheter aortic valve replacement patients. They proposed an Essential Frailty Toolset consisting of chair rise test, cognitive testing (MMSE), hemoglobin and albumin (or Mini Nutritional Assessment)

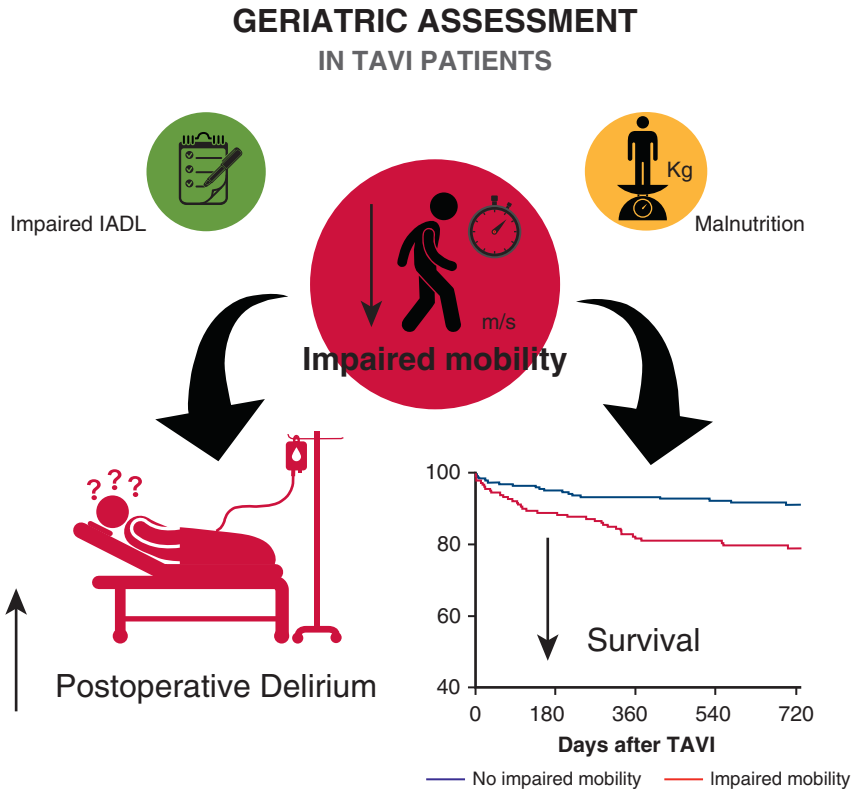

FIGURE 2. Geriatric assessment in the prediction of delirium and long-term survival after TAVI. In this study, geriatric cognitive, functional, mobility, and nutritional tests were assessed for the association with delirium and long-term mortality after TAVI. Postoperative delirium was prospectively assessed in 511 patients during hospitalization after TAVI. Mortality tracking was performed by consulting municipal registries. Impaired mobility was the strongest predictor for both delirium and mortality. Impairment of IADL and malnutrition were the second-best predictors of delirium and mortality, respectively. *TAVI*, Transcatheter aortic valve implantation; *IADL*, Instrumental Activities of Daily Living.

assessment.[12] Except for chair rise testing, which would potentially identify similar patients as mobility testing does in our setting, all proposed components were analyzed in our study. Based on our results, impaired mobility must be seen as a red flag in patients who are candidates for TAVI. Additional information about IADL and nutritional status should be considered, given their association with POD and long-term mortality, respectively. Future implementation of imaging techniques, such as computed tomography with volume assessment of the psoas muscle area, could support multidimensional testing[31] and help to better objectify geriatric complications and mortality following TAVI procedures.

