Delirium after Aortic Valve Therapy.

A Prospective Cohort Study of Octogenarian Patients following Surgical Aortic Valve Replacement and Transcatheter Aortic Valve Implantation.

Leslie SP Eide

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Author: Leslie Sofia Pareja Eide

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Scientific environment

This study is carried out as part of the Patient-Reported Outcomes in Cardiology (PROCARD) Research Group at the Department of Heart Disease, Haukeland University Hospital and the Department of Clinical Science, University of Bergen, Norway.

Main supervisor: Tone Merete Norekvål. Associate professor. Department of Heart Disease, Haukeland University Hospital and Department of Clinical Science, University of Bergen, Norway.

Co-supervisors: Bengt Fridlund. Professor. School for Health and Welfare, Jönköping University, Jönköping, Sweden. Department of Heart Disease, Haukeland University Hospital, Bergen, Norway.

Jan Erik Nordrehaug. Professor. Department of Cardiology, Stavanger University Hospital, Stavanger & Department of Clinical Science, University of Bergen, Norway.

Anette Hylen Ranhoff. Professor. Kavli Research Center for Geriatrics and Dementia, Haraldsplass Hospital & Department of Clinical Science, University of Bergen, Norway.

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Abbreviations

4AT	4 “A”s Test
ADL	Activities of Daily Living
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
CARDELIR	Delirium in Octogenarians undergoing Cardiac Surgery or Intervention
DMS	Diagnostic and Statistical Manual of Mental Disorders
DOSS	Delirium Observation Screening Scale
DRS	Delirium Rating Scale
IADL	Instrumental Activities of Daily Living
ICD-10	International Classification of Diseases, 10^{th} edition
MCS	Mental Component Summary
MMSE	Mini-Mental State Examination
NDSC	Nursing Delirium Screening Scale
PD	Postoperative Delirium
PCS	Physical Component Summary
PROCARD	Patient-Reported Outcomes in Cardiology
RCT	Randomized Control Trial
SAVR	Surgical Aortic Valve Replacement
SD	Standard Deviation

SF-12	The 12-Item Short Form Health Survey
TAVI	Transcatheter Aortic Valve Implantation

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Leslie Sofia Pareja Eide

Abstract

Introduction

Untreated and symptomatic aortic stenosis (AS) is associated with high mortality. Surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) are two treatment options for patients with severe AS. Patients receiving SAVR and TAVI are often 80 years and older.
Delirium, an acute state of confusion characterized by temporary and fluctuating decline in attention and cognition, is common in older patients after cardiac surgery. Yet, knowledge about octogenarians undergoing invasive cardiovascular therapy is scarce, and delirium after TAVI remains to be systematically explored.

Aims

The overall aim of this study was to investigate delirium in octogenarian patients undergoing SAVR or TAVI by determining its incidence, identifying risk factors, describing its onset and time course, and by determining if delirium can be used to predict physical and cognitive function, self-reported health status, first-time hospital readmissions and mortality 1 and 6 months after aortic valve treatment.

Materials and Methods

This is a prospective cohort study of octogenarian patients with AS, scheduled for elective treatment with SAVR or TAVI at a tertiary university hospital in western Norway. Delirium was the main outcome of the study. Inclusion criteria were: age 80 years-old and older and previous acceptance for treatment with SAVR or TAVI. Exclusion criteria were: denied consent to participate in the study and inability to speak Norwegian. Between 2011 and 2013, 143 patients were included in the study.

Demographic and clinical information was collected from hospital information system registers, patients' medical records or by interviewing included patients, as appropriate. Delirium was assessed for 5 postoperative days with the Confusion Assessment Method. Activities of daily living, instrumental activities of daily living

and self-reported health status were measured with the Barthel Index, the Nottingham Extended Activities of Daily Living Scale (IADL) and The 12-Item Short Form Health Survey (SF-12), at baseline and at 1 and 6-month follow-up. Cognitive status was assessed at baseline and at 6-month follow-up with the Mini-Mental State Examination (MMSE).

Results

The mean age of included patients was 83.5 years (SD 2.7) and TAVI was performed in 46% of them. Patients undergoing SAVR had a higher incidence of delirium than patients treated with TAVI (66% vs 44%, $p = 0.01$). Multivariate logistic regression analysis revealed that reduced cognitive function at baseline ($p = 0.03$) and treatment with SAVR ($p = 0.02$) are risk factors for delirium in octogenarian patients after aorta valve treatment. No differences in the number of days with delirium were found between patient groups ($p = 0.20$) but the onset and course of delirium in patients treated with SAVR was more unpredictable ($p = 0.003$) than it was in patients treated with TAVI (*Paper I*).

Patients with and without delirium after SAVR had lower IADL function at 1-month follow-up (scores from 58 to 42 and from 58 to 50 respectively $p \leq 0.02$). However, this function returned to baseline levels after 6 months. Improvements in the Physical Component Summary score of SF-12 were found in patients not having delirium and treated with SAVR (from 39 to 48, $p < 0.001$). No differences between patient groups in other outcomes were identified. Regression models suggest that delirium after SAVR might predict IADL scores1-month after treatment (not significant, p-values $\leq$ 0.07) but does not predict large differences in ADL, cognitive function or SF-12 scores in octogenarian AS patients. Patients experiencing delirium after TAVI had a lower ADL (from 19 to 16, $p < 0.001$) and IADL function (from 49 to 40, $p = 0.003$) 1 month after the procedure. In TAVI patients without delirium, the physical component score of SF-12 increased after 1 and 6 months (30 to 35, $p = 0.04$ and 30 to 35, $p = 0.02$ respectively). Regression analyses established that delirium following

TAVI predicted lower ADL and IADL function at 1 but not at 6-month follow-up *(Paper II)*.

First-time readmissions and death 1 and 6 months after SAVR or TAVI were more common in octogenarian patients who experienced delirium. The effect of delirium was greatest during the first two months after discharge (adjusted hazard ratio 2.9 (95% CI: 1.5 to 5.7).The most common discharge diagnosis at readmission was related to the circulatory system (*Paper III*).

Conclusions

Delirium is often present after aortic valve treatment, especially in patients receiving SAVR. In addition to be a risk factor for delirium in octogenarian patients, SAVR was associated with a more unpredictable onset and course of delirium. Patients who experienced delirium, regardless treatment type, appear to have lower short-term IADL function. Yet, delirium does not seem to confer long-term reductions in physical, mental or self-reported health status in this patient group. Compared to patients without delirium, first-time readmissions and mortality were more common 6 months after hospital discharge in patients who had experienced delirium.

Our study provides additional evidence showing that delirium is a serious hospital complication that could be associated with negative outcomes such as lower physical function, morbidity and mortality 1 and 6 months after aortic valve treatment, also when more gentle techniques like TAVI are used. These findings are also relevant when designing future studies and implementing strategies that could lead to the prevention of delirium in other older patient populations.

List of publications

Paper I

Eide LSP, Ranhoff AH, Fridlund B, Haaverstad R, Hufthammer KO, Kuiper KJK, Nordrehaug JE, Norekvål TM. "Comparison of Frequency, Risk Factors, and Time Course of Postoperative Delirium in Octogenarians after Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement". American Journal of Cardiology. 2015, March 15;115(6):802-9.

Paper II

Eide LSP, Ranhoff AH, Fridlund B, Haaverstad R, Hufthammer KO, Kuiper KJK, Nordrehaug JE, Norekvål TM. "Delirium as a Predictor of Physical and Cognitive Function in Octogenarians after Transcatheter or Surgical Aortic Valve Replacement." Journal of the American Geriatrics Society, 2016 Apr 23. Doi: 10.1111/jgs.14165. [Epub ahead of print]

Paper III

Eide LSP, Ranhoff AH, Fridlund B, Haaverstad R, Hufthammer KO, Kuiper KJK, Nordrehaug JE, Norekvål TM. "Readmissions and mortality in delirious and non-delirious octogenarian patients after aortic valve therapy. A prospective cohort study." Submitted manuscript.

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1. Introduction

Delirium is a disorder characterized by an acute, reversible and fluctuating reduction of attention and cognition.[1] Delirium can develop at any age[2] but older hospitalized patients are especially vulnerable.[1] Even though it has been described since antiquity,[3] delirium remains insufficiently identified and little understood,[1,4] also in cardiac wards.

Cardiology has witnessed a paradigm change following increases in life expectancy,[5] and technological advances have allowed the safe performance of cardiac surgery in patients 80 years-old and older.[6 7] In industrialized countries, aortic stenosis (AS) has become an increasingly common valvular heart disease.[8 9] The mortality rate of severe and untreated AS is high after symptoms of angina, syncope and heart failure appear.[10] Great efforts have been made to improve survival in patients with severe AS, being surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) two invasive treatments for the condition.[11-13] More often than before, cardiology has come in contact with older patients to which outcomes of surgery in terms of physical function, cognitive status and quality of life are as important as survival.[5] Delirium is common after cardiac surgery,[1] yet the majority of studies in this area have been done in patients younger than 80 years and they have combined several cardiac procedures.[14-19] It remains to be established if delirium following the novel and less invasive TAVI has the same incidence and follows the same pattern as delirium after SAVR.

A clear understanding about differences (and/or similarities) in the incidence, risk factors, onset and course of delirium following SAVR and TAVI is needed. Increased evidence has shown that the burden of delirium on patients, families and health care systems can be long lasting.[20-23] Delirium after TAVI has not been systematically studied and the predictive value of delirium on physical and cognitive function, self-reported health, readmissions and mortality following hospital discharge remains to be established. Increased knowledge about SAVR and TAVI, and their interaction with delirium might provide important clinical contributions that will eventually be

reflected on the wellbeing of patients and relatives, and in an increased quality of care from health care professionals.

1.1 Delirium

1.1.1 The concept of delirium

Before 1980, terms such as "sundown syndrome," "acute confusion state," "postoperative psychosis" and "intensive care psychosis" were used to address delirium.[24 25] The concept of delirium remains somehow vague, but there is a consensus about it being a state of altered cerebral function that appears as a consequence of stressors[26] or physical illness.[27] A new era within the field of delirium started after a method to operationalize its diagnosis was published.[28] Based on the third revised version of the Diagnostic and Statistical Manual of Mental Disorders (DMS), Inouye et al. comprised the clinical features of delirium to create the Confusion Assessment Method (CAM).[28] The CAM focuses on the four core features of delirium; 1. acute onset and fluctuating course, 2. inattention, 3. disorganized thinking, and 4. altered level of consciousness. Delirium is diagnosed when feature 1 and 2 are present, and either 3 or 4 are displayed.[28] New and revised versions of the DMS have allowed a more inclusive and clinically safe interpretation of delirium.[29]

It can be difficult to differentiate delirium from other disorders such as dementia or depression. In general, delirium can be defined as a fluctuating state of confusion characterized by acute changes in cognition and disturbance of consciousness.[30] Dementia, on the other hand, is a chronic and progressive neurodegenerative condition that leads to cognitive decline and that interferes with daily life.[31] It is still uncertain whether delirium leads to dementia or vice versa, and studies elucidating the relationship between the two conditions have been warranted.[1 31] According to the World Health Organization, depression is a "disorder characterized by sadness, loss of interest or pleasure, feelings of guilt or self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration."[32] Patients with depression and delirium

can display apathy, extreme need for sleep and concentration problems. Table 1 shows differences and similarities between delirium, dementia and depression.

Table 1: Comparison between features of delirium, dementia and depression.

Criteria	***Delirium***	***Dementia***	***Depression***
Onset	Acute within hours to days	Slow and progressive	Progressive
Duration	Reversible. Hours to days and fluctuating course	Irreversible over months or years	Reversible. From week to months
Attention	Reduced ability to focus, sustain or shift attention	Generally intact until late in the progression of the disease	Reduced
Orientation	Reduced	Generally intact until later in the progression of the disease	Generally intact
Consciousness	Fluctuating	Generally intact until late in the progression of the disease	Generally intact
Speech	Incoherent and disorganized	Ordered but development of anomia or aphasia is possible	Normal to slow
Origin	Underlying medical condition, substance intoxication or side effect on drugs	Underlying neurological process	
Sleep	Sleep disturbances	Sleep disturbances	Insomnia or hypersomnia
Activity	Periods of high and low physical activity	Periods of high physical activity	In severe cases, lethargy

Adapted from Fong et al. (2015)[31] and Downing et al. (2013)[33]

1.1.2 Different manisfestations of delirium

The presentation of delirium is heterogeneous and this heterogeneity might complicate its identification. Based on psychomotor behavior, Lipowski (1980)[34] classified delirium as hyperactive, hypoactive and mixed. *Hyperactive delirium* is characterized by hallucinations, agitation, irritability and hypervigilance.[30 33] This presentation is probably easier to identify in a hospital setting as patients can become agitated, and because they are prone to pull out intravenous lines, cardiac monitoring equipment and/or urinary catheters. Patients with *hypoactive delirium,* on the other hand, can show signs of lethargy and little spontaneous movement.[30] These patients are easily overseen as they can stay quietly in their beds and demand little attention from the staff.[4] Nevertheless, it is common that patients with delirium experience a combination between the hypoactive and hyperactive form.

1.1.3 Epidemiology

The prevalence of delirium in the general population has been estimated to be 0.7%.[35] However, this prevalence increases with age, and could be as high as to 10% for community-dwelling individuals 85 years-old and older.[36] In hospital settings, the highest incidence of delirium is found in intensive care units (19-85%), orthopedic wards (12-51%) and in cardiac surgery departments (11-46%).[1]

1.1.4 Etiology of delirium

The scientific field of delirium is relatively new, and a clear understanding of why some patients become delirious is still unclear. It has been suggested that delirium can be understood as an “acute brain failure” that results as a response to one or several pathophysiological stressors.[26] Predisposing and precipitating factors might propitiate the development of delirium.[1] *Predisposing* factors refer to intrinsic individual characteristics that make some patients more vulnerable to develop delirium.[1 37]Advanced age (≥ 70 years-old), cognitive and physical impairment, several comorbidities and previous history of stroke, are examples of predisposing risk factors for delirium.[1] *Precipitating* factors also influence the development of

delirium, but they have the potential of being modifiable.[37] Surgery, infections, use of physical restraints and sleep deprivation are examples of *precipitating* factors.[1] When interacting, predisposing and precipitating factors can lead to delirium.[1 37] An undernourished individual with i.e. multiple comorbidities, polypharmacy and dementia might be more vulnerable to develop delirium when facing a simple diagnosis such as a urinary tract infection. On the other hand, in a robust patient, delirium will develop only when severe conditions are present.

1.1.5 Diagnosis

The diagnosis of delirium is mostly based on clinical observation of the features defined by the DSM or by the International Classification of Diseases, 10th edition (ICD-10)[38]. The CAM[28] is perhaps the most used diagnostic tool for delirium,[39] and the instrument with best psychometric properties.[40]. A new version that can be applied on three minutes (3D-CAM) was recently published.[41] More specialized diagnostic instruments such as the Family-CAM,[42] CAM-Intensive Care Unit[43] and the paediatric-CAM[44] have emerged from the original CAM.

Other instruments used to evaluate the presence of delirium are; the Delirium Observation Screening Scale (DOSS)[45], Delirium Rating Scale (DRS),[46] and NEECHAM Confusion Scale.[47] A new but increasingly more used screening tool is the 4 "A"s Test (4AT).[48] This instrument provides a rapid initial assessment of four of the core features of delirium: alertness, age and orientation, attention and acute change or fluctuating course of cognition or other mental functions.[48]

Instruments used to diagnose delirium can be classified according to its administration form as "observational," "interactive" or "mixed."[40] For observational instruments, the diagnosis is done by scrutinizing whether the features of delirium are present. Interactive instruments rely on information gathered with an active interaction between rater and the patient, while mixed instruments depend on both observational and interactive data. Table 2 presents an overview of the most widely known and validated instruments for the detection of delirium in older hospitalized patients, including its administration form.[40]

Table 2: Overview of commonly used and validated instruments for the detection of delirium in older hospitalized patients, including its administration form.[40]

Name of the instrument	*Type of instrument according to administration form*			*Number of validating studies*	*Sensitivity*	*Specificity*
	Observational	Interactional	Mixed			
Delirium Observation Screening Scale (DOS)	X			2	89% and 100%	87% and 97%
Nursing Delirium Screening Scale (Nu-DESC)	X			4	Range 32% to 96%	Range 69% to 92%
Confusion Assessment Method (CAM)			X	11	Range 46% to 94%	Range 63% to 100%
Confusion Assessment Method –			X	6	Range 28% to 92%	Range 89% to 99%

Intensive Care Unit (CAM-ICU)				
Delirium Rating Scale - Revised-98 (DRS-R-98)	X	3	56%, 57% and 93%	82%, 95% and 98%

1.1.6 Consequences of delirium after cardiac surgery

Delirium has been associated with several negative outcomes. Among hip fracture patients, delirium has been identified as a risk factor for institutionalization and functional decline,[22] and as a predictor of dementia 6 months later[49]. Patients with delirium after cardiac surgery are more susceptible to in-hospital falls ($p < 0.001$),[50] have a longer length of hospital stay ($p < 0.001$)[50 51] and they more often require skilled assistance by the time of hospital discharge ($p < 0.001$).[50 51] Additionally, hospital readmissions[21] and increased risk of mortality[51 52] are more often found in patients having delirium after cardiac surgery.