GA was used in all patients in this study. The true effect of GA on the occurrence of POD is unclear. So far, no randomized controlled trials have been performed to investigate the effect of anesthesia on the occurrence of POD in TAVI. Retrospective studies described a favorable postprocedural course in patients treated with TAVI under local anesthesia/conscious sedation (LACS). After LACS, lower incidence of POD (2.5% after LACS and 3.9% after GA), a briefer length of stay (6 vs 6.5 days, respectively), and lower in-hospital and 30-day mortality were observed (1.5% vs 2.4% and 2.3% vs 4.0%, respectively).[32,33] Sedation can be induced by different sedatives (eg, propofol, dexmedetomidine, fentanyl, and/or midazolam). In cardiac surgery, lower incidences and shorter duration of POD have been observed after dexmedetomidine as compared with propofol sedation.[34] These results could, however, not be replicated in patients undergoing TAVI, sedated with either propofol, dexmedetomidine or fentanyl, and/or midazolam.[35] Performing TAVI using LACS, allows neurologic monitoring and avoids invasive ventilation. Yet, it should be questioned whether these advantages overrule the unknown effects of procedural unrest and pain on the incidence of POD.

Limitations

Patients were excluded from current analysis (and TAVI treatment) based on geriatric assessments, especially in case

of dementia. Regarding mobility testing, slightly more than one fifth of patients (n = 111/511) had no gait speed data reported. We have no information to determine why these tests were not performed but observed that patients in whom mobility testing was not performed were younger and had greater body mass indices. There were no significant differences in other geriatric assessment tools between patients in whom mobility testing was performed or not. We are aware that POD incidences can strongly differ between different patient populations based on patient-, procedural, and in-hospital characteristics. Moreover, general anesthesia is no longer the standard of care in many centers. A parsimonious model was strived for, moreover the sample size and number of events limited the number of adjusting variables in the regression analysis. Future multicenter research is warranted to further explore the feasibility and applicability of geriatric assessment tools in the identification of frail, elderly patients undergoing TAVI.

CONCLUSIONS

This study shows that impaired mobility should serve as a red flag for the likelihood of POD or mortality following TAVI procedures in older patients (Figure 2). Together with IADL and nutritional status, impaired mobility was independently associated with POD and 2-year mortality in patients who are candidates for TAVI. Prospective multicenter studies are needed to optimize and to further explore geriatric frailty objectification.

Clinical Implications

In contrast to the frequently described late and irreversible outcome mortality, POD is a marker of frailty that can be observed in the first days after TAVI. This study contributes to a better understanding of risk factors for POD and survival following TAVI procedures. Impaired mobility should be seen as a red flag, identifying vulnerable patients. The early identification of such high-risk patients will enable the clinician to further optimize care, and probably reduce the incidence of POD and its deleterious effects and costs.

Conflict of Interest Statement

Dr van Wely has been a proctor and consultant for Abbott Vascular. Dr Verkroost has been a proctor for Medtronic. Dr Gehlmann has been a proctor for Abbott Vascular and Medtronic. Dr van Garsse has been a proctor for Edwards Lifesciences. Prof Dr Morshuis has been a consultant for Vascutek. Prof Dr van Royen is a consultant for Abbott and Medtronic and has received grants from AstraZeneca, grants from Biotronik, grants from Philips, grants and personal fees from Abbott, and personal fees from Medtronic, outside the submitted work. All other authors have nothing to disclose with regard to commercial support.

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Key Words: TAVI, frailty assessment, mobility, delirium, survival

TABLE E1. Procedural outcome

		Delirium		
	Overall (n = 511)	**Yes (n = 66)**	**No (n = 445)**	***P* value**
Device success	480 (93.9)	61 (92.4)	419 (94.2)	.579
Access				
Axillary	365 (71.4)	50 (75.8)	315 (70.8)	.404
Femoral	108 (21.1)	9 (13.6)	99 (22.2)	.110
Transapical	38 (7.4)	7 (10.6)	31 (7.0)	.293
Procedural time, min	51 [40-64]	49 [40-61]	51 [40-64]	.542
Pre-dilatation	427 (83.6)	55 (83.3)	372 (83.6)	.957
Post-dilatation	50 (9.8)	3 (4.5)	47 (10.6)	.125
TAV-in-TAV deployment	19 (3.7)	2 (3.0)	17 (3.8)	1.000
Conversion to surgery	3 (0.6)	3 (4.5)	0 (0.0)	.002
Resuscitation during procedure	17 (3.3)	3 (4.5)	14 (3.1)	.471
Contrast volume, mL	57 [40-80]	53 [40-80]	60 [40-80]	.586

Data are presented as median [interquartile range] or n (%). *TAV*, Transcatheter aortic valve.