For older patients, the opportunity to keep physical function and independence is perhaps as important as survival. Koster et al.[21] studied a group of individuals after cardiac surgery and found that mobility was significantly reduced in patients who experienced delirium.[21] Rudolph and colleagues,[17] reported important reductions in IADL performance 1 month after cardiac surgery in patients who experienced delirium, although these differences were not significant at 6-month follow-up[17]. As frightening as loss of mobility and IADL function, is cognitive dysfunction. Several studies have reported an increased risk of cognitive problems the first month after cardiac surgery,[53-55] even though cognitive function seems to return to baseline levels by the time 6-month follow-up is performed.[54 55]

1.2 Aortic stenosis

AS is a narrowing of the aortic valve emerging as a consequence of progressive fibrosis and calcification.[56] It is the most common form for valvular cardiac lesion in individuals from industrialized countries[57 58] and its prevalence increases with age.[59] A meta-analysis of 9723 patients, age 75 years-old and older, established a prevalence of AS of 12%. Of these patients, 3.4% had a diagnosis of severe AS.[60] These numbers seem to support an important Norwegian study, not included in the mentioned meta-analysis, which reported a prevalence rate of AS of 3.9% in a cohort of patients between 70-79 years of age.[59]

1.2.1 Etiology and course of aortic stenosis

Anatomical, genetic and clinical factors lead to fibrosis and calcification of the aortic valve, and can eventually result in AS.[61] Regarding anatomical factors, individuals born with a two leaflets aortic valve, rather than the normal trileaflet, are more likely to experience hemodynamic stress, calcification, rigidity and narrowing of the aortic orifice.[58] Older age, hypertension and diabetes are clinical factors that have traditionally been associated with AS.[62] In underdeveloped countries, rheumatic heart disease is still leading to an inflammation and fibrosis of the valve leaflets that might create narrowing of the aortic valve.[58] This narrowing causes stiffness, reduction in the valve area, increases in leaf ventricular afterload and work, and eventually death.

1.2.2 Classification

Based on symptoms, leaflet anatomy, valve hemodynamic and left ventricular function AS can be classified in four stages.[61] [63]Table 3 shows the stages of the disease as proposed by the American College of Cardiology and the American Heart Association.[63]

Table 3: Disease stages in aortic stenosis

Stage	***Definition***	***Valve anatomy***	***Symptoms***
A	At risk of AS	• Bicuspid aortic valve or other congenital valve anomaly • Aortic valve sclerosis	None
B	Progressive AS	• Mild-to-moderate leaflet calcification of a bicuspid or tricuspid valve with some reduction of systolic motion or • Rheumatic valve changes with commissural fusion	None
C	Asymptomatic severe AS		
C1	Asymptomatic severe AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	None: exercise testing might reveal symptom status
C2	Asymptomatic severe AS with LV dysfunction	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	None
D	Symptomatic severe AS		
D1	Symptomatic severe high gradient AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Dyspnea or decreased exercise tolerance • Exertional syncope or pre-syncope • Exertional angina

D2	Symptomatic severe low flow/ low gradient AS with reduced LVEF	Severe leaflet calcification with severely reduced leaflet opening	• HF • Angina • Syncope or presyncope
D3	Symptomatic severe low gradient AS with normal LVEF or paradoxical low flow severe AS	Severe leaflet calcification with severely reduced leaflet opening	• HF • Angina • Syncope or presyncope

(Adapted from Nishimura et al. 2014[63])

AS, aortic stenosis; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction.

1.2.3 Treatment

Once AS has been identified, patients should receive education, regular medical controls, treatment for other comorbidities and echocardiography on regular bases.[62] [63] Currently, no medical treatment is sufficient to address severe AS[58] and without invasive treatment, live expectancy is reduced when symptoms in form of angina, syncope and heart failure, appear.[8] [10]

SAVR is the standard approach in patients with a low to intermediate surgical risk.[61] Even though age is not a contraindication to SAVR,[58] before the introduction of TAVI, as many as 33% of patients 75 years-old and older were denied aortic valve surgery.[64] SAVR is a highly invasive procedure, performed under general anaesthesia and requiring sternotomy and cardiopulmonary bypass.[65] Two types of artificial aortic valves are available in the market; bioprosthetic and mechanical and bioprosthetic, being the first one the recommended option for patients 65 years-old and older.[63] [66]

TAVI is a novel procedure, initially designed for high-risk patients, not able to undergo SAVR.[13] Treatment with TAVI can be performed under local anaesthesia and without sternotomy or cardiopulmonary bypass.[65] Under TAVI, the diseased aortic valve is replaced with a bioprosthetic valve inserted through a catheter.[13] TAVI is an alternative to patients when survival is expected to be at least 1 year after the procedure.[62]

2. Rationale for the study

Delirium and severe AS are associated with negative outcomes. Technical advances in the field of cardiology have allowed successful treatment for AS that can also be used in older patients with high surgical risk.[13] As the oldest population continues to grow, it is expected that surgical procedures in this group will escalate.

There is a growing amount of knowledge related to delirium. Yet, research focusing on delirium in octogenarian patients following treatment for aortic stenosis is scarce. Even though older surgical patients are especially vulnerable to delirium,[67] multicomponent interventions can reduce its occurrence.[68 69]

Delirium is a phenomenon that requires a multidisciplinary approach, and close contact with patients is decisive. Nurses have an especial role as they are among the health care professionals standing closer to the patient. They are also in close contact to patients' relatives and are often the first receiving information about abrupt changes in arousal, attention and cognition. Physicians rely on nurses for information when assessing these changes, and when identifying the fluctuations that characterize delirium. Other health care professionals such as physiotherapist or laboratory personal might chose nurses to discuss what they perceive as deficits in attention or disruption in mental function.

Delirium after treatment for AS in octogenarian patients brings together two specialities within nursing; cardiology and geriatrics. A better understanding of the incidence, potential risk factors, course and consequences of delirium after SAVR and TAVI might increase its identification, rise acknowledgment about cost associated with its development systems and enable the design of multicomponent strategies to prevent and address a phenomenon with high burden for patients and their relatives.

3. Aims

The overall objective of the study was to describe and understand delirium in octogenarian patients undergoing SAVR or TAVI by determining its incidence, identifying risk factors, describing its onset and time course, and by determining if delirium can be used to predict physical and cognitive function, self-reported health status, first-time readmission and mortality 1 and 6 months after aortic valve therapy.

More specifically, the aims of the study were:

- To determine the incidence of postoperative delirium (PD) in octogenarian patients with AS requiring SAVR or TAVI, to identify risk factors for the development of delirium, and to describe possible differences in the onset and course of PD in octogenarians treated with SAVR or TAVI.
- To determine how delirium could predict activities of daily living (ADL), instrumental activities of daily living (IADL), cognitive function, and self-reported health status in octogenarian patients 1 and 6 months after treatment with SAVR or TAVI.
- To determine if delirium can predict first-time readmissions and mortality in octogenarians 1 and 6 months after SAVR and TAVI.

4. Materials and methods

4.1 Design and setting

In order to address the aims of this study, an observational, prospective cohort study of octogenarian patients with severe and symptomatic AS undergoing elective SAVR or TAVI was conducted. This study was part of the "Delirium in octogenarians undergoing cardiac surgery or intervention – CARDELIR". The main outcome of CARDELIR was the presence/absence of postoperative delirium. Patients were included at Haukeland University Hospital, a tertiary university hospital performing all SAVR and TAVI procedures in western Norway.

4.2 Study population

Between February 2011 and August 2013, patients fulfilling the inclusion criteria were invited to participate in the study.

Inclusion criteria were:

- Age 80 years and older
- Previous acceptance for SAVR or TAVI

Exclusion criteria were:

- Inability to speak and understand Norwegian
- Declined consent to participate in the study

A heart team including cardiologists, thoracic surgeons and interventionists evaluated octogenarians with severe AS previously referred to our hospital, and identified those not suitable for SAVR. Severe AS was defined as follows: aortic valve area < 0.6 cm2/m2, mean gradient of > 40mmHg and maximum jet velocity > 4.0 m/s.[70] Patients disqualified for SAVR had previously received CABG or thoracic radiotherapy, had severe respiratory insufficiency, or other comorbidities that could compromise their recovery.[71]

During the inclusion period, 162 octogenarians were treated for AS with SAVR or TAVI at our hospital. Eligibility criteria were fulfilled by 147 patients, and 144 of them agreed to participate. One of the included patients withdrew consent before surgery, and 7 additional patients were either not responsive or died within 5 days after treatment, leaving complete data for 136 patients.

4.3 Assessments

4.3.1 Registers *(Paper I-III)*

Hospital information system registers

The hospital surgery data base ORBIT was used to identify patients 80 years-old and older scheduled to receive treatment with SAVR or TAVI before arrival to the hospital. It was also used to gather information regarding cardiac operative mortality risk (EuroSCORE)[72] (*Paper I*).

The *electronic patient record system* helped to schedule 1 and 6-month follow-up appointments and to identify patients who, in the meantime, had died (*Paper II*). The system also provided the information required to come in contact with patients unable to attend follow-up consultations *(Paper II)*, and to identify first-time readmissions and mortality 1 and 6 months after discharge (*Paper III*).

Patients' medical records

Electronic patient medical records provided baseline clinical characteristics and information regarding the American Society of Anaesthesiologists (ASA) Physical Status Classification System.[73] Patient medical records were also used to track reports about acute changes in attention, abnormal motoric activity, sleep disturbances, use of postoperative medications and date of hospital discharge *(Paper I and III)*.

4.3.2 Delirium *(Paper I-III)*

Assessment of the main outcome (delirium), was performed with the Confusion Assessment Method (CAM).[28]A commonly used tool[39] that has proven to be valid and reliable.[28]

4.3.3 Cognitive function *(Paper I and II)*

The Mini Mental State Examination

The Mini-Mental State Examination[74] (MMSE) is a widely known cognitive test[75] that evaluates orientation, registration, recall and naming, and which requires a short amount of time to administer.[74] The MMSE has proven to be a valid and reliable instrument to test global cognitive function.[74]

4.3.4 Physical function (*Paper I and II*)

Barthel Index (Paper I and II)

The Barthel Index assesses 10 basic self-care activities: bowel and bladder control, toilet use, feeding, grooming, transfer, mobility, dressing, use of stairs and bathing[76]. Even though the initial scoring system of the Barthel Index ranged between 0–100, a modified version with scores from 0-20[77] is often used.[78] Higher scores in the index represent higher levels of independence.[76 79] The psychometric properties of the Barthel Index have been shown in several studies.[78 79]

Nottingham Extended Activities of Daily Living Index (Paper II)

This index evaluates 22 complex activities of daily living, distributed within 4 major areas: mobility, kitchen, domestic and leisure activities.[80] Scores are placed in a range between 0 and 66, with low scores representing worse levels of independence.[81] The index has shown sufficient psychometric properties to assess extended activities of daily living.[80]

Frailty (Paper I)

The Study of Osteoporotic Fractures (SOF) Frailty Index was used to evaluate frailty.[82] This index identifies individuals at risk of negative outcomes by using 3

items: weight loss, inability to rise from a chair five times without using the arms as body support, and reduced energy level.[83] Patients giving a positive answer to two or more of the items are considered to be frail.[83] The SOF frailty index is a valid and reliable instrument.[83 84]

4.3.5 Assessment of health status (*Paper II*)

The Short-form 12-item Health Survey (SF-12) (Paper II)

The SF-12 was used to evaluate subjective general health.[85] This instrument is based on 12 items that lead to two summary scores: A physical component summary (PCS) and a mental component summary (MCS). The highest score in each of the component summaries is 100, with high scores representing higher levels of perceived health.[85] The SF-12 has proven to be a valid and reliable instrument.[85]

Information regarding assessments and measuring times can be found in Table 4.

Table 4: Instruments or questionnaires presented in alphabetical order, and measuring times.

Construct	*Questionnaire/ instrument*	*Subscale*	*Number of items per subscale*	*Response categories*	*Scoring*	*Time point measured*
Activities of daily living	Barthel Index	Feeding, Bathing, Grooming, Dressing, Bowel, Bladder, Toilet use, Transfer, Walking, Use of stairs.	3 2 2 3 3 3 3 4 4 3	Categories ranging from 0 to 3. The response category varies according to the functional activity being tested.	0-20. High scores indicate higher functional independence.	Baseline, 1 and 6-month follow-up.
Cardiac operative risk	Logistic European System for Cardiac Operative Risk Evaluation I (Logistic EuroSCORE I)	Patient-related factors, Cardiac-related factors, Operation-related factors.	9 4 4	Scores ranging from 0-4.	Higher scores represent increased operative mortality risk.	Baseline
Cognitive function	Mini-Mental State Examination	Orientation, Memory, Registration, Attention and Calculation, Recall, Language.	2 1 1 1 6	0 to 1 where 1 represents the ability to perform the measured cognitive task	0-30 where higher scores indicate a higher global cognitive function. A score of 27 or less can indicate reduced cognitive function.	Baseline and 6-month follow-up

Comorbidity	Charlson Comorbidity Index	Myocardial infarct, Congestive heart failure, Cerebrovascular disease Dementia, Chronic pulmonary disease, Connective tissue disease, Ulcer disease, Mild lever disease, Diabetes mellitus, Hemiplegia Moderate or severe renal disease, Diabetes mellitus with end organ damage, Any tumor Leukemia Lymphoma Moderate or severe liver disease, Metastatic solid tumor, Acquired immunodeficiency	1 1 1 1 1 1 1 1 2 2 2 2 2 2 3 6 6	Comorbidities are assigned a score of 1, 2, 3 or 6.	A total score is obtained by summing the scores assigned to each disease. Higher scores represent higher risk of mortality.	Baseline

		syndrome	6			
Delirium	Confusion assessment method (CAM)	Acute onset, Fluctuating course, Inattention, Disorganized thinking, Altered level consciousness	1 1 1 1 1	Yes/No.	Delirium is diagnosed when features 1 and 2 are present and either 3 or 4 are displayed	From the 1st to the 5th postoperative day.
Frailty	Study of Osteoporotic Fractures (SOF) Frailty Index SOF					Baseline
Instrumental activities of daily living	Nottingham IADL	Mobility, Kitchen, Domestic, Leisure	4 4 4 4			Baseline, 1 and 6-month follow-up.
Self-reported health status	The Short-form 12-item Health Survey (SF-12)					Baseline, 1 and 6-month follow-up.

4.4 Data Collection

4.4.1 Preoperative data

Patients filling the inclusion criteria were approached by the time they arrived at the hospital, usually the day before surgery or intervention. Information about the CARDELIR study was presented individually by a member of the research team. Patients interested in joining the study signed a consent form. Information required for the Barthel index, the SOF-frailty index and the MMSE was collected at the time of inclusion by interview and/or observation as appropriate. At the end of inclusion procedure, patients received a set of self-administered questionnaires intended to evaluate IADL and subjective general health. These questionnaires were then collected before SAVR or TAVI was performed. Demographic and clinical data were gathered from medical records or interview, as appropriate.

4.4.2 Assessment of delirium

Members of the research group trained in the use of CAM were responsible for assessing delirium. Nursing staff at the Section of Thoracic Surgery received regular information about delirium and its features, and were encouraged to report symptoms of delirium at every shift. After surgery or intervention, included patients were approached and assessed for delirium daily, around noon, from postoperative day 1 to 5, including weekends and holidays. Patients were assessed for inattention, disorganized thinking, and altered level of consciousness and disorientation. Medical, nursing and physiotherapist' reports from the previous 24 hours were also considered when CAM was scored.

4.4.3 One- and six-month assessments

Follow-up visits were scheduled at the hospital 1 and 6 months after treatment. Information regarding ADL function, current living conditions (living at home, nursing home or at a rehabilitation unit) and hospital readmissions was collected by interviewing the patient at follow-up times. Data regarding hospital readmissions and

length of hospital stay was also controlled with the electronic patient record system. Self-report forms containing IADL and SF-12 questionnaires were provided to the patients. If a patient was unable to attend a follow-up visit and a new appointment could not be scheduled within a window of 2 weeks, telephone contact was attempted. Over the phone, information required to fill out the Barthel Index, to list current living conditions and to register hospital readmissions was gathered. Self-report forms containing IADL and SF-12 questionnaires were then mailed, together with an additional envelope addressed to CARDELIR investigators, to the patients for completion at home. Frailty and cognitive function was assessed after 6 months, but only for patients attending follow-up visits.

4.4.4 One- and six-month first-time readmission and mortality

Since patients in this study belong to five different regional hospitals (Helse Førde, Helse Fonna, Helse Stavanger, Haraldsplass Deaconess Hospital and Helse Bergen), especial approval from each of these institutions was gathered to access date of first-time hospital readmission and discharge diagnosis. Close contact between the principal investigation of the CARDELIR-study (TMN) and a person representing the electronic hospital systems was required to collect the information needed without threatening confidentiality.

4.5 Statistical data analysis

Data management and initial statistical analyses were performed with IBM SPSS for Windows, Version 21.0 (*Paper I*) and 22.0 (*Paper II)* and 23.0 (P*aper III*) (IBM SPSS Statistics for Windows, Armonk, NY, USA). For other analyses, R 3.0.2. (*Paper I*), R 3.1.1 (*Paper II),* R 3.2.3 *(Paper III*) (R Foundation for Statistical Computing, Vienna, Austria)[86] were used. Power analyses (*Paper I*) was calculated with Sample Power 2 in SPSS (IBM SPSS Statistics for Windows, Armonk, NY, USA).

4.5.1 Descriptive statistics

Descriptive statistics of continuous variables were performed using means and standard deviations (SD). Categorical variables were analyzed as absolute numbers and percentages (*Paper I-III*).

4.5.2 Comparisons

Group comparisons (Delirium/Non-delirium *and* SAVR/TAVI) were performed with chi-squared or Fisher's exact tests for categorical variables, and Welch's test (test not assuming equal variances) for continuous variables (*Paper I-III*).

4.5.3 Regressions

Univariate and multivariate logistic regression analysis were used to determine risk factors for delirium after aortic valve treatment (*Paper I).*

4.5.4 Longitudinal models

In *Paper II*, longitudinal linear models were fitted (separately) to estimate the mean ADL, IADL, MMSE, SF-12 Physical Component Summary, and SF-12 Mental Component Summary scores at baseline, 1- and 6-month follow-up. These longitudinal linear models were fitted with time, delirium and the interaction between time and delirium as explanatory factors. For estimating how delirium could improve predictions over baseline scores alone or baseline scores *and* other risk/comorbidity factors, linear longitudinal models were fitted for the scores at 1- and 6-month follow-up, using the baseline score as an explanatory variable (for the unadjusted analysis), or the baseline score, gender, Charlson Comorbidity Index, and logistic EuroSCORE I as explanatory variables (for the adjusted analysis). All longitudinal models were fitted separately for each treatment (SAVR/TAVI), using generalized least squares with an unstructured correlation matrix.

4.5.5 Sensitivity analysis

Sensitivity analyses were used in *Paper II*. As it was not possible to assume that data were missing completely at random (MCAR), a likelihood-based longitudinal model that required only the much weaker missing at random (MAR) assumption was used. Since there could be informative censoring not captured by the model (for example, patients with greater improvements from baseline were more likely to respond to the follow-up questionnaire), sensitivity analysis for the changes from baseline were performed. In these analyses, all missing data was replaced with the patients' baseline values, and then the statistical analyses were repeated.

4.5.6 Survival models

Differences in the time to onset of delirium following SAVR and TAVI was explored using a logrank test for interval-censored data (*Paper I*).[87 88] Kaplan–Meier curves and an exact Gehan–Breslow test stratified by treatment were used to examine and test for differences in time to first time readmission and death for patients with and without delirium (*Paper III*). Cox proportional hazard regression stratified by treatment (SAVR/TAVI) was used to adjust for gender, age (as a nonlinear/quadratic effect), MMSE and comorbidities (*Paper III*).

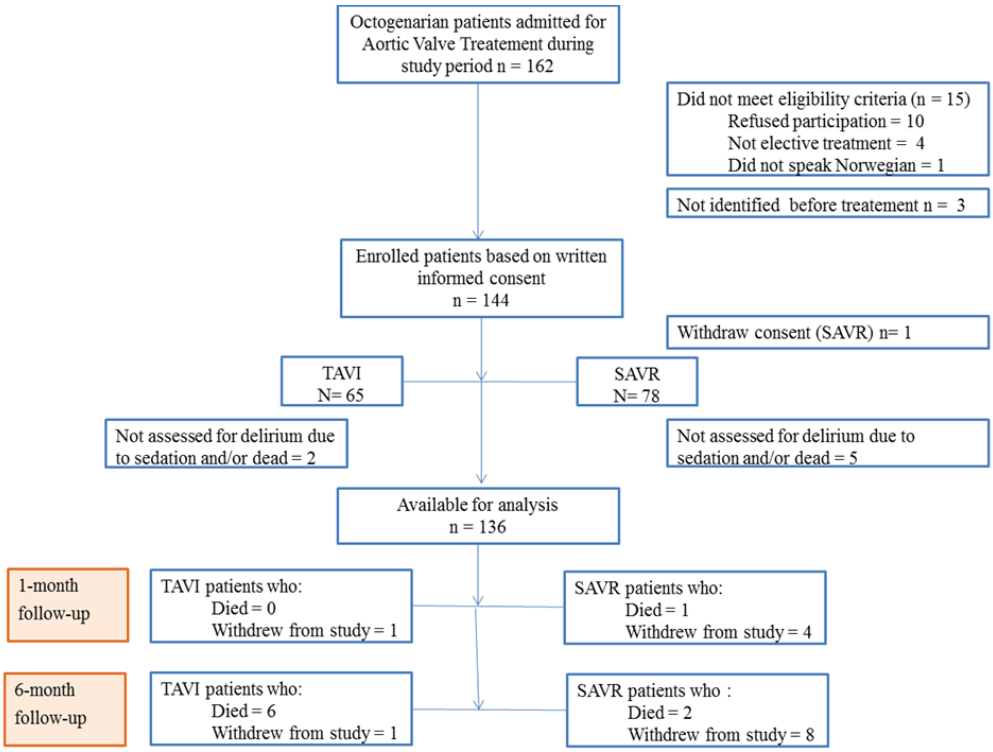
4.5.7 Statistical significance

For all three studies, a two-tailed p-value of ≤ 0.05 was considered statistically significant.

4.5.8 Missing data

Missing data can be especially challenging in aging research.[89] It was anticipated that due to the advanced age of the participants in this study, a certain amount of missing data would be present. Therefore, a coding system for missing was designed ("patient did not answer the item," "patient withdrew from the study," "patient died," "administrative reasons prevented data collection," "patient lost-to-follow-up").

By the time 6 month-follow up was performed, 8 of the 136 patients discharged alive had died and 9 had withdrew from the study (8 of them treated with SAVR) (Figure 1). Cognitive screening 6 months after SAVR or TAVI was not performed in 39 patients (29%). Twenty-three of these patients did not attend 6-month follow-up at the hospital. The majority of these non-attendees were living more than 2 hours away from the hospital: 5 stated that the hospital was too far away from their residence to attend the consultation, 9 expressed that they were not well enough to travel, 4 declared that they were healthy and did not need further follow-up checks, 3 did not indicate their reason for not attending the follow-up, and 2 could not be contacted. Patients who did not attend their 6-month follow-up did not differ from those attending in terms of gender ($p = 0.27$), baseline comorbidities ($p = 0.74$), or baseline MMSE scores ($p = 0.83$).



(Based on figure by Hufthammer KO, 2016)

Figure 1: Flow-chart of included patients.

4.6 Ethical Aspects

CARDELIR was approved by the Regional Committee for Ethics in Medical Research in Norway (REK Vest 2010/2936-6) and conducted in accordance with the Declaration of Helsinki. Research focusing on old patients brings challenges not always present in studies with younger populations. Comorbidities, polypharmacy, reduced mobility and sense impairment require special considerations in order to compel with the ethical principles of beneficence (doing good), non-maleficence, autonomy and justice[90 91]. The following session discusses on how these challenges were addressed.

4.6.1 Beneficence

The principle of beneficence obligates to maximize patients' benefits.[90 91] This principle was particularly important in included patients who had experienced delirium after SAVR or TAVI. Several individuals expressed, in verbal and written form, the benefits of having a person with whom they could discuss the experience of being delirious. Some felt that this was a difficult issue to talk about with spouses or other family members, and were grateful for having a health care professional to communicate with.

Another benefit of this study lies in the fact that, as far as we know, it is the first to systematically evaluate delirium for five consecutive days in octogenarian patients undergoing TAVI and has therefore, the potential of providing benefits for future elderly patients undergoing the procedure.

4.6.2 Non-maleficence

Researchers have an obligation to minimize harm.[91] This study did not require additional blood samples, invasive examination or practices. Nevertheless, it is fair to assume that, due to the advanced age of the patients and the nature of the cardiac procedures being performed, some individuals might have experienced emotional distress. This distress could have increased after they agreed to participate in the study. In order to address this issue, only members of the research team with extensive experience dealing with geriatric and/or cardiac patients were trusted to perform data collection. Whenever verbal and non-verbal signs of discomfort or fatigue were identified, data collection was stopped.

4.6.3 Autonomy

The principle of respect for human dignity incorporates the right to self-determination and the right to full-disclosure.[90 91] All patients received understandable verbal and written information about this study at the time of inclusion. They were also informed about their right to withdraw consent to further participation without giving any explanation, or worrying for future treatment or care. Ten patients did not want to

participate in the study; TAVI was scheduled in five of them. Additionally, one patient scheduled for SAVR decided to withdraw consent to further participation before surgery was performed. By the time of 1-month follow-up, five patients had decided to withdraw from the study. By 6-month follow-up, four more had left (Figure 1).

4.6.4 Justice

The principle of justice is related to the patient's need for confidentiality and fair treatment.[90 91] Confidentiality was assured by entering non-identifiable data in a secure database provided by Haukeland University Hospital. A list containing patients' name and identification number was placed on a second database with access restricted to the principal investigation of the CARDELIR-study (TMN) and the PhD candidate (LSPE). Fair treatment is closely related to the principle of self-determination. As pointed out earlier, patients received information reassuring them that declining to participate in the study would not interfere with the regular care they were entitled to receive after surgery or intervention, or in the future.

5. Results

The main findings of this study are presented in the following pages.

5.1 Sample characteristics (*Paper I-III*)

The mean age of the included patients was 83.5 (SD 2.7) and 4 of them were 90 years-old or older, the oldest being 92 years. The majority of patients were women (57%) and married (54%). TAVI was performed in 46% of the patients. Compared to patients treated with SAVR, TAVI patients were older ($p < 0.001$), had lower cognitive scores ($p = 0.007$), more comorbidities ($p = 0.001$), higher logistic EuroSCORE ($p < 0.001$) and were more often placed in an ASA score between III-IV ($p = 0.001$). Detailed information regarding socio-demographic and clinical characteristics according to treatment (SAVR vs. TAVI), and presence/absence of delirium are presented in *Paper I*.

5.2 Paper I

Comparison of Frequency, Risk Factors and Time Course of Postoperative Delirium in Octogenarians after Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement.

Delirium occurred at least once during the 5 days of evaluation in 56% of patients. Patients developing delirium were more often treated with SAVR than TAVI ($p = 0.01$). Delirium was identified in 66% of octogenarians treated with SAVR and in 44% of those patients treated with TAVI. Multivariate regression analysis established that reduced cognitive function ($p = 0.003$) and treatment with SAVR ($p = 0.02$) were risk factors for delirium in octogenarian patients treated for severe AS.

No differences in the number of days with delirium were identified between patient groups. Delirium in patients undergoing SAVR lasted on average 1.5 days compared to 1.1 days for patients treated with TAVI ($p = 0.20$). Yet, the course of delirium between treatment groups was different (exact logrank test for interval-censored data; $p = 0.03$). Delirium could develop at any time during the 5 days of assessment in

patients treated with SAVR. Patients in the TAVI group without delirium the first postoperative day usually did not develop delirium in the succeeding days.

5.3 Paper II

Delirium as a predictor of Physical and Cognitive Function in Octogenarians after Transcatheter or Surgical Aortic Valve Replacement.

Patients treated with SAVR had lower IADL scores at 1-month follow-up, independently of presence or absence of delirium (from 58 to 42 and from 58 to 50 respectively, $p \leq 0.02$). Yet, these scores returned to baseline levels by the time 6-month follow-up was performed. Improvements in the Physical Component Summary score of SF-12 were identified 6 months after SAVR, especially in patients without delirium (from 39 to 48 $p < 0.001$). No other differences in the remaining outcomes were identified. Delirium after SAVR could be used to predict IADL function, although it does not predict ADL, cognitive function, or SF-12 scores. These findings persisted also after adjusting for other variables.

TAVI patients with delirium had lower ADL and IADL scores 1 month after treatment (from 19 to 16, $p < 0.001$, and from 49 to 40 $p = 0.003$ respectively). The Physical Component Summary scores of SF-12 increased in TAVI patients without delirium at 1-month follow-up (from 30 to 35, $p = 0.04$) and at 6-months follow-up (from 30 to 35, $p = 0.02$). Regression analyses established that delirium following TAVI predicted lower ADL and IADL function only at 1-month follow-up.

5.4 Paper III

Readmissions and mortality in delirious and non-delirious octogenarian patients after aortic valve therapy. A prospective cohort study.

Survival analyses show differences in first-time readmissions and mortality, 1 and 6 months after treatment. When adjusted for type of treatment (SAVR/TAVI), the differences in readmissions and death between delirious and non-delirious were significant 6 months after the initial discharge ($p = 0.02$). These differences were

already present during the first month (p=0.006). Initial analyses revealed that the effect of delirium was not well described by a Cox proportional hazard model (p = 0.03 in a test for the proportional hazard assumption). Examination of Schoenfeld residuals indicated that the effect of delirium on the hazard diminished over time, and this was particularly pronounced from about 60 days after initial discharge. We therefore fitted a time-dependent effect of delirium, constant up to 60 days (i.e. assuming proportional hazards up to this time point) and linear with time from 60 days. This greatly improved the model fit. Hazard ratio up to 60 days was estimated to be 2.9 (95% CI: 1.5 to 5.7). The effect was reduced over time (an estimated reduction of about 3% for each day after the 60^{th}).

The majority (24) of the total amount (30) of first-time readmissions 1 month after treatment belonged to patients who had experienced delirium. In patients with and without delirium, first-time readmissions were related to the circulatory system. One patient, who did not experience delirium, died within 30 days after treatment. After 6 months, 37 of 58 first-time readmissions belong to patients in the delirium group. Patients who experienced delirium were also accountable for 6 of 8 deaths within 6 months after treatment.

6. Discussion

The overall aim of this study was to investigate delirium in octogenarian patients undergoing SAVR or TAVI by determining its incidence, identifying risk factors, describing its onset and time course, as well as to determine how delirium can predict physical and cognitive function, self-reported health status, readmissions and mortality 1 and 6 months after treatment.

The main results from the papers constituting this study will be first discussed in light of methodological issues. Further discussion will be based on previous knowledge and future clinical implications.

6.1 Methodological issues

The strength of this study lies in the consecutive inclusion of octogenarian patients with severe AS scheduled for SAVR and TAVI. Since Haukeland University Hospital performs all AVR in western Norway, it is fair to assume that a representative group of octogenarian patients from this part of the country and referred to this hospital has been included. Another strength comes from the psychometric properties of the CAM,[28] a highly recommended instrument to assess delirium.[1 39 40 92] In this study, contact with included patients was performed by the time of hospitalization, and baseline assessments provided the opportunity to make a general assessment of cognitive function, arousal and attention that could later be used to evaluate acute and fluctuating changes in these areas. CAM was used for five consecutive days, including weekends and holidays. Additionally, patients' hospital records from the previous 24 hours were examined closely when CAM was scored. To the best of our knowledge, no other study has systematically evaluated delirium exclusively in octogenarians receiving TAVI, for an equal amount of consecutive days and in two follow-up periods. Yet, some limitations that can potentially threat the validity of our results[93] should be acknowledged. These limitations will be discussed on the following pages, as appropriate.

6.1.1 Study design

Prospective cohort and observational studies have strengths and limitations. Some of the strengths of this study have been addressed earlier in this chapter. Prospective cohort and observational studies have been criticized for being vulnerable to confounding factors and for not holding the same position as randomized control trials (RCT) in the hierarchical "pyramid of evidence".[94] However, in the present study, a RCT was not possible since SAVR and TAVI are designed to treat two different patient groups.[13] Additionally, in recent years, well-designed observational studies have been considered to provide results comparable to RCTs.[94]

6.1.2 Sample

In a prospective study, researchers should be confident that all participants are free from the effect that a potential independent variable might impose on a dependent variable.[95] The prevalence of delirium in the general population is relatively low,[35] although it increases with age in clinical settings.[36] In this study, the presence/absence of delirium was measured only in the postoperative phase. Therefore, we cannot be completely sure that all included patients were free from delirium by the time they arrived to the hospital. Although MMSE was part of baseline measurement, this instrument is insufficient to identify delirium.[39 96] Yet, as early mentioned, data collection at baseline provided the opportunity to make an overall assessment of patients cognitive function, arousal and attention. Other instruments could have been used to evaluate delirium at baseline, but at the time the study was designed we considered that this might have imposed an extra burden in the octogenarian patients included in our study.

The field of cardiology is facing challenges in an increasing older population.[97] Increased knowledge in the area is needed, as several cardiac guidelines and standards of care are designed for younger population groups.[5 98] Our hospital is the only one entitled to provide advanced cardiac treatments, such as SAVR and TAVI in a region of approximately 1.3 million inhabitants[99], allowing our research group to focus on octogenarians with AS referred to the hospital, and to achieve the

homogeneity needed to study delirium after SAVR and TAVI in this patient group. This study includes data from 143 of 147 eligible patients (97%), 80 years-old and older, with severe AS and living on the west part of Norway. Even though the homogeneity of our patient group gives strength in terms of *internal validity*, it might also pose a threat to *external validity* since the results might have limited applicability to patient populations undergoing other invasive treatments.[93] Yet, it is important to emphasize that the high participation rate of octogenarian patients poses strength to *external validity* for octogenarian patients in need of SAVR or TAVI in other hospital settings.

The fact that the majority of patients in this study had a good cognitive and ADL function might also be a threat to *external validity*. Even though the high scores in the Barthel Index and the MMSE might suggest a patient selection bias before referral to our hospital (*Paper I-III*), this was an issue difficult for us to control.

According to Polit and Beck (2012), *statistical conclusion validity* "concerns the validity of inferences that there truly is an empirical relationship between the presumed cause and effect" (page 236). In 2010, by the time the study was designed, a power analysis based on previous research on cardiac surgery populations and the primary outcome (delirium/non-delirium) was performed. According to this calculation, 100 patients undergoing SAVR and 40 undergoing TAVI would be needed to reach a statistical power of 80%. These numbers would allow detecting a reliable risk difference, given that 31% of patients in the SAVR group and 10% in the TAVI group actually developed delirium. However, after two years of inclusion, it became clear that a lower number of octogenarians, than we had initially anticipated, were treated with SAVR. At the same time, more patients were offered TAVI. A new power calculation was performed and it determined that by including 84 patients in the SAVR group and 65 patients in the TAVI group we would be able to achieve a power of 89% to detect a reliable risk difference given that 31% of patients in the SAVR group and 10% in the TAVI group actually developed delirium.[71] Consequently, the latter power calculation used in this study showed increased power than initially anticipated.

6.1.3 Assessments

The instruments in this study are proven valid and reliable, yet some limitations should be taken into consideration. The CAM has been used in previous Norwegian studies,[22 49 96 100 101] however it remains to be validated to Norwegian settings. Despite this minus, the CAM was considered the most appropriate instrument in our study as it has been widely used, either in its original form or in as CAM-ICU, to identify delirium in older cardiac patients.[14 15 17 21 50 102] The CAM was recently validated for cardiac patients 70 years-old and older in Sweden, reporting a sensitivity of 68% and a specificity of 90% indicating false-negative rather than false-positive results for delirium.[103] These two Scandinavian countries have several similarities, and it is fair to assume that the results from Sweden are applicable to Norway. A second limitation regarding assessment is the lack of instruments evaluating levels of arousal in patients with delirium.[104 105] Scales such as The Glasgow Coma Scale[106] or the Richmond Agitation-Sedation Scale[107] could have complemented our data. However, by the time the study protocol was designed, we considered that the battery of instruments and measurements was extensive enough considering the age of our group.

Construct validity refers to the degree to which "an investigator believes that his instrument reflects a particular construct."[108] A threat to *construct validity* can be found in the fact that the author of this study had a major responsibility for assessing the presence/absence of delirium. Other members of the research team performed assessment of delirium but we did not examine inter observer reproducibility of delirium diagnosis. We attempted to minimize the threat by following guidelines,[28] having strict timeframes as to when to assess delirium and by reviewing patient medical records. In case of uncertainty regarding the presence/absence of delirium, an experienced geriatrician (AHR) was consulted to review the information available about symptoms of delirium.