TABLE E2. In-hospital outcome

		Delirium		
	Overall (n = 511)	**Yes (n = 66)**	**No (n = 445)**	***P* value**
Stroke	11 (2.2)	5 (7.6)	6 (1.3)	.008
Infection	46 (9.0)	10 (15.2)	36 (8.1)	.061
New onset of heart failure	119 (23.3)	17 (25.8)	102 (22.9)	.611
Life-threatening/major bleeding	42 (8.2)	7 (10.6)	35 (7.9)	.449
Major vascular complication	19 (3.7)	3 (4.5)	16 (3.6)	.724
Myocardial infarction	10 (2.0)	0 (0.0)	10 (2.2)	.374
New onset of atrial fibrillation	30 (5.9)	8 (12.1)	22 (4.9)	.042
Permanent pacemaker implantation	47 (9.2)	5 (7.6)	42 (9.4)	.625
Acute kidney-injury (grade 3)	2 (0.4)	0 (0.0)	2 (0.4)	1.000
Hospital stay duration, d	5 [3-7]	7 [5-9]	5 [3-7]	<.001

Data are presented as median [interquartile range], mean ± standard deviation, or n (%).

TABLE E3. Uni- and multivariable analyzes of geriatric assessment measures corrected for known risk factors of postoperative delirium

	Univariable		Multivariable	
Postoperative delirium	**OR [95% CI]**	***P* value**	**Adjusted OR [95% CI]**	***P* value**
Age	1.1 [1.0-1.2]	**<.001**	1.1 [1.0-1.1]	.161
BMI	0.9 [0.9-1.0]	**.006**	0.9 [0.9-1.0]	**.012**
Previous delirium	2.7 [1.5-5.0]	**.001**	1.9 [0.9-4.1]	.104
AVA < 0.75	3.0 [1.7-5.4]	**<.001**	2.7 [1.4-5.3]	**.004**
MMSE < 27 points	2.1 [1.2-3.6]	**.008**	1.2 [0.6-2.3]	.637
BADL (Barthel) ≤19 points	2.0 [1.1-3.3]	**.014**	1.8 [0.9-3.7]	.096
IADL (Lawton) ≤6 points	1.8 [1.1-3.1]	**.028**	1.9 [1.0-3.6]	**.048**
Malnutrition	1.8 [1.0-3.2]	**.035**	1.3 [0.6-2.7]	.461
Impaired Mobility	2.2 [1.2-3.9]	**.008**	2.1 [1.1-4.2]	**.028**
Anemia	1.0 [0.6-1.6]	.899	–	–

Uni- and multivariable logistic regression analyzes of covariates and their association with Postoperative delirium. Adjusted ORs are shown. Statistically significant *P* values are shown in bold. *OR*, Odds ratio; *CI*, confidence interval; *BMI*, body mass index; *AVA*, aortic valve area; *MMSE*, Mini Mental State Examination; *BADL*, Basic Activities of Daily Living; *IADL*, Instrumental Activities of Daily Living.

TABLE E4. Uni- and multivariable analyzes of geriatric assessment measures corrected for known risk factors of mortality

	Univariable		Multivariable	
Mortality	**HR [95% CI]**	***P* value**	**Adjusted HR [95% CI]**	***P* value**
Male sex	1.4 [0.9-2.2]	.153	1.0 [0.6-1.9]	.937
Creatinine	1.3 [1.0-1.6]	**.027**	1.3 [1.0-1.8]	.060
COPD	1.5 [0.9-2.4]	.090	1.6 [0.9-2.8]	.126
Permanent atrial fibrillation	1.8 [1.1-2.8]	**.020**	1.5 [0.8-2.8]	.166
MMSE <27 points	1.2 [0.7-1.9]	.510	–	–
BADL (Barthel) ≤19 points	1.9 [1.2-2.9]	**.008**	1.6 [0.9-2.9]	.133
IADL (Lawton) ≤6 points	1.5 [0.9-2.3]	.089	–	–
Malnutrition	2.3 [1.4-3.7]	**.001**	2.3 [1.3-4.0]	**.004**
Impaired mobility	2.5 [1.4-4.4]	**.001**	2.5 [1.4-4.5]	**.003**
Anemia	1.1 [0.7-1.7]	.640	–	–