The high ADL and cognitive scores provided by the Barthel Index and the MMSE might represent a selection bias probably present before patients were referred to our hospital. The use of the Nottingham IADL scale might have helped to attenuate these

high scores, especially in terms of ADL function. The internal consistency of Nottingham IADL scale in this study was of 0.84. The range of internal consistency values can be placed between 0.00 to +1.00, with higher values reflecting higher internal consistency.[109] Values between 0.7 to 0.8 are considered satisfactory.[110]

The SF-12 has been used to evaluate subjective general health and it has provided important results regarding health related quality of life in cardiac patients after the use TAVI.[111 112] Although, as far as we know, it remains to be used to detect changes between baseline and follow-up times in older cardiac populations that had experienced delirium.

6.1.4 Follow-up data

The relatively short follow-up times in this study might limit its *internal validity.*[93] This is especially relevant in terms of the instruments used to evaluate ADL, IADL, cognitive function and self-reported health status, as we cannot be sure that patients were able to remember some of the questions and that their responses were adjusted accordingly. We could have performed other measurements or scheduled follow-up times with longer intervals, yet, follow-up times were planned according to ordinary clinical follow-up. The advanced age of our patients also contributed to limit the length and number of follow-up times in this study. Besides, other studies have used similar follow-up times, providing the opportunity to compare our results with those obtained by other important publications.[17 21 55] The *objectivity* of this study can have been threatened by the fact that the author was present during follow-up times. We intended to minimize the threat by using robust instruments to evaluate ADL (Barthel Index),[76 77 79] IADL (Nottingham IADL)[80 113 114], cognitive function (MMSE)[74 115] and self-reported health status (SF-12)[85 116] at baseline and follow-up times.

6.1.5 Quality of the data

Data was entered in a secure database. At the end of the inclusion period, a person different from the one who had entered the data, checked its quality and guarantee that it had been typed correctly. When errors were present, data was rectified and

mistakes documented in an independent logbook. Before statistical analyses were performed, data was screened and controlled for outliers or odd numbers *(Paper I-III)*.

6.1.6 Missing data

A threat to *internal validity*[93] is loss of data due missing units (questionnaires) and items, drop-outs and mortality. As reported earlier (Chapter 3, part 3.5.8 Missing data), a coding system for missing data was implemented. Baseline data shows no missing units or items on the Barthel Index or in the MMSE. Complete units of Nottingham IADL were identified in 83% of included patients. Yet, 10% did not answer 1 item, 1% did not answer 2 and 5% did not answer any of the IADL-items. No differences in terms of gender ($p = 0.27$), marital status ($p = 1.00$), education ($p = 0.14$), comorbidity ($p = 0.14$) or AS treatment ($p = 0.82$) were found between patients with complete units vs. those with incomplete units. Regarding baseline data for SF-12, 85% of patients had complete units, 7% did not answer any of the 12 items, 4% did not answer 1 item and 1% did not answered 3, 6 or 7 items. Those with incomplete SF-12 units were more often males (p=0.02). No differences in marital status ($p = 0.81$), education ($p = 1.00$), comorbidity ($p = 0.355$) or treatment were identified ($p = 0.47$) (*Paper I - III*).

At 1-month follow-up, 87% of patients had complete Barthel Index units. No missing items were found. Complete Nottingham IADL units were identified in 63% of patients, while 20% did not answer any item, 11% did not answer 1 item, 3% did not answer 2 and 1% did not answer 3, 6 and 7 items. On the SF-12, 69% of patients had complete units, 20% did not answer 12 items, 8% did not answer 1 item, 3% did not answer 2 and 1% did not answer 6 items (*Paper II*).

At 6-month follow-up, 83% of patients completed the Barthel Index unit. Remaining patients did not answer any of the items on the index. Nottingham IADL was completed by 63% of patients, 23% did not answered any of the items, 10% did not answered 1 item, 1% did not answer 2 and 2% did not answer 3. Complete SF-12 units were found in 69% of patients, 24% did not answer any item, 8% did not answer

1 item and 2% did not answer 2 items. MMSE at 6-month follow-up was not performed in 45 patients (31%), who for different reasons did not attend 6-month follow-up at the hospital. The majority of those non-attendees, were living more than two hours away from the hospital: 5 stated that the hospital was too far away from their residence to attend the consultation, 9 expressed that they were not fit enough to travel, 4 declared that they were healthy and did not need further controls, 3 did not want to indicate the motive for not attending follow-up, and 2 patients were unable to be contacted. Of the remaining patients without MMSE scores at 6-month follow-up, 9 withdrew from the study and 13 were dead. Patients who did not attend 6-month follow-up did not differ from those attending in terms of sex ($p = 0.27$), baseline comorbidities ($p = 0.74$) or baseline MMSE scores ($p = 0.83$).

Missing data is specially challenging in research that involves older patients.[89] Close examination of missing data and use of statistical techniques allowing account for death or dropout have been warranted.[117] In order to reduce missing data in our study, telephone contact with included patients was attempted before follow-up consultations and self-rapport questionnaires were send by mail to patients unable to attend the follow-up consultation. Together with the questionnaires, a pre-stamped and pre-addressed return envelope was provided. When data analysis was performed, sensitivity analysis was used to manage the challenging issue of missing data.

6.2 Discussion of main findings

This study provides additional evidence placing delirium as an unwanted outcome in older hospitalized adults.[1] As the number of older individuals in need of treatment for severe AS is raising, [8 59 60] and TAVI is successfully being performed in patients 80 years-old and older,[60 118] it is important to address the high incidence of delirium found in hospital settings and discuss the differences in the course of delirium between patients treated with SAVR and TAVI. The lower levels of performance in terms of physical and cognitive function for patients having delirium, especially those treated with TAVI, might suggest a vulnerability in this patient group that has not been properly uncovered. This study also provides valuable knowledge by

determining that delirium can be used to predict first-time hospital readmissions and mortality in octogenarian patients 1 and 6 months after treatment with SAVR or TAVI. The knowledge presented in this study could be used by health care professionals and administrators of health care systems to design and implement strategies directed to prevent and reduce the personal and socioeconomic costs of delirium.

6.2.1 Development and course of delirium after SAVR versus TAVI

A high incidence of delirium was found in patients 80 years and older after treatment, especially in the group of patients treated with SAVR. In this study, SAVR not only emerged as a new risk factor for delirium in our sample, but was also associated with a more unpredictable onset and course. These findings are of interest, taking into consideration that several risk factors for delirium, such as higher age, lower cognitive scores, higher number of comorbidities and higher operative risk [14 15 17 119] were more often found among patients in the TAVI group.

A possible explanation to the higher incidence of delirium in an apparently less vulnerable population can be found in the more aggressive treatment approach SAVR represents, and in the multifactorial causation model of delirium.[1] As explained by Inouye and colleagues, each episode of delirium might have a unique set of contributors, and each set is composed by several interacting factors that might eventually lead to it.[1] In the light of the multifactorial model, several postoperative patterns differentiate patients treated with SAVR to those treated with TAVI; reduced mobility due to the invasive SAVR procedure and use of physical restraints, and inflammation. Physical restrains are one of the leading predisposing factors for delirium in medical inpatients.[1] SAVR requires an aggressive approach with general anesthesia, sternotomy and extracorporeal circulation. Consequently, patients treated with SAVR use cardiac monitoring devices, intravenous lines and urine catheters that might reduce their mobility for longer periods of time. Direct brain insults and aberrant stress responses have been proposed as two basic etiological factors leading to delirium.[120] Although a deep analysis of the complex brain function (or

dysfunction) related to delirium is beyond the scope of this study, is worth mentioning that pathologically sustained elevated cortisol levels, like those occurring with inflammation and acute stress from surgery and pain, might precipitate delirium.[120,121] TAVI can be performed without general anesthesia, and the more gentle technique that characterizes TAVI might lead to less tissue damage, potentially less inflammation and reduced patient distress. It can partially explain why in our population group, SAVR patients developed more delirium despite the fact that patients in the TAVI group had several predisposing factors. This might also imply that health care professionals should be more aware of sudden and fluctuating changes in attention and cognition for patients receiving SAVR, and strategies for prevention, early detection and treatment of delirium should be part of hospitals guidelines and protocols.

No differences in the number of days with delirium between patient treated with SAVR or TAVI were identified. However, we were able to determine that the majority of patients in the TAVI group developed delirium during the first postoperative day, while delirium could develop at any time during the five days of assessment for patients in the SAVR group (*Paper I, Figure 2*). As far as we know, no other study has systematically studied the onset and course of delirium, consecutively for 5 days and focusing on octogenarians undergoing aortic valve treatment. This approach enabled the identification of such a distinction. An explanation to the differences in onset and course could be found in the possible relationship between physical restraints and delirium.[1] In the setting in which this study was conducted, cardiac monitoring equipment and urine catheters in TAVI patients are often removed after the first 24 hours. Additionally, our hospital protocols strongly encourage mobility in patients undergoing TAVI. Mobility is also promoted for SAVR patients, and nurses and physiotherapist work hard assuring appropriate levels of activity in surgical patients. Yet, the presence of several other precipitating risk factors for delirium such as; inflammation,[121] sleep disturbances,[122] use of psychoactive drugs such as sedatives and opioids,[123] together with physical restraints[124] might place an extra burden that, for this particular group of patients, will

lead to a more unpredictable onset of delirium. Note, however, that our findings are limited by our small sample and demand further studies.

6.2.2 Physical and cognitive function following hospital discharge for patients with and without delirium.

All patients in the SAVR group, had reductions in ADL function 1-month after treatment for AS being this reduction statistically significant in patients without delirium. Abrupt falls in ADL function at 1-month follow-up were identified for patients in the TAVI-group with delirium, while ADL scores in TAVI patients without delirium remained stable both at 1 and 6-month follow-up. Even though ADL scores increased in all patient groups by the time 6-month follow-up was performed, a distinct trend to lower ADL performance can be seen in TAVI patients who had delirium (*Paper II, Figure 1*). A reduction in ADL function can be expected in octogenarian patients undergoing the more aggressive SAVR. The physical burden of the SAVR treatment is higher during their hospital stay because of the use of general anesthesia, cardiopulmonary bypass, sternotomy and cardio monitoring devices. By the time of hospital discharge, sternotomy might still limit the performance of ADL in areas such as taking a shower or dressing. It is however interesting to see that patients treated with TAVI and experiencing delirium also had big reductions in ADL scores.

Delirium has been associated with poor physical[17 21 50] and cognitive outcomes.[1 21 54 55] A recent review article[125] explores the association between acute critical illness, reduced physical function and delirium. The authors underline the need to reduce immobility and delirium in hospitalized critically ill older patients, claiming that changes in the structure and function of skeletal muscle make elderly more vulnerable to develop physical disability when immobility and delirium are present.[125] This theory finds support in one of the most interesting results from our study; the stable ADL scores of TAVI patients without delirium at 1 and 6-month follow-up. ADL performance in octogenarian patients undergoing the more invasive SAVR did not show the same degree of decrease, even though a borderline decrement at 1-month follow-up can be seen in SAVR patients without delirium. These findings might

imply that TAVI patients who experienced delirium were more vulnerable, and that especial strategies should be designed not only to identify patients at risk to develop delirium but also to increase the physiological resources of these patients. Increased focus on early mobility and their benefits should also be taken into consideration when older patients are schedule for treatment for AS.

Significantly lower IADL scores were found in patients developing delirium in both treatment groups (SAVR/TAVI). IADL scores in TAVI patients without delirium remained constant at both follow-up points, following the same pattern as for ADL scores (*Paper II, Figure 1*). These findings are of particular interest, as IADL function measures levels of performance in activities that are more dependent on intact cognitive functioning, such as the use of public transportation or managing own money.[17]

Cognitive function is an important outcome for older patients. Our data shows a patient group with high levels of cognitive performance compared to, for example, hip fracture patients.[126] We did not find significant differences between baseline and 6-month follow-up in any of the treatment groups, supporting findings from other studies.[54 55] However, note that MMSE scores in TAVI patients with delirium were lower at baseline and remained low at 6 months follow-up (*Paper II, Figure 1*). Variations in cognitive scores beyond 1-month follow-up remain inconclusive,[127, 54 55] and strategies to identify patients at risk and approaches aimed to reduce the risk of developing delirium should be part of hospital setting where SAVR and TAVI are performed.

6.2.3 Self-reported health status following delirium, SAVR and TAVI

SF-12 Physical Component Summary

Lower (yet non-significant) scores at 1-month follow-up, compared to baseline, and significant increases 6 months after treatment were present in SAVR patients, independently of delirium. PCS scores increased in all TAVI patients, being these statistically significant for individuals who did not experience delirium (*Figure 1,*

Paper II). The lower self-reported scores for SAVR patients can be related to the more aggressive approach of the treatment that included more tissue damage, higher levels of inflammation, reduced levels of mobility and bed rest for longer periods of time. Immobilization over prolonged periods of time results on lower muscle strength and reduced aerobic capacity in healthy adults.[128] Patients admitted to critical care units also experience reductions in bone mineral density and impairment in other body systems.[129]

Octogenarian patients with and without delirium after SAVR reported reduced levels of physical function at 1-month follow-up, as these patients had already done when scoring the Nottingham IADL scale. Yet the PCS scores improved notable after 6 months, especially for patients without delirium. The moderated but steady increase in PCS scores from baseline to 1-month follow-up and further on after 6 months for all patients undergoing TAVI might also reflect baseline vulnerability in this patient group that requires more time to recover. Our findings are consistent with studies showing improvements in the PCS scores of SF-12 for patients undergoing TAVI, although the increases in our patient group, despite being significant, are not as high as the other studies presented.[111 112 130] It is possible that the inclusion of delirium in our analyses contributed to reveal an additional element, partly responsible for this difference (*Paper II*). Current guidelines regarding older patients with cardiovascular diseases[98] advocate for the inclusion of health status and quality of life because these measurements provide important information regarding physical functioning in older hospitalized patients.[131] Therefore patient-reported outcomes should also be part of risk assessment in settings where older adults are receiving treatment for AS with SAVR or TAVI.

SF-12 Mental Component Summary

A continuous increase in MCS scores, from baseline to 1 and 6-month follow-up, was found in patients experiencing delirium after TAVI. The remaining groups showed patterns that crossed each other (*Figure 1, Paper II*). Note, however, that baseline MCS scores for TAVI patients are as low (baseline score: 47) as the lowest scores present in SAVR patients (those who experienced delirium at 30 days: 47.1),

indicating once more the underline vulnerability of octogenarians undergoing TAVI. Another interesting aspect is that baseline MCS scores in the TAVI group are higher than those reported in an European study including elderly patients treated with TAVI and which did not find significant differences between baseline scores and 1 and 6-month follow-up.[111] These results might reflect the diversity present in older populations,[5] but they can also depict the mental distressing experience of having delirium.[132] Patient reported outcomes are particularly important in this field and strong efforts should be made to increase knowledge regarding delirium and its association with mental health.

6.2.4 Readmissions and mortality. The impact of delirium following SAVR and TAVI.

The number of first-time readmissions was higher 1 and 6 months after treatment in octogenarian patients belonging to the delirium group (*Paper III Figure 2*), and the majority of deaths 6 months after treatment were found in patients who experienced delirium. It is difficult to be entirely certain on whether delirium leads to an additional vulnerability that is reflected on the higher number of readmissions, or if these patients were vulnerable at baseline and this is reflected upon the development of delirium and later readmissions. It is somehow puzzling that SAVR and TAVI patients without delirium had the lowest risk for readmissions and mortality 6 months after discharge (*Paper III, Figure 3*), and this might support the assumption of delirium imposing an extra burden in octogenarian patients, especially during the first two months after treatment. These findings are supported by a recent study showing that delirium was associated with higher rates of adverse outcomes in older patients undergoing elective surgery.[20] Studies evaluating the impact of delirium, exclusively in elderly after SAVR or TAVI, are scarce. A literature review done as late as April 15th 2016, shows the work of Maniar et al[133] as the only one exploring delirium and mortality in SAVR and TAVI patients. This study found a 3-fold increased risk of mortality during the first year after AVR. Despite the increased interest in delirium, larger studies with longer follow-up times are necessary in order to establish possible changes in the rates of readmissions and mortality. It is also of interest to study the

course of disability in the last years of life in delirious and non-delirious octogenarian patients after treatment for severe AS. For health care professionals these findings emphasize the importance of prevention and identification of patients at risk of having delirium.

7. Conclusion and implications

7.1 Conclusions

Conclusions from the three papers that constitute this study are:

- The incidence of delirium in octogenarians after aortic valve treatment is high, especially for those receiving SAVR. This treatment also emerged as a predisposing factor for delirium. According to our data, a more unpredictable onset and course of delirium could be expected when SAVR was used (*Paper I*).
- Delirium after SAVR and TAVI is followed by short-term reduction in IADL function. However, it does not seem to confer long-term reductions in physical, mental or self-reported health (*Paper II*).
- The number of first-time readmissions and death 1 and 6 months after aortic valve treatment was higher in octogenarian patients who experienced delirium (*Paper III*).

Delirium is a major postoperative complication that might predict lower IADL performance and a higher risk of hospital readmissions and death in octogenarian patients following treatment for AS with SAVR or TAVI.

7.2 Implications of the study

Delirium is a serious phenomenon that can lead to unwanted outcomes, both during the initial hospital stay and within the first 6 months after AVR. The implications that delirium has on socioeconomically levels, clinical contexts and on the individual sphere are of big importance. The prevalence of AS increases with age and it is fair to anticipate that older patients, more often than before, will be recipients of advanced cardiac treatments such as SAVR and TAVI. This implies that delirium after cardiothoracic surgery or intervention will be more often present in hospital settings.

Increased knowledge on all levels of patient care is required to prevent and address delirium. Health care systems should be aware about the incidence, potential risk factors and consequences of delirium in octogenarian cardiac patients. This knowledge could provide health care administrators with the opportunity to envision future challenges and to design strategies to prevent delirium and prompt early intervention. The quality of care that our patients receive could be enhanced if health care providers are aware of delirium as a phenomenon that is common and that could lead to potentially serious outcomes.

Identification of patients at risk of developing delirium, tools to prevent its development, recognition and management of its features demand an interdisciplinary approach.[134] This was emphasised in a recent publication supporting multicomponent interventions[68]. Nurses, physicians and physiotherapist are some of several professions in close contact with hospitalized patients and having an important task in the prevention and identification of delirium in cardio surgery departments. Educational programs focusing on delirium could be an important addition to introduction courses for new employees and the information provided in these courses could be complemented with regular reminders about delirium and its features.[134-136] E-learning has also provided a way to increase knowledge [137] that should be further studied. The inclusion of personal with geriatric knowledge into a cardiac surgery ward could also provide valuable contributions that will eventually help to identify and reduce the incidence of delirium in hospital settings.

Older cardiac patients and their families might also benefit from information regarding delirium and its features. Increased knowledge about this phenomenon might help patients and their relatives to rapidly identify acute changes in arousal, attention and cognition that could, otherwise, take longer time for health care professionals to be aware of. This knowledge could also help to diminish the anxiety that patients and relatives might experience when delirium appears.

Special efforts should be made to provide a secure environment that could reduce the development of delirium, independently of treatment. *Precipitating* factors for

delirium have the potential of being modifiable.[37] Correction of sense impairment (use of adequate corrective glasses and hearing aids), adequate environment for easy reorientation (calendars, clocks, daylight) reduction in sleep disturbances, pain control, correct balance between activity and bed rest, and treatment of underlying causes that might cause delirium are some of the multidisciplinary strategies that could be implemented to reduce the development of delirium.[134 135] In a thoracic surgery unit, patients treated with SAVR, having long intubation times, blood transfusion and abnormal albumin levels should be closely followed. For future octogenarians, as important as the type of AS treatment is the identification of modifiable risk factors and actions that could prevent delirium not only after AS treatment but also while waiting to receive SAVR or TAVI.

8. Suggestions for further research

Several issues emerge from our findings. From a macro to an individual level they can be placed as follows:

- Studies with larger populations and longer follow-up times are needed to establish if the rates of first-time readmissions and death, according to delirium status, are comparable with other patient groups.
- Additional prospective studies about delirium following less invasive cardiac procedures are needed. Minimally invasive aortic valve surgery, for example is a new treatment form that should be closely examined in terms of delirium.
- Prevention strategies could help to reduce the incidence of delirium. Whether these strategies lead to less delirium in elderly patients receiving the more invasive SAVR compared to those who are treated with TAVI require further investigation.
- Research is needed to evaluate the severity of delirium after treatment with SAVR and TAVI, and the possible implications that the levels of intensity can have in short and long term outcomes for older patients.
- Increased knowledge in patients and families about delirium, can lead to early identification. This issue should be systematically studied.
- Further research focusing on SF-12, older cardiac patients and delirium should be prioritized.
- The use of patient reported outcomes within delirium have not been enough studied. Strong efforts should be made to increase the knowledge that patient reported outcomes in cardiology have within the field of delirium.

9. References

1. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet 2014;**383**(9920):911-22.
2. Silver G, Traube C, Gerber LM, et al. Pediatric delirium and associated risk factors: a single-center prospective observational study. Pediatr Crit Care Med 2015;**16**(4):303-9.
3. Lipowski ZJ. Delirium: how its concept has developed. Int Psychogeriatr 1991;**3**(2):115-20.
4. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. Nat Rev Neurol 2009;**5**(4):210-20.
5. Forman DE, Rich MW, Alexander KP, et al. Cardiac Care for Older Adults: Time for a New Paradigm. J Am Coll Cardiol 2011;**57**(18):1801-10.
6. Filsoufi F, Rahmanian PB, Castillo JG, et al. Results and predictors of early and late outcomes of coronary artery bypass graft surgery in octogenarians. J Cardiothorac Vasc Anesth 2007;**21**(6):784-92.
7. Scandroglio AM, Finco G, Pieri M, et al. Cardiac surgery in 260 octogenarians: a case series. BMC Anesthesiol 2015;**15**:15.
8. Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: a population-based study. Lancet 2006;**368**(9540):1005-11.
9. Finn M, Green P. Transcatheter aortic valve implantation in the elderly: who to refer? Prog Cardiovasc Dis 2014;**57**(2):215-25.
10. Sawaya F, Liff D, Stewart J, et al. Aortic stenosis: a contemporary review. Am J Med Sci 2012;**343**(6):490-6.
11. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012;**366**(18):1696-704.
12. Haverich A, Wahlers TC, Borger MA, et al. Three-year hemodynamic performance, left ventricular mass regression, and prosthetic-patient mismatch after rapid deployment aortic valve replacement in 287 patients. J Thorac Cardiovasc Surg 2014;**148**(6):2854-60.
13. Leon MB, Smith CR, Mack M, et al. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. N Engl J Med 2010;**363**(17):1597-607.
14. Bakker RC, Osse RJ, Tulen JH, et al. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. Eur J Cardiothorac Surg 2012;**41**(3):544-9.
15. Guenther U, Theuerkauf N, Frommann I, et al. Predisposing and precipitating factors of delirium after cardiac surgery: a prospective observational cohort study. Ann Surg 2013;**257**(6):1160-7.
16. Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. J Card Surg 2012;**27**(4):481-92.
17. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: An Independent Predictor of Functional Decline After Cardiac Surgery. J Am Geriatr Soc 2010;**58**(4):643-49.
18. Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation 2009;**119**(2):229-36.
19. Smulter N, Lingehall HC, Gustafson Y, et al. Delirium after cardiac surgery: incidence and risk factors. Interact Cardiovasc Thorac Surg 2013;**17**(5):790-6.
20. Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults. JAMA Surg 2015:1-7.

21. Koster S, Hensens AG, Schuurmans MJ, et al. Consequences of Delirium After Cardiac Operations. The Annals of Thoracic Surgery 2012;**93**(3):705-11.
22. Krogseth M, Wyller TB, Engedal K, et al. Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients. J Psychosom Res 2014;**76**(1):68-74.
23. Leslie DL, Inouye SK. The importance of delirium: economic and societal costs. J Am Geriatr Soc 2011;**59 Suppl 2**:S241-3.
24. Deksnyte A, Aranauskas R, Budrys V, et al. Delirium: its historical evolution and current interpretation. Eur J Intern Med 2012;**23**(6):483-6.
25. Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. Br J Anaesth 2009;**103 Suppl 1**:i41-46.
26. MacLullich AM, Hall RJ. Who understands delirium? Age Ageing 2011;**40**(4):412-4.
27. Neufeld KJ, Thomas C. Delirium: definition, epidemiology, and diagnosis. J Clin Neurophysiol 2013;**30**(5):438-42.
28. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990;**113**(12):941-8.
29. The DSM-5 criteria, level of arousal and delirium diagnosis: inclusiveness is safer. BMC Med 2014;**12**:141.
30. Inouye SK. Delirium in Older Persons. N Engl J Med 2006;**354**(11):1157-65.
31. Fong TG, Davis D, Growdon ME, et al. The interface between delirium and dementia in elderly adults. Lancet Neurol 2015;**14**(8):823-32.
32. World Health Organization. Depression: definition. 2015. http://www.euro.who.int/en/health-topics/noncommunicable-diseases/pages/news/news/2012/10/depression-in-europe/depression-definition.
33. Downing LJ, Caprio TV, Lyness JM. Geriatric psychiatry review: differential diagnosis and treatment of the 3 D's - delirium, dementia, and depression. Curr Psychiatry Rep 2013;**15**(6):365.
34. Lipowski ZJ. Delirium updated. Compr Psychiatry 1980;**21**(3):190-6.
35. Davis DH, Kreisel SH, Terrera GM, et al. The Epidemiology of Delirium: Challenges and Opportunities for Population Studies. Am J Geriatr Psychiatry 2013.
36. Davis DH, Barnes LE, Stephan BC, et al. The descriptive epidemiology of delirium symptoms in a large population-based cohort study: results from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). BMC Geriatr 2014;**14**:87.
37. Field RR, Wall MH. Delirium: Past, Present, and Future. Semin Cardiothorac Vasc Anesth 2013.
38. World Health Organization. International Classification of Diseases Version 2015. http://apps.who.int/classifications/icd10/browse/2015/en.
39. Wong CL, Holroyd-Leduc J, Simel DL, et al. Does this patient have delirium?: value of bedside instruments. JAMA 2010;**304**(7):779-86.
40. van Velthuijsen EL, Zwakhalen SM, Warnier RM, et al. Psychometric properties and feasibility of instruments for the detection of delirium in older hospitalized patients: a systematic review. Int J Geriatr Psychiatry 2016.
41. Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. Ann Intern Med 2014;**161**(8):554-61.
42. Steis MR, Evans L, Hirschman KB, et al. Screening for delirium using family caregivers: convergent validity of the Family Confusion Assessment Method and interviewer-rated Confusion Assessment Method. J Am Geriatr Soc 2012;**60**(11):2121-6.

43. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001;**286**(21):2703-10.
44. Smith HA, Boyd J, Fuchs DC, et al. Diagnosing delirium in critically ill children: Validity and reliability of the Pediatric Confusion Assessment Method for the Intensive Care Unit. Crit Care Med 2011;**39**(1):150-7.
45. Schuurmans MJ, Shortridge-Baggett LM, Duursma SA. The Delirium Observation Screening Scale: a screening instrument for delirium. Res Theory Nurs Pract 2003;**17**(1):31-50.
46. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. Psychiatry Res 1988;**23**(1):89-97.
47. Sorensen Duppils G, Johansson I. Predictive value and validation of the NEECHAM Confusion Scale using DSM-IV criteria for delirium as gold standard. Int J Older People Nurs 2011;**6**(2):133-42.
48. Bellelli G, Morandi A, Davis DH, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age Ageing 2014;**43**(4):496-502.
49. Krogseth M, Wyller TB, Engedal K, et al. Delirium is an important predictor of incident dementia among elderly hip fracture patients. Dement Geriatr Cogn Disord 2011;**31**(1):63-70.
50. Mangusan RF, Hooper V, Denslow SA, et al. Outcomes associated with postoperative delirium after cardiac surgery. Am J Crit Care 2015;**24**(2):156-63.
51. Pauley E, Lishmanov A, Schumann S, et al. Delirium is a robust predictor of morbidity and mortality among critically ill patients treated in the cardiac intensive care unit. Am Heart J 2015;**170**(1):79-86, 86.e1.
52. Gottesman RF, Grega MA, Bailey MM, et al. Delirium after coronary artery bypass graft surgery and late mortality. Ann Neurol 2010;**67**(3):338-44.
53. Hudetz JA, Iqbal Z, Gandhi SD, et al. Postoperative delirium and short-term cognitive dysfunction occur more frequently in patients undergoing valve surgery with or without coronary artery bypass graft surgery compared with coronary artery bypass graft surgery alone: results of a pilot study. J Cardiothorac Vasc Anesth 2011;**25**(5):811-6.
54. Rudolph JL, Marcantonio ER, Culley DJ, et al. Delirium is associated with early postoperative cognitive dysfunction. Anaesthesia 2008;**63**(9):941-47.
55. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. N Engl J Med 2012;**367**(1):30-9.
56. Sverdlov AL, Ngo DT, Chapman MJ, et al. Pathogenesis of aortic stenosis: not just a matter of wear and tear. Am J Cardiovasc Dis 2011;**1**(2):185-99.
57. Paradis JM, Fried J, Nazif T, et al. Aortic stenosis and coronary artery disease: what do we know? What don't we know? A comprehensive review of the literature with proposed treatment algorithms. Eur Heart J 2014;**35**(31):2069-82.
58. Ramaraj R, Sorrell VL. Degenerative aortic stenosis. BMJ 2008;**336**(7643):550-5.
59. Eveborn GW, Schirmer H, Heggelund G, et al. The evolving epidemiology of valvular aortic stenosis. the Tromso study. Heart 2013;**99**(6):396-400.
60. Osnabrugge RL, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol 2013;**62**(11):1002-12.
61. Otto CM, Prendergast B. Aortic-valve stenosis--from patients at risk to severe valve obstruction. N Engl J Med 2014;**371**(8):744-56.

62. Rashedi N, Otto CM. Aortic Stenosis: Changing Disease Concepts. J Cardiovasc Ultrasound 2015;**23**(2):59-69.
63. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg 2014;**148**(1):e1-e132.
64. Iung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J 2005;**26**(24):2714-20.
65. Martin E, Dagenais F, Voisine P, et al. Surgical aortic valve replacement outcomes in the transcatheter era. J Thorac Cardiovasc Surg 2015.
66. Lindman BR, Bonow RO, Otto CM. Current management of calcific aortic stenosis. Circ Res 2013;**113**(2):223-37.
67. Inouye SK. Predisposing and precipitating factors for delirium in hospitalized older patients. Dement Geriatr Cogn Disord 1999;**10**(5):393-400.
68. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. The Cochrane database of systematic reviews 2016;**3**:Cd005563.
69. Hshieh TT, Yue J, Oh E, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. JAMA internal medicine 2015;**175**(4):512-20.
70. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European journal of cardio-thoracic surgery 2012;**42**(4):1-44.
71. Eide LS, Ranhoff AH, Fridlund B, et al. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. Am J Cardiol 2015;**115**(6):802-9.
72. Nashef SA, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;**16**(1):9-13.
73. Wolters U, Wolf T, Stutzer H, et al. ASA classification and perioperative variables as predictors of postoperative outcome. Br J Anaesth 1996;**77**(2):217-22.
74. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;**12**(3):189-98.
75. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res 2009;**43**(4):411-31.
76. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J 1965;**14**:61-5.
77. Wade DT, Collin C. The Barthel ADL Index: a standard measure of physical disability? Int Disabil Stud 1988;**10**(2):64-7.
78. Roedl KJ, Wilson LS, Fine J. A systematic review and comparison of functional assessments of community-dwelling elderly patients. J Am Assoc Nurse Pract 2015.
79. Collin C, Wade DT, Davies S, et al. The Barthel ADL Index: a reliability study. Int Disabil Stud 1988;**10**(2):61-3.
80. Lincoln NB, Gladman JRF. The Extended Activities of Daily Living scale: a further validation. Disabil Rehabil 1992;**14**(1):41-43.

81. Parker CJ, Gladman JR, Drummond AE, et al. A multicentre randomized controlled trial of leisure therapy and conventional occupational therapy after stroke. TOTAL Study Group. Trial of Occupational Therapy and Leisure. Clin Rehabil 2001;**15**(1):42-52.
82. Ensrud KE, Ewing SK, Taylor BC, et al. Frailty and Risk of Falls, Fracture, and Mortality in Older Women: The Study of Osteoporotic Fractures. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 2007;**62**(7):744-51.
83. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 Frailty Indexes for Prediction of Falls, Disability, Fractures, and Death in Older Women. Arch Intern Med 2008;**168**(4):382-89.
84. Ensrud KE, Ewing SK, Cawthon PM, et al. A Comparison of Frailty Indexes for the Prediction of Falls, Disability, Fractures, and Mortality in Older Men. J Am Geriatr Soc 2009;**57**(3):492-98.
85. Ware JEJ, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. Med Care 1996;**34**(3):220-33.
86. R Core Team. R: A language and environment for statistical computing. 2015. https://www.R-project.org/.
87. Sun J. A non-parametric test for interval-censored failure time data with application to AIDS studies. Stat Med 1996;**15**(13):1387-95.
88. Fay MP, Shaw PA. Exact and Asymptotic Weighted Logrank Tests for Interval Censored Data: The interval R package. Journal of Statistical Software 2010;**36**(2):1-34.
89. Hardy SE, Allore H, Studenski SA. Missing data: a special challenge in aging research. J Am Geriatr Soc 2009;**57**(4):722-9.
90. Seppet E, Paasuke M, Conte M, et al. Ethical aspects of aging research. Biogerontology 2011;**12**(6):491-502.
91. Polit D, Beck CT. Ethics in Nursing Research. Nursing Research Generating and Assessing Evidence for Nursing Practice. Ninth ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012:150-73.
92. Wei LA, Fearing MA, Sternberg EJ, et al. The Confusion Assessment Method: a systematic review of current usage. J Am Geriatr Soc 2008;**56**(5):823-30.
93. Polit D, Beck CT. Rigor and Validity in Quantitative Research. Nursing Research Generating and Assessing Evidence for Nursing Practice. 9th ed. Philadelphia: Wolters Kluwer/Lippincot Williams & Wilkins, 2012:236-56.
94. Song JW, Chung KC. Observational studies: cohort and case-control studies. Plast Reconstr Surg 2010;**126**(6):2234-42.
95. Polit D, Beck CT. Quantitative Research Design. Nursing research Generating and assessing evidence for nursing practice. Philadelphia: Wolters Kluger/Lippincot Williams & Wilkins, 2012:201-35.
96. Ringdal GI, Ringdal K, Juliebo V, et al. Using the Mini-Mental State Examination to screen for delirium in elderly patients with hip fracture. Dement Geriatr Cogn Disord 2011;**32**(6):394-400.
97. Bell SP, Orr NM, Dodson JA, et al. What to Expect From the Evolving Field of Geriatric Cardiology. J Am Coll Cardiol 2015;**66**(11):1286-99.
98. Rich MW, Chyun DA, Skolnick AH, et al. Knowledge Gaps in Cardiovascular Care of the Older Adult Population: A Scientific Statement From the American Heart Association, American College of Cardiology, and American Geriatrics Society. J Am Coll Cardiol 2016.
99. Statistics Norway. Population and population changes. 2016. https://www.ssb.no/statistikkbanken/selectvarval/saveselections.asp.

100. Juliebø V, Bjøro K, Krogseth M, et al. Risk Factors for Preoperative and Postoperative Delirium in Elderly Patients with Hip Fracture. J Am Geriatr Soc 2009;**57**(8):1354-61.
101. Juliebø V, Krogseth M, Skovlund E, et al. Delirium Is Not Associated with Mortality in Elderly Hip Fracture Patients. Dement Geriatr Cogn Disord 2010;**30**(2):112-20.
102. Afonso A, Scurlock C, Reich D, et al. Predictive model for postoperative delirium in cardiac surgical patients. Semin Cardiothorac Vasc Anesth 2010;**14**(3):212-7.
103. Smulter N, Lingehall HC, Gustafson Y, et al. Validation of the Confusion Assessment Method in Detecting Postoperative Delirium in Cardiac Surgery Patients. Am J Crit Care 2015;**24**(6):480-7.
104. Neerland BE, Ahmed M, Watne LO, et al. New consciousness scale for delirium. Tidsskr Nor Laegeforen 2014;**134**(2):150.
105. Tieges Z, McGrath A, Hall RJ, et al. Abnormal level of arousal as a predictor of delirium and inattention: an exploratory study. Am J Geriatr Psychiatry 2013;**21**(12):1244-53.
106. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet 1974;**2**(7872):81-4.
107. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;**166**(10):1338-44.
108. Cronbach LJ, Meehl PE. Construct validity in psychological tests. Psychol Bull 1955;**52**(4):281-302.
109. Polit D, Beck CT. Measurement and Data Quality. Nursing Research Generating and Assessing Evidence for Nursing Practice. 9th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2012:333.
110. Bland JM, Altman DG. Cronbach's alpha. BMJ 1997;**314**(7080):572.
111. Fairbairn TA, Meads DM, Mather AN, et al. Serial change in health-related quality of life over 1 year after transcatheter aortic valve implantation: predictors of health outcomes. J Am Coll Cardiol 2012;**59**(19):1672-80.
112. Ussia GP, Barbanti M, Cammalleri V, et al. Quality-of-life in elderly patients one year after transcatheter aortic valve implantation for severe aortic stenosis. EuroIntervention 2011;**7**(5):573-9.
113. Gladman JR, Lincoln NB, Adams SA. Use of the extended ADL scale with stroke patients. Age Ageing 1993;**22**(6):419-24.
114. Wu CY, Chuang LL, Lin KC, et al. Responsiveness, minimal detectable change, and minimal clinically important difference of the Nottingham Extended Activities of Daily Living Scale in patients with improved performance after stroke rehabilitation. Arch Phys Med Rehabil 2011;**92**(8):1281-7.
115. Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992;**40**(9):922-35.
116. Gandek B, Ware JE, Aaronson NK, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 1998;**51**(11):1171-8.
117. Van Ness PH, Charpentier PA, Ip EH, et al. Gerontologic biostatistics: the statistical challenges of clinical research with older study participants. J Am Geriatr Soc 2010;**58**(7):1386-92.
118. Bekeredjian R, Krumsdorf U, Chorianopoulos E, et al. Usefulness of percutaneous aortic valve implantation to improve quality of life in patients >80 years of age. Am J Cardiol 2010;**106**(12):1777-81.

119. Koster S, Hensens AG, van der Palen J. The Long-Term Cognitive and Functional Outcomes of Postoperative Delirium After Cardiac Surgery. Ann Thorac Surg 2009;**87**(5):1469-74.
120. Maclullich AM, Ferguson KJ, Miller T, et al. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. J Psychosom Res 2008;**65**(3):229-38.
121. Maclullich AM, Anand A, Davis DH, et al. New horizons in the pathogenesis, assessment and management of delirium. Age Ageing 2013;**42**(6):667-74.
122. Watson PL, Ceriana P, Fanfulla F. Delirium: is sleep important? Best Pract Res Clin Anaesthesiol 2012;**26**(3):355-66.
123. Lauretani F, Ceda GP, Maggio M, et al. Capturing side-effect of medication to identify persons at risk of delirium. Aging Clin Exp Res 2010;**22**(5-6):456-8.
124. Mehta S, Cook D, Devlin JW, et al. Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. Crit Care Med 2015;**43**(3):557-66.
125. Brummel NE, Balas MC, Morandi A, et al. Understanding and reducing disability in older adults following critical illness. Crit Care Med 2015;**43**(6):1265-75.
126. Olofsson B, Lundstrom M, Borssen B, et al. Delirium is associated with poor rehabilitation outcome in elderly patients treated for femoral neck fractures. Scand J Caring Sci 2005;**19**(2):119-27.
127. Patel N, Minhas JS, Chung EM. Risk Factors Associated with Cognitive Decline after Cardiac Surgery: A Systematic Review. Cardiovasc Psychiatry Neurol 2015;**2015**:370612.
128. Kortebein P, Symons TB, Ferrando A, et al. Functional impact of 10 days of bed rest in healthy older adults. J Gerontol A Biol Sci Med Sci 2008;**63**(10):1076-81.
129. Parry SM, Puthucheary ZA. The impact of extended bed rest on the musculoskeletal system in the critical care environment. Extreme physiology & medicine 2015;**4**:16.
130. Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). J Am Coll Cardiol 2012;**60**(6):548-58.
131. Parlevliet JL, MacNeil-Vroomen J, Buurman BM, et al. Health-Related Quality of Life at Admission Is Associated with Postdischarge Mortality, Functional Decline, and Institutionalization in Acutely Hospitalized Older Medical Patients. J Am Geriatr Soc 2016;**64**(4):761-8.
132. Instenes I, Gjengedal E, Eide LS, et al. A black mask covered his face…a death-mask. Experiences of delirium in octogenarians after aortic valve replacement. 5th Annual Meeting of the American Delirium Society. Baltimore, USA: Johns Hopkins University, 2015.
133. Maniar HS, Lindman BR, Escallier K, et al. Delirium after surgical and transcatheter aortic valve replacement is associated with increased mortality. J Thorac Cardiovasc Surg 2015.
134. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. J Am Geriatr Soc 2015;**63**(1):142-50.
135. Schwartz AC, Fisher TJ, Greenspan HN, et al. Pharmacologic and nonpharmacologic approaches to the prevention and management of delirium. Int J Psychiatry Med 2016;**51**(2):160-70.
136. Abraha I, Trotta F, Rimland JM, et al. Efficacy of Non-Pharmacological Interventions to Prevent and Treat Delirium in Older Patients: A Systematic Overview. The SENATOR project ONTOP Series. PLoS One 2015;**10**(6):e0123090.

137. Detroyer E, Dobbels F, Debonnaire D, et al. The effect of an interactive delirium e-learning tool on healthcare workers' delirium recognition, knowledge and strain in caring for delirious patients: a pilot pre-test/post-test study. BMC Med Educ 2016;**16**(1):17.

Papers I-III

Paper I

I

Eide LS, Ranhoff AH, Fridlund B, Haaverstad R, Hufthammer KO, Kuiper KK, Nordrehaug JE, Norekval TM, on behalf of the CARDELIR Investigators. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. *Am J Cardiol* 2015;115:802-809.

Comparison of Frequency, Risk Factors, and Time Course of Postoperative Delirium in Octogenarians After Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement

Leslie S.P. Eide, RN, MA[a,*], Anette H. Ranhoff, MD, PhD[a,b], Bengt Fridlund, RNT, PhD[c], Rune Haaverstad, MD, PhD[a,d], Karl Ove Hufthammer, PhD[e], Karel K.J. Kuiper, MD, PhD[d], Jan Erik Nordrehaug, MD, PhD[a,f], and Tone M. Norekvål, RN, PhD[a,d], On behalf of the CARDELIR Investigators

Postoperative delirium (PD) after transcatheter aortic valve implantation (TAVI) remains to be explored. We sought to (1) determine the incidence of PD in octogenarians who underwent TAVI or surgical aortic valve replacement (SAVR), (2) identify its risk factors, and (3) describe possible differences in the onset and course of PD between treatment groups. A prospective cohort study of consecutive patients aged ≥80 years with severe aortic stenosis who underwent elective TAVI or SAVR (N = 143) was conducted. The incidence of PD was assessed for 5 days using the Confusion Assessment Method (CAM). Risk factors for PD were studied with logistic regression. Patients treated with TAVI were older (p ≤0.001), had lower cognitive scores (p = 0.007), and more co-morbidities (p = 0.003). Despite this, significantly fewer (p = 0.013) patients treated with TAVI (44%) experienced PD compared to patients treated with SAVR (66%). Undergoing SAVR (p = 0.02) and having lower cognitive function (p = 0.03) emerged as risk factors for PD, whereas gender, activities of daily living, frailty, atrial fibrillation, and postoperative use of opioids and anxiolytics did not. Patients treated with TAVI and without PD during the first 2 postoperative days were unlikely to experience PD on subsequent days. The onset of PD after SAVR could occur at any time during the postoperative evaluation. In conclusion, SAVR in octogenarian patients with aortic stenosis might be considered as a predisposing factor for PD. Our data also suggest that the onset of PD was more unpredictable after SAVR. **(Am J Cardiol 2015;■:■−■)**

Older patients undergoing cardiac surgery often develop postoperative delirium (PD).[1] Transcatheter aortic valve implantation (TAVI) is offered to patients with aortic stenosis (AS) without reasonable surgical alternatives.[2] Many TAVI patients are 80 years and older.[3] Delirium, an acute and fluctuating change in cognition and attention,[4] is often associated with adverse short- and long-term health implications.[5,6] Although the cause of PD is not fully understood, it is known that impairment in cognition and activities of daily living (ADL), advanced age, co-morbidities, preoperative atrial fibrillation (AF), major surgery, and use of opioids and benzodiazepines are risk factors.[4,7,8] The relation between PD and the patients' status score in The American Society of Anesthesiologists (ASA) Physical Status Classification System, logistic EuroScore,[9] and general anesthesia has been questioned.[10] Frailty[11] is a predictor of adverse health outcomes and death in the elderly,[12] but whether frailty is also a risk factor for PD in octogenarian patients with AS remains to be established. Because TAVI is a less-invasive treatment currently offered to individuals with higher surgical risk, it is warranted to investigate if patients undergoing TAVI are less likely to develop PD. Knowledge about octogenarians undergoing invasive cardiovascular therapy is scarce. Although the incidence of PD after cardiac surgery has been explored,[1,13,14] these studies included younger patients (<80 years) needing coronary artery bypass grafting (CABG) alone or combined with surgical aortic valve replacement (SAVR). Further predisposing factors can be identified by restricting the study population to octogenarians with severe AS who underwent elective treatment. A recent study[15] described the incidence of PD after TAVI, studying only the first postoperative day and including few octogenarians. Therefore, the aims of this study were to (1) determine the incidence of PD in octogenarians with AS requiring SAVR or TAVI, (2) identify risk factors for its development, and (3) describe possible differences in the onset and course of PD in the 2 treatment groups.

[a]Department of Clinical Science, University of Bergen, Bergen, Norway; [b]Kavli Research Center for Geriatrics and Dementia, Haraldsplass Hospital, Bergen, Norway; [c]School for Health Sciences, Jönköping University, Jönköping, Sweden; [d]Department of Heart Disease and [e]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway; and [f]Department of Cardiology, Stavanger University Hospital, Stavanger, Norway. Manuscript received October 8, 2014; revised manuscript received and accepted December 23, 2014.

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See page 7 for disclosure information.

*Corresponding author: Tel: (47) 55 97 30 50; fax: (47) 55 97 58 90.
E-mail address: Leslie.Eide@k2.uib.no (L.S.P. Eide).

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Methods

We conducted an observational, prospective cohort study of consecutive octogenarian patients who had undergone elective TAVI or SAVR in a tertiary university hospital in western Norway. Patients aged 80 years and older previously accepted for TAVI or SAVR were eligible. The study was entitled "Delirium in octogenarians undergoing cardiac surgery or intervention (CARDELIR)", and presence of delirium was the primary outcome. A group of experts in cardiothoracic surgery and invasive cardiology evaluated octogenarian patients with AS and identified those not suitable for SAVR. Exclusion criteria were inability to speak and understand Norwegian and declining consent to participate. Severe AS was defined as aortic valve area <0.6 cm^2/m^2, mean gradient of >40 mm Hg, and maximum jet velocity >4.0 m/s.[16] The main reasons disqualifying patients for standard SAVR included previous CABG, severe respiratory insufficiency, co-morbidities that could compromise recovery, and previous thoracic radiotherapy. From February 2011 to August 2013, 162 octogenarians were admitted for TAVI or SAVR. Of these, 147 fulfilled the eligibility criteria and 144 agreed to participate. One patient withdrew consent before surgery, and 7 were either not responsive or died within 5 days after treatment, leaving us with data for 136 patients (Figures 1 and 2). One patient who underwent TAVI was discharged on the fourth postoperative day.

Assessment of the presence of PD was performed with the Confusion Assessment Method (CAM).[17] CAM is based on operationalized criteria derived from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and assesses 4 features: (1) acute-onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. Delirium is diagnosed when features 1 and 2 are present and either 3 or 4 are displayed.[17] The accuracy of CAM has

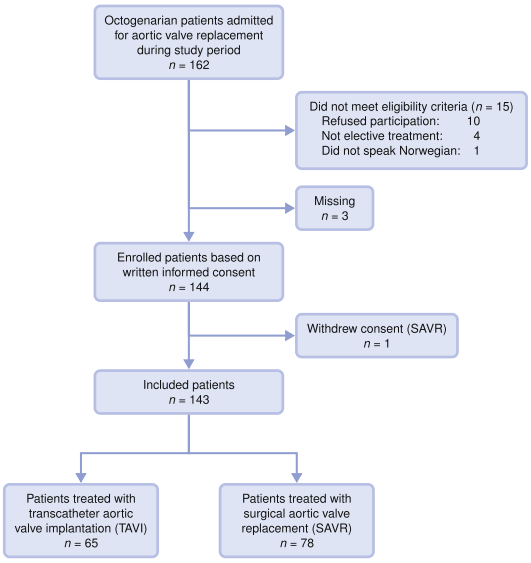

Figure 1. Recruitment flow diagram of octogenarian aortic stenosis patients who underwent TAVI or SAVR.

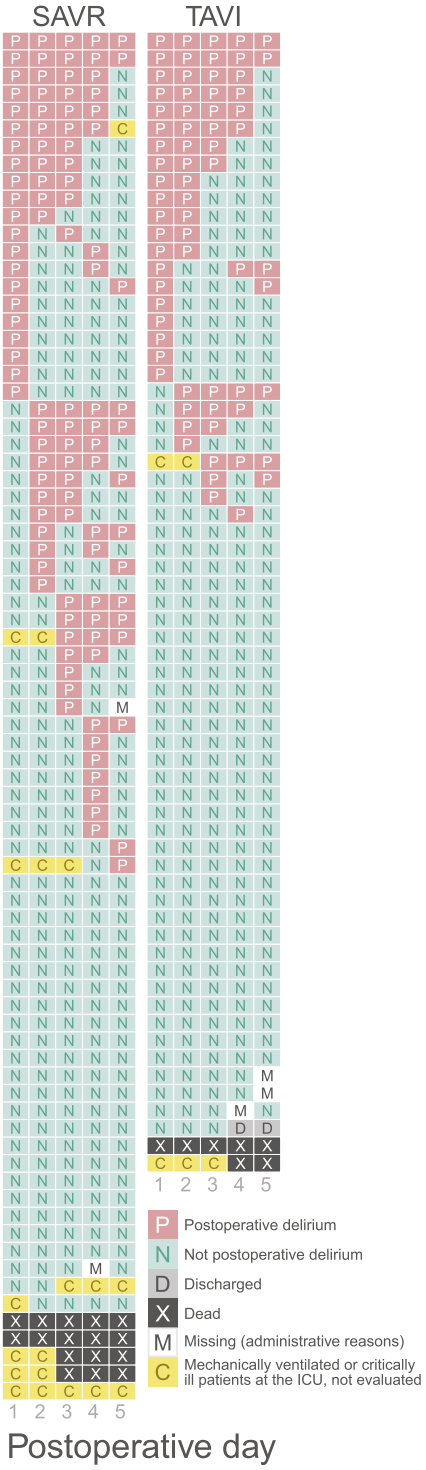

Figure 2. Diagram of TAVI and SAVR patient (N = 143) status, displayed sequentially for each postoperative day.

Table 1
Characteristics of delirious and non-delirious octogenarian patients undergoing Transcatheter Aortic Valve Implantation (TAVI) or Surgical Aortic Valve Replacement (SAVR)

Variables	Total (N=143) Mean or count	±SD or (percent)	Non-delirium n=60 Mean or count	±SD or (percent)	Delirium n=76 Mean or count	±SD or (percent)	Univariate P-value
Age (years)	83.5	±2.7	83.4	±2.8	83.5	±2.7	0.76
Women	81	(57%)	37	(62%)	39	(51%)	0.23
Marital Status							0.68
Married	77	(54%)	31	(52%)	42	(55%)	
Cohabital status							0.21
Live alone	67	(47%)	31	(53%)	31	(41%)	
SOF Frailty Index							0.36
Robust	48	(34%)	19	(32%)	27	(36%)	
Prefrail	39	(27%)	20	(33%)	17	(22%)	
Frail	56	(39%)	21	(35%)	32	(42%)	
MMSE	27.2	±2.9	27.6	±2.3	26.9	±3.3	0.14
MMSE≤27	63	(44%)	24	(40%)	34	(45%)	0.58
BI	18.9	±1.5	19.2	±1.4	18.8	±1.5	0.11
BI≤18	44	(31%)	16	(27%)	26	(34%)	0.34
BMI (Kg/m^2)	25.5	±4.1	25.4	±4.8	25.6	±3.8	0.72
BMI (Kg/m^2) ≤20	13	(9%)	8	(13%)	5	(7%)	0.18
Charlson Comorbidity Index	2.1	±1.2	2.1	±1.2	2.1	±1.2	0.91
Logistic EuroScore*	14.0	(9.2%)	15.4	(9.3%)	12.9	(9.1%)	0.11
NYHA function class							0.33
I-II	48	(38%)	19	(34%)	28	(42%)	
III-IV	80	(62%)	37	(66%)	38	(58%)	
Left ventricle ejection fraction (%)	56.4	±10.3	56.4	±11.1	56.6	±9.7	0.89
Max aorta gradient (mmHg)	79.3	±24.9	78.6	±25.5	79.4	±24.1	0.85
Mean aorta gradient (mmHg)	48.2	±16.6	48.0	±16.5	48.1	±16.5	0.99
Aortic valve area (cm^2/m^2)	0.4	±0.2	0.4	±0.1	0.4	±0.2	0.30
Preoperative atrial fibrillation	39	(27%)	14	(23%)	25	(33%)	0.22
Hemoglobin (g/dL)	13.1	±1.4	13.0	±1.3	13.2	±1.5	0.25
Creatinine concentration, (μmol)	91.3	±27.8	88.6	±26.7	93.2	±26.9	0.32
GFR, (mL/min/1.73m^2)	54.8	±9.0	55.6	±8.6	54.5	±8.8	0.47
Albumin, (g/L)	44.0	±3.0	43.7	±2.9	44.2	±2.8	0.32
Perioperative variables							
Type treatment: TAVI	65	(45%)	35	(58%)	25	(42%)	0.01
ASA-Classification							0.28
III	120	(84%)	48	(80%)	66	(87%)	
IV	23	(16%)	12	(20%)	10	(13%)	
Anesthesia time (hours)	3.9	±1.6	3.4	±1.3	4.1	±1.5	0.005
Type of anesthesia (sedation)	34	(24%)	20	(33%)	13	(17%)	0.03
Preoperative medication							0.02
Oxazepam (Sobril)	51	(36%)	29	(49%)	21	(28%)	
Morfin scopolamine	77	(55%)	24	(41%)	21	(28%)	
None	12	(9%)	6	(10%)	5	(7%)	
Blood transfusion	29	(20%)	8	(13%)	17	(22%)	0.18
Hypotension	75	(52%)	29	(48%)	41	(54%)	0.52
Tachycardia	8	(6%)	4	(7%)	4	(5%)	0.73
Hypoxia†	6	(4%)	0	(0%)	5	(7%)	0.07
Post-operative medication							
Opioids required	117	(83%)	45	(76%)	67	(88%)	0.07
Loop diuretics required	127	(89%)	50	(83%)	73	(96%)	0.01

ASA = American Society of Anesthesiologists; BI = Barthel Index; BMI = Body Mass Index; MMSE = Mini Mental Status Examination; NYHA function class = New York Heart Association Function Classification; SOF = Study of Osteoporotic Fractures; TAVI = transcatheter aortic valve implantation.
* P-value based on log-transformed values.
† Fisher's exact test.

been confirmed in several studies.[18] We studied this primary outcome as the presence of PD on daily basis and as the presence of PD in a period of 5 days after AS treatment.

ADL function, atrial fibrillation, cognitive function, co-morbidity, and postoperative use of opioids and anxiolytics as potential risk factors for PD were selected on the basis of review of reports[4,7,18,19] and clinical experience. Treatment with TAVI and baseline frailty were also included in the regression analysis. We assessed patient's self-care abilities with the Barthel Index[20] which evaluates

Table 2
Characteristics of octogenarian patients undergoing Transcatheter Aortic Valve Implantation (TAVI) or Surgical Aortic Valve Replacement (SAVR)

Variables	Total (N=143) Mean or count	±SD or (percent)	TAVI n=65 Mean or count	±SD or (percent)	SAVR n=78 Mean or count	±SD or (percent)	Univariate p-value
Age (years)	83.5	±2.7	84.8	±2.8	82.4	±2.0	<0.001
Female	81	(57%)	41	(63%)	40	(51%)	0.16
Marital Status							0.18
Married	77	(54%)	31	(48%)	46	(59%)	
Cohabital status							0.13
Live alone	67	(47%)	35	(54%)	32	(41%)	
SOF- Frailty Index							0.11
Robust	48	(34%)	16	(25%)	32	(41%)	
Prefrail	39	(27%)	21	(32%)	18	(23%)	
Frail	56	(27%)	28	(43%)	28	(36%)	
MMSE	27.2	±2.9	26.5	±3.1	27.8	±2.6	0.007
MMSE≤27	63	(44%)	36	(55%)	27	(35%)	0.01
BI mean	18.9	±1.5	18.8	±1.5	19.0	±1.5	0.37
BI≤18	44	(31%)	23	(35%)	21	(27%)	0.27
BMI (Kg/m^2)	25.5	±4.1	25.0	±4.4	25.9	±3.9	0.20
BMI≤20	13	(9%)	9	(14%)	4	(5%)	0.07
Charlson Comorbidity index	2.1	±1.2	2.5	±1.3	1.8	±1.0	<0.001
Logistic EuroScore*	14.0	±9.2	19.6	±10.6	9.4	±3.6	<0.001
NYHA function Class							<0.001
I-II	48	(38%)	11	(20%)	37	(51%)	
III-IV	80	(62%)	45	(80%)	35	(49%)	
Left ventricle ejection fraction (%)	56.4	±10.3	55.9	±10.1	56.8	±10.5	0.59
Max aorta gradient (mmHg)	79.3	±24.9	74.4	±23.8	83.6	±25.2	0.03
Mean aorta gradient (mmHg)	48.2	±16.6	45.6	±16.3	50.6	±16.7	0.08
Aortic valve area (cm^2/m^2)	0.4	±0.2	0.4	±0.1	0.4	±0.2	0.64
Preoperative atrial fibrillation	39	(27%)	22	(34%)	17	(22%)	0.11
Hemoglobin (g/dL)	13.1	±1.4	12.7	±1.6	13.5	±0.12	0.001
Creatinine concentration (μmol)	91.3	±27.8	93.9	±28.1	89.2	±27.5	0.32
Albumin, (g/L)	44.0	±3.0	43.5	±3.0	44.4	±2.9	0.07
Perioperative variables							
ASA Classification							<0.001
III	120	(84%)	44	(68%)	76	(97%)	
IV	23	(16%)	21	(32%)	2	(3%)	
Anesthesia time (hours)	3.9	±1.6	2.8	±0.7	4.9	±1.5	<0.001
Preoperative medication							<0.001
Oxazepam (Sobril)	51	(36%)	50	(81%)	1	(1%)	
Morfin scopolamine	77	(55%)	0	(0%)	77	(99%)	
None	12	(9%)	12	(19%)	0	(0%)	
Blood transfusion	29	(20%)	6	(9%)	23	(29%)	0.003
Tachycardia	8	(6%)	4	(6%)	4	(5%)	0.79
Hypoxia†	6	(4%)	5	(8%)	1	(1%)	0.09
Post-operative medication							
Opioids required	117	(83%)	40	(62%)	77	(100%)	<0.001
Loop diuretics required	127	(89%)	51	(78%)	76	(99%)	<0.001

ASA = American Society of Anesthesiologists Classification; BI = Barthel Index; BMI = Body Mass Index; MMSE = Mini Mental Status Examination; NYHA Function Class = New York Heart Association Function Classification; SOF = Study of Osteoporotic Fractures.

* P-value based on log-transformed values.

† Fisher's exact test.

ADL in 10 basic areas. This index is reliable and valid[21] and provides a score from 0 to 20, with 19 or more indicating functional independence.[20] General cognitive functioning was measured with the Mini-Mental State Examination (MMSE), a 20-item instrument, with maximum score of 30 points.[22] Co-morbidities were quantified using the Charlson comorbidity index. It predicts mortality in patients with co-morbid disorders, assigning a score of 1, 2, 3, or 6, summed to predict mortality.[23] Several studies have demonstrated the reliability and validity of the index.[23] Frailty was defined using the Study of Osteoporotic Fractures (SOF) Frailty Index.[12] It identifies subjects at risk of adverse health outcomes on the basis of weight loss, inability to rise from a chair 5 times without using his/her arms, and reduced energy level.[24] The SOF Frailty Index classifies patients as robust, prefrail, or frail. Its psychometrical properties have been confirmed.[12,24] We used patients' medical records to identify the presence of preoperative atrial fibrillation, as assessed by a cardiologist, and to recognize postoperative use of opioids and anxiolytics.

Table 3
Logistic regression model of risk factors for delirium in octogenarian aortic stenosis patients (n=135)

	Unadjusted			Adjusted		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	*P*-value
Gender			0.26			0.60
Male (ref.)	1	–		1	–	
Female	0.67	0.34–1.34		0.82	0.38–1.76	
ADL score	0.82	0.63–1.05	0.12	0.81	0.60–1.07	0.14
Atrial fibrillation	1.58	0.74–3.46	0.24	1.84	0.79–4.49	
Comorbidity score	1.02	0.76–1.36	0.92	1.08	0.78–1.51	0.64
Frailty			0.54			0.59
Robust (ref.)	1	–		1	–	
Prefrail/frail	0.80	0.38–1.64		0.80	0.35–1.81	
MMS score	0.91	0.79–1.02	0.11	0.85	0.73–0.98	0.03
Postoperative use of opioids	2.32	0.94-5.99	0.07	1.61	0.52–5.17	0.41
Postoperative use of anxiolytics	0.97	0.47-2.03	0.94	1.09	0.49–2.45	0.83
Treatment TAVI	0.43	0.21–0.85	0.02	0.34	0.14–0.82	0.02

ADL = Activities of Daily Living; MMSE = Mini Mental Status Examination; SOF = Study of Osteoporotic Fractures; TAVI = transcatheter aortic valve implantation.

Patients were approached for consent 1 day before intervention, and preoperative data were gathered that day. Demographic and clinical information was collected by interview or from medical records, as appropriate. ADL and cognitive function were measured at baseline, and data needed to score the SOF Frailty Index were collected at this time. Nursing staff were instructed about PD features regularly as reminders and were encouraged to report PD symptoms during every shift. However, research assistants trained to use the CAM were responsible for assessing PD after visiting the patients daily at noon, from postoperative days 1 to 5, including weekends. Patients were assessed for inattention, disorganized thinking, altered level of consciousness, and disorientation. Medical, nursing, and physiotherapist' reports from the previous 24 hours and results from meetings with health professionals in charge of the study patients were also considered when CAM was scored.

The study was approved by the Regional Committee for Ethics in Medical Research (REK Vest 2010/2936-6) and conducted in accordance with the Declaration of Helsinki. Patients were invited to participate in the study after receiving oral and written information. Registered nurses with extensive experience with geriatric and cardiac patients, but not involved in the care of the patients, were responsible for enrollment and data collection. Because of patients' advanced age and the nature of the procedure, we were particularly alert for verbal and nonverbal signs indicating displeasure or exhaustion during data collection.

Previous research on cardiac surgery populations and the primary outcome guided our power analysis. We determined a priori that 100 patients who underwent SAVR and 40 who underwent TAVI would be required to reach a statistical power of 80%, which would allow us to detect a reliable risk difference, given that 31% of patients in the SAVR group[25] and 10% in the TAVI group actually developed delirium. Because the incidence of PD after TAVI had not been previously studied, the last percent was estimated. Two years after the start of the study, fewer eligible patients than we initially anticipated received SAVR. A new power analysis showed that including 84 patients who underwent SAVR and 65 patients who underwent TAVI would give a power of 89%.

Data are presented as counts and percentages or means and standard deviations. Differences between groups were tested with the chi-square or Fisher's exact tests for categorical variables and the Welch t test (i.e., a t test not assuming equal variances) for continuous variables. Logistic regression was used to determine the impact of proposed risk factors on PD. A log-rank test for interval-censored data[26,27] was used to study differences in the time to onset of delirium. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY), and R 3.0.2. (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed p value of $\leq$0.05 was considered statistically significant.

Results

Characteristics of the participants, stratified by the presence of delirium, are presented in Table 1. Table 2 summarizes differences between patients in the TAVI and SAVR groups. TAVI was performed in 46% of the patients. General anesthesia was used in 48% of patients who underwent TAVI and in all patients who underwent SAVR ($p \leq 0.001$). The mean length of stay in patients who underwent TAVI was 8.8 days (SD 6.0) versus 7.9 days (SD 4.7) after SAVR. The relatively long length of stay after TAVI was partly related to the general condition of the patients and to the risk of postoperative AV blockage and pacemaker requirement up to a week after CoreValve implantation.

New cases of PD occurred at least once in 56% of octogenarians during the 5-day study period. Of patients in the TAVI group, 44% developed PD compared to 66% of patients in the SAVR group ($p = 0.01$). Of the TAVI patients developing PD, 54% received general anesthesia ($p = 0.40$). The logistic regression model revealed that PD was associated with cognitive function and treatment type

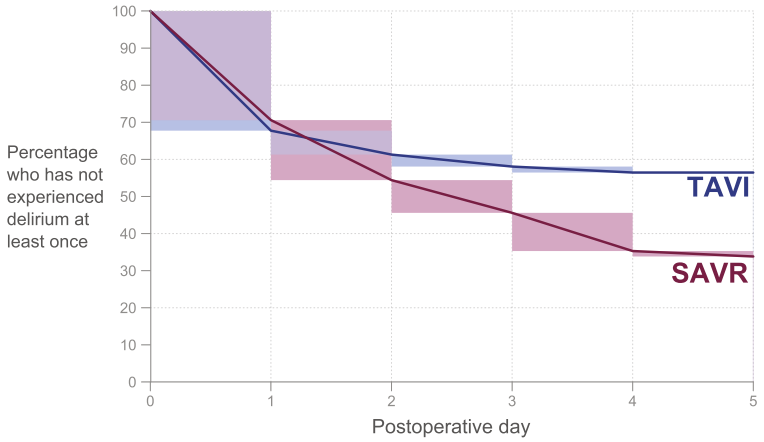

Figure 3. Kaplan–Meier survival curves showing time to onset of PD for TAVI and SAVR. Patients who died or became critically ill are excluded. Patients with data missing for administrative reasons or who were discharged were censored for the remaining duration of their hospital stay (n = 130).

(Table 3). The average number of days with PD for patients observed for all 5 days did not differ between patients treated with TAVI and SAVR (1.1 vs 1.5, p = 0.20), but the course of PD did. Figure 2 shows that patients in the TAVI group, who did not develop PD during the first postoperative day, usually did not experience PD in the succeeding 4 days. Seventy-four percent of patients in the TAVI group experienced PD on the first day, whereas only 46% of patients in the SAVR group did (Figure 2). Figure 3 shows PD-free survival for the treatment groups. The groups differed with respect to time to the first onset of PD (exact log-rank test for interval-censored data; p = 0.03).

Discussion

To the best of our knowledge, this is the first study to systematically explore factors associated with PD during 5 consecutive postoperative days in octogenarian patients needing TAVI or SAVR. The incidence of PD was significantly higher in octogenarians with reduced cognitive function and in those treated with SAVR. Differences in PD onset were also found between treatment groups.

The incidence of PD after cardiac surgery is high.[4,14] In general, patients accepted for TAVI have a higher surgical risk than patients receiving SAVR.[2,3] In our sample, patients who underwent TAVI were older, had lower MMSE scores, greater comorbidity scores, higher logistic EuroScore, and were classified in more-severe ASA categories. Despite this, 44% of patients scheduled for TAVI experienced PD compared to 66% of patients in the SAVR group, suggesting that TAVI is better tolerated with regards to PD.

Cognitive and ADL impairment are well-established risk factors for PD in cardiac and noncardiac patients,[4,19] and our analyses provide additional evidence linking lower cognitive function to higher risk for PD. Although entry of ADL function in the regression model did not reach significance, a ceiling effect may have been present and our results must be interpreted with caution. The relatively good cognitive function of our cohort is similar to other cardiac populations in which PD has been studied.[6,13] Yet, it must be taken into account that in recent years, the accuracy of MMSE in diagnosing mild cognitive impairment has been questioned.[28]

In our study, co-morbidity, ASA score, and EuroScore were not associated with PD, according to univariate and multivariate analysis. However, because of 90% of our patients had 1 or more co-morbidities, we had insufficient power to detect a difference between patients lacking and those having some co-morbidities. General anesthesia, sternotomy, and extracorporeal circulation are procedures related to SAVR that might put excessive burden on octogenarian patients. Sedation might moderate the adverse effects of general anesthesia that could lead to PD.[10] Univariate analysis showed a relation between PD and anesthesia type (general vs sedation). However, when controlling for other variables, this relation disappeared.

Stress and inflammation responses are associated with PD.[4] Lower activation of stress hormones might be present in patients who underwent TAVI as less tissue damage and inflammation is associated with the procedure. The SAVR procedure involved full sternotomy. Hence, we were unable to determine whether less-invasive procedures such as ministernotomy or minithoracotomy would influence the incidence or onset of PD in patients who underwent SAVR. It is still unknown if the new sutureless valve prostheses designed for fast deployment in the aortic root might reduce postoperative complications such as PD.

Appropriate pain management and mobilization can prevent PD after surgery; still, opioids have been associated with the onset of PD.[19] We did not find any statistical association between opioids and PD after adjusting for other risk factors. The postoperative use of anxiolytics was also entered in the regression model without reaching statistically significant values. Yet, the confidence intervals of these 2 variables are wide and results should be interpreted with caution. Our data revealed that patients who underwent TAVI received less amounts of postoperative opioids and paracetamol and earlier mobilization. It can be speculated that the gentler TAVI leads to lower postoperative pain and

easier mobilization. Postoperative routines in our hospital encourage patients to leave bed the same day TAVI is performed, and by the first postoperative day, patients who underwent TAVI are ambulating the cardiology ward. Mobilization after SAVR starts the day after surgery but is restricted by the use of electrocardiography devices, pulmonary tubes, temporal pacemaker, urine catheters, and intravenous lines during the first 48 hours, supporting evidence that physical restraints might precipitate PD.[4]

Delirium and frailty have been proposed to be different representations of the inability to compensate for stressors.[29] Additionally, the relation between frailty and delirium has been questioned.[29] Using the SOF Frailty Index, this study is one of the first to assess preoperative frailty as a risk factor for PD. The logistic regression analysis showed that frailty plays a limited role as a predictor of PD in octogenarian patients with AS.

PD developed at different times in the 2 groups of patients. During the first postoperative day, PD occurred in several patients regardless of the treatment (Figure 2). Differences emerged from the second postoperative day. Our data indicate that patients in the TAVI group who did not develop PD during the first postoperative day were unlikely to develop PD thereafter. In patients treated with SAVR, the onset of PD could occur at any time during the 5 days of assessment (Figure 2).

The strengths of this study lie in its prospective design and use of valid and reliable instruments. PD was assessed by trained research assistants who performed the assessments for 5 days, including weekends. Additionally, our hospital is 1 of 5 centers in Norway performing TAVI, and in western Norway all TAVI and SAVR procedures are performed in our hospital setting. This allowed us to study a representative group of octogenarian patients with AS from this part of the country. Few patients (6%) refused to participate, and <2% were not identified before treatment. Thus, these factors argue for generalizability. The high incidence of PD (56%) in our study can be explained by the robust method used to evaluate PD, which included a highly recommended tool used to identify delirium,[18] bedside contact with eligible patients, review of medical, nursing, and physiotherapist reports written 24 hours before assessment with CAM, and direct contact with nurses during the morning shift.

Limitations of the study include a nonrandomized treatment location. Yet, as pointed out in the PARTNER trial,[3] a randomized study to compare treatment modalities was not possible because TAVI and SAVR were used to treat distinctly different patient populations. Body Mass Index, sensory impairment, ASA, and EuroScore are important variables that could not be included in the logistic regression because of our modest sample size. This limitation warrants bigger studies of octogenarians patients with AS who underwent AVR. The lack of preoperative and postoperative information regarding brain pathology is also a limitation. However, important information about brain reserve and vulnerability for delirium comes from assessment of patients' preoperative cognitive function using the MMSE. Nevertheless, it is possible that other cognitive measurements should have complemented our data. Preoperative organic cerebral disease, precerebral vascular lesions, and thoracic aortic atherosclerosis may all be important risk factors for postoperative cerebral dysfunction. However, as cerebral computed tomography or magnetic resonance imaging or imaging of the thoracic aorta or precerebral vascularity was not part of the study protocol, we were unable to conduct any further evaluation of organic risk factors related to general atherosclerosis or embolic risk. The relatively good cognitive and ADL function of our patients might indicate the presence of patient selection bias before referral to our hospital. This can limit the generalizability of our results to populations living in areas where selection criteria for AS intervention are less strict. Additionally, our study did not evaluate the severity of PD.

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Disclosures

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1. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, Khuri SF, Lipsitz LA, Ramlawi B, Levitsky S, Marcantonio ER. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation* 2009;119:229−236.
2. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB; Investigators PT. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med* 2012;366:1696−1704.
3. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597−1607.
4. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911−922.
5. Rudolph JL, Marcantonio ER, Culley DJ, Silverstein JH, Rasmussen LS, Crosby GJ, Inouye SK. Delirium is associated with early postoperative cognitive dysfunction. *Anaesthesia* 2008;63:941−947.
6. Rudolph JL, Inouye SK, Jones RN, Yang FM, Fong TG, Levkoff SE, Marcantonio ER. Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc* 2010;58:643−649.
7. Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Risk factors of delirium after cardiac surgery: a systematic review. *Eur J Cardiovasc Nurs* 2011;10:197−204.
8. Lin Y, Chen J, Wang Z. Meta-analysis of factors which influence delirium following cardiac surgery. *J Card Surg* 2012;27:481−492.
9. Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Prediction of delirium after cardiac surgery and the use of a risk checklist. *Eur J Cardiovasc Nur* 2013;12:284−292.
10. Strom C, Rasmussen LS, Sieber FE. Should general anaesthesia be avoided in the elderly? *Anaesthesia* 2014;69(Suppl 1):35−44.
11. Fried LP, Xue QL, Cappola AR, Ferrucci L, Chaves P, Varadhan R, Guralnik JM, Leng SX, Semba RD, Walston JD, Blaum CS, Bandeen-Roche K. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci* 2009;64:1049−1057.
12. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA, Tracy JK, Hochberg MC, Rodondi N, Cawthon PM; Group ftSoOFR. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *J Gerontol A Biol Sci Med Sci* 2007;62:744−751.

13. Bakker RC, Osse RJ, Tulen JH, Kappetein AP, Bogers AJ. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. *Eur J Cardio-thorac* 2012;41:544−549.
14. Smulter N, Lingehall HC, Gustafson Y, Olofsson B, Engstrom KG. Delirium after cardiac surgery: incidence and risk factors. *Interact Cardiovasc Thorac Surg* 2013;17:790−796.
15. Egerod I, Nielsen S, Lisby KH, Darmer MR, Pedersen PU. Immediate post-operative responses to transcatheter aortic valve implantation: an observational study. *Eur J Cardiovasc Nurs* 2014. http://dx.doi.org/10.1177/1474515114525521; E-pub ahead of print February 18, 2014.
16. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardio-thorac* 2012;42:1−44.
17. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941−948.
18. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. *JAMA* 2010;304:779−786.
19. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. *Anesth Analg* 2011;112:1202−1211.
20. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965;14:61−65.
21. Collin C, Wade DT, Davies S, Horne V. The Barthel ADL Index: a reliability study. *Int Disabil Stud* 1988;10:61−63.
22. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189−198.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373−383.
24. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Cawthon PM, Stone KL, Hillier TA, Cauley JA, Hochberg MC, Rodondi N, Tracy JK, Cummings SR; for the Study of Osteoporotic Fractures Research Group. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. *Arch Intern Med* 2008;168:382−389.
25. Rolfson DB, McElhaney JE, Rockwood K, Finnegan BA, Entwistle LM, Wong JF, Suarez-Almazor ME. Incidence and risk factors for delirium and other adverse outcomes in older adults after coronary artery bypass graft surgery. *Can J Cardiol* 1999;15:771−776.
26. Sun J. A non-parametric test for interval-censored failure time data with application to AIDS studies. *Stat Med* 1996;15:1387−1395.
27. Fay MP, Shaw PA. Exact and asymptotic weighted logrank tests for interval censored data: the interval R package. *J Stat Softw* 2010;36:1−34.
28. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. *J Psychiatr Res* 2009;43:411−431.
29. Quinlan N, Marcantonio ER, Inouye SK, Gill TM, Kamholz B, Rudolph JL. Vulnerability: the crossroads of frailty and delirium. *J Am Geriatr Soc* 2011;59(Suppl 2):S262−S268.

Paper II

Eide LS, Ranhoff AH, Fridlund B, Haaverstad R, Hufthammer KO, Kuiper KK, Nordrehaug JE, Norekval TM. Delirium as a Predictor of Physical and Cognitive Function in Individuals Aged 80 and Older After Transcatheter Aortic Valve Implantation or Surgical Aortic Valve Replacement. *J Am Geriatr Soc* 2016 Apr 23.DOI:10.1111/jgs.14165. [Epub ahead of print]

II

Delirium as a Predictor of Physical and Cognitive Function in Individuals Aged 80 and Older After Transcatheter Aortic Valve Implantation or Surgical Aortic Valve Replacement

Leslie S. P. Eide, MA, Anette H. Ranhoff, PhD,*† Bengt Fridlund, PhD,‡§ Rune Haaverstad, PhD,*§ Karl Ove Hufthammer, PhD,‖ Karel K. J. Kuiper, PhD,§ Jan E. Nordrehaug, PhD,*# and Tone M. Norekvål, PhD,*§ on behalf of the Delirium in Octogenarians Undergoing Cardiac Surgery or Intervention–CARDELIR Investigators*

OBJECTIVES: To determine how development of delirium after surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) could predict activity of daily living (ADL) and instrumental ADLs (IADL) disability, cognitive function, and self-reported health in individuals aged 80 and older.

DESIGN: Prospective cohort study.

SETTING: Tertiary university hospital.

PARTICIPANTS: Individuals aged 80 and older undergoing elective SAVR or TAVI (N = 136).

MEASUREMENTS: Delirium was assessed for 5 days using the Confusion Assessment Method. The Barthel Index, Nottingham Extended ADL Scale, and SF-12 were used to determine ADL and IADL ability and self-reported health at baseline and 1- and 6-month follow-up. Cognition was assessed using the Mini-Mental State Examination at baseline and 6-month follow-up.

RESULTS: Participants had lower IADL scores 1 month after SAVR than at baseline (baseline 58, 1 month: delirium 42, no delirium 50, $P \leq .02$), but scores had returned to baseline levels at 6 months. The Medical Outcomes Study 12-item Short-Form Health Survey (SF-12) Physical Component Summary (PCS) score was higher at 6-month follow-up (48) than at baseline (39), especially in participants who did not develop delirium ($P < .001$). No differences in other outcomes were found. Regression models suggest that delirium may help predict IADL disability 1 month after baseline ($P \leq .07$) but does not predict large differences in ADL disability, cognitive function, or SF-12-scores. Individuals who underwent TAVI and developed delirium had lower ADL (baseline 19, 1-month 16, $P < .001$) and IADL (baseline 49, 1-month 40, $P = .003$) scores at 1-month follow-up. SF-12 PCS score (baseline 30) increased from baseline to 1- (35, $P = .04$) and 6- (35, $P = .02$) month follow-up in individuals who underwent TAVI and did not develop delirium. Delirium after TAVI predicted greater ADL and IADL disability at 1-month but not at 6-month follow-up.

CONCLUSION: Individuals who develop delirium after SAVR and TAVI have poorer short-term IADL function but do not seem to have long-term reductions in physical, mental, or self-reported health. **J Am Geriatr Soc 2016.**

Key words: aortic stenosis; delirium; self-reported health status; TAVI

A high incidence of delirium occurs in elderly adults undergoing cardiac surgery.[1–3] The prevalence of aortic stenosis is greater in elderly adults than in the general population.[4] Even though symptomatic aortic stenosis has high mortality when untreated,[5] the risk of performing surgical aortic valve replacement (SAVR) might be too high in frail elderly adults with several comorbidities.[6] Transcatheter aortic valve implantation (TAVI) is an option for individuals for whom SAVR is unsuitable.[6,7]

Functional and cognitive decline have been reported in individuals experiencing delirium after hip fracture[8] and cardiac surgery.[9–11] For aortic stenosis, current knowledge about delirium is mostly based on individuals treated with SAVR and those younger than 80.[9,11] Individuals aged 80 and older undergoing TAVI have a lower incidence of delirium than those undergoing SAVR,[12] although it is unclear whether delirium after the less-invasive TAVI leads to equally adverse

From the *Department of Clinical Science, University of Bergen; †Kavli Research Center for Geriatrics and Dementia, Haraldsplass Hospital, Bergen, Norway; ‡School of Health and Welfare, Jönköping University, Jönköping, Sweden; §Department of Heart Disease, Haukeland University Hospital; ‖Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway; and #Department of Cardiology, Stavanger University Hospital, Stavanger, Norway.

Address correspondence to Leslie S. P. Eide, Department of Clinical Science, University of Bergen, Laboratory building, 8th floor, Jonas Lies veg 87, 5021 Bergen, Norway. E-mail: Leslie.Eide@k2.uib.no

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effects in terms of activities of daily living (ADLs), instrumental activities of daily living (IADLs), and cognitive function when assessed 1 and 6 months after treatment.

Perception of health is important when longevity is not a dominant priority.[13] Measurement of self-reported health status in elderly populations has been suggested as being important,[14] and quality of life after TAVI has been studied to some extent,[15,16] but little is known about how delirium affects the self-reported health of individuals aged 80 and older after aortic valve implantation. The aim of this study was therefore to determine how delirium could predict ADL and IADL function, cognitive function, and self-reported health status in individuals aged 80 and older 1 and 6 months after treatment with SAVR or TAVI.

METHODS

This was a prospective cohort study of individuals consecutively undergoing elective TAVI or SAVR in a tertiary hospital in western Norway.

Study population

Individuals were recruited into the larger Delirium in Octogenarians Undergoing Cardiac Surgery or Intervention (CARDELIR) study.[12] Inclusion criteria were aged 80 and older, severe aortic stenosis, and elective treatment with TAVI or SAVR. Exclusion criteria were inability to speak and understand Norwegian or declined consent to participate. According to guidelines on management of valvular heart diseases, severe aortic stenosis is defined as aortic valve area of less than 0.6 cm^2/m^2, mean gradient of greater than 40 mmHg, and maximum jet velocity of greater than 4.0 m/s.[17] A specialist heart team comprising cardiothoracic surgeons and invasive cardiologists identified individuals who were unsuitable for SAVR. Previous coronary artery bypass graft, severe respiratory insufficiency, comorbidities that could compromise recovery, calcified ascending aorta, and prior thoracic radiotherapy were the main reasons for being ineligible for treatment with SAVR.

From February 2011 until August 2013, 162 individuals aged 80 and older were treated with SAVR or TAVI. Of these, 15 failed to fulfill the inclusion criteria. The remaining 147 received study information, and 144 of these agreed to participate, although data analyzed for this study included those from only 136 individuals, because one withdrew consent before treatment, and delirium was not established in seven because they were nonresponsive or had died. An individual was classified as having experienced delirium if delirium was identified on at least 1 of the 5 postoperative days. Individuals who were not tested for delirium because of administrative or other reasons were classified according to delirium status for the days that they were tested.

Measurements

Delirium

The Confusion Assessment Method (CAM), which identifies delirium based on acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness, was used to assess delirium.[18] Delirium is diagnosed when the first two features and the third or the fourth are present.[18] The psychometric properties of the CAM are good.[19]

Physical Function

Activities of Daily Living

The Barthel Index, which evaluates self-care abilities in feeding, bathing, grooming, dressing, bowel, bladder, toilet use, transferring, walking, and using stairs, was used as one measure of activity level. The maximum score is 20, and a score of at least 19 indicates functional independence.[20] When administered in an interview, the Barthel Index has sufficient psychometric properties to provide a valid measure ADLs.[21]

Instrumental Activities of Daily Living

The Nottingham Extended Activities of Daily Living Scale uses 22 items to evaluate an individual's ability to perform complex levels of functioning, such as cooking, household management, and use of public transportation. Each item is scored from 0 to 3, and the items are summed, with 66 being the highest score. Higher scores indicate greater levels of independence.[22] This index is reliable and valid.[23]

Cognitive Function

Cognitive function was assessed using the Mini-Mental State Examination (MMSE),[24] which has a range of 0–30 points, with 30 indicating the best cognition. In the Norwegian version, a score of 27 or less indicates poor cognitive function. The MMSE is a valid instrument for assessing global cognitive function.[24]

Self-Reported Health Status

Medical Outcomes Study 12-Item Short-Form Health Survey

The Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12) was used to measure subjective general health.[25] It is a generic, self-assessed health index based on 12 items and is combined into two summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Scores range from 0 to 100, with higher scores indicating better self-reported health status. The psychometric properties of the SF-12 are good.[25]

Other Study Variables

Comorbidity

The Charlson Comorbidity Index, which predicts mortality in individuals with comorbid disorders, was used to quantify comorbidities.[26] It has been shown to have good psychometric properties.[26,27]

Cardiac Operative Risk

The Logistic European System for Cardiac Operative Risk Evaluation I (Logistic EuroSCORE I), which uses a scoring system that calculates operative mortality for individuals

undergoing cardiac surgery, was used to evaluate mortality risk.[28] The Logistic EuroSCORE I takes into consideration 17 risk variables that predict mortality. Higher scores indicate greater operative mortality risk.[29]

The selection of explanatory variables included in the prediction models for the present study was based on previous research exploring the consequences of delirium after cardiac surgery,[9,11,30,31] taking into account clinical experience and the limited sample size.

Data Collection

Preoperative Data and Postoperative Assessment of Delirium

A detailed description of preoperative data collection and assessment of delirium was presented in a previous article.[12] Briefly, the day before treatment, ADL and cognitive function were evaluated in individuals fulfilling the inclusion criteria. A self-report form containing IADL and SF-12 questionnaires was given to participants at the end of the inclusion process and collected before surgery. Demographic and clinical data were gathered from medical records or in an interview, as appropriate.

The presence of delirium was measured daily, including weekends, at approximately noon from Postoperative Day 1–5. Research nurses trained in CAM performed clinical assessments at participants' bedsides. Medical, nursing, and physiotherapist reports from the previous 24 hours and meetings with health professionals in charge of the participants were taken into consideration when scoring the CAM.

One- and 6-Month Assessments

Follow-up visits were scheduled at the hospital 1 and 6 months after treatment. Information about ADL function was collected at this time, and self-report forms containing IADL and SF-12 questionnaires were provided. If a participant was unable to attend a follow-up visit, and a new appointment could not be scheduled within a window of 2 weeks, telephone contact was attempted. Information required for the Barthel Index was collected over the telephone, and then self-report forms containing IADL and SF-12 questionnaires were mailed for completion at home. The MMSE was administered after 6 months in participants attending follow-up visits.

Data Analyses

Data are presented as counts and percentages or means and standard deviations or confidence intervals. Longitudinal linear models were fitted separately, with time, delirium, and the interaction between time and delirium as explanatory factors to estimate mean ADL, IADL, MMSE, SF-12 PCS, and SF-12 MCS scores at baseline and 1- and 6-month follow-up. To estimate how delirium could improve predictions over baseline scores alone or baseline scores and other risk or comorbidity factors, linear longitudinal models for the scores were fitted at 1- and 6-month follow-up using baseline score as an explanatory variable for the unadjusted analysis and baseline score, sex, Charlson Comorbidity Index, and logistic EuroSCORE I as explanatory variables for the adjusted analysis.

All longitudinal models were fitted separately for each treatment (SAVR, TAVI) using generalized least squares with an unstructured correlation matrix. $P \leq .05$ was considered statistically significant. Reported *P*-values were not adjusted for multiple comparisons. Data management and initial statistical analyses were conducted using SPSS version 22.0 (IBM SPSS Statistics for Windows, Armonk, NY) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all reported statistical analyses except those reported in Table 1. The R package "nlme" was used for longitudinal analyses.

Missing Data

Data were screened and checked for missing units (questionnaires) and loss of single items.[32] Before data collection started, a coding system for missing data was implemented (participant did not answer item, participant withdrew from study, participant died). Participants with incomplete baseline SF-12 units were more likely to be male ($P = .02$). Otherwise, no differences were found at baseline or follow-up in terms of sex, comorbidity, or marital or educational status between participants with complete and incomplete units.

By the time data collection ended, 22 participants were lost-to-follow-up, nine of whom had withdrawn from the study (8 treated with SAVR) and 13 of whom had died (8 treated with TAVI). Including participants who were lost to follow-up, cognitive screening 6 months after treatment was not performed in 45 (31%). Twenty-two of these participants did not attend 6-month follow-up at the hospital. The majority of these nonattendees were living more than 2 hours away from the hospital; five said that the hospital was too far away from their residence to attend the consultation, nine that they were not well enough to travel, and four that they were healthy and did not need further follow-up examination; three did not indicate their reason for not attending the follow-up; and two could not be contacted. Participants who did not attend their 6-month follow-up visit did not differ from those attending in terms of sex ($P = .27$), baseline comorbidities ($P = .74$), or baseline MMSE score ($P = .83$).

Handling of Missing Data

Because it could not be assumed that data were missing completely at random, a likelihood-based longitudinal model, requiring only the much weaker missing at random assumption