Uni- and multivariable Cox regression analyzes of covariates and their association with mortality. Adjusted HRs are shown. Statistically significant *P* values are shown in bold. *HR*, Hazard ratio; *CI*, confidence interval; *COPD*, chronic obstructive pulmonary disease; *MMSE*, Mini Mental State Examination; *BADL*, Basic Activities of Daily Living; *IADL*, Instrumental Activities of Daily Living.

TABLE E5. Baseline characteristics of patients with impaired or normal mobility

Baseline assessment	Impaired mobility (n = 180)	Normal mobility (n = 220)	*P* value
Age, y	81 [77-85]	80 [76-84]	**.048**
Male	36.1 (65)	51.4 (113)	**.002**
BMI, kg/m^2	27.2 [24.4-30.6]	26.1 [23.7-29.3]	**.010**
Logistic EuroSCORE I	14.7 [9.4-23.2]	12.7 [8.7-19.9]	**.034**
NYHA functional class III-IV	78.3 (141)	69.1 (152)	**.038**
Diabetes mellitus	34.4 (62)	30.9 (68)	.453
Creatinine, mg/dL	1.0 [0.9-1.3]	1.0 [0.9-1.3]	.971
COPD	24.4 (44)	25.0 (55)	.898
Coronary artery disease	63.3 (114)	56.8 (125)	.186
Permanent atrial fibrillation	23.3 (42)	21.8 (48)	.718
Previous stroke or TIA	22.8 (41)	20.9 (46)	.652
Peripheral artery disease	33.9 (61)	38.6 (85)	.327
Use of walking aid	54.2 (96)	22.9 (50)	**<.001**
Psychoactive drug use*	31.1 (56)	19.5 (43)	**.008**
History of delirium	15.6 (28)	14.1 (31)	.681
LVEF, %	55 [45-57]	55 [50-60]	**.002**
Aortic valve area, cm^2	0.73 [0.60-0.90]	0.74 [0.61-0.90]	.712
MMSE <27 points	39.0 (67)	22.5 (47)	**<.001**
BADL (Barthel) ≤19 points	66.5 (119)	34.2 (75)	**<.001**
IADL (Lawton) ≤6 points	43.9 (79)	29.8 (64)	**.001**
Malnutrition	32.2 (56)	19.7 (41)	**.005**
Anemia	49.4 (89)	40.9 (90)	.088

Mobility was impaired in case gait speed ≤0.83 m/s or Timed Up and Go ≥20 seconds. Statistically significant *P* values are shown in bold. *BMI*, Body mass index; *EuroSCORE*, European System for Cardiac Operative Risk Evaluation; *NYHA*, New York Heart Association; *COPD*, chronic obstructive pulmonary disease; *TIA*, transient ischemic attack; *LVEF*, left ventricular ejection fraction; *MMSE*, Mini Mental State Examination; *BADL*, Basic Activities of Daily Living; *IADL*, Instrumental Activities of Daily Living. *Psychoactive drug use, use of benzodiazepine, antidepressants, and antipsychotic medication.

TABLE E6. Incidences of POD and mortality within 2-year in different groups based on gait speed

	Gait speed, m/s			
	<0.5 (n = 28)	**0.5-0.83 (n = 146)**	**>0.83 (n = 223)**	***P* value**
POD incidence	7 (25.0)	28 (19.2)	22 (9.9)	**.011**
30-d mortality	1 (3.6)	7 (4.8)	6 (2.7)	.563
2-y mortality	8 (28.6)	28 (19.2)	19 (8.5)	**.001**

Data are presented as n (%). Statistically significant *P* values are shown in bold. Correction for multiple testing was performed by means of Bonferroni correction. *POD*, Postoperative delirium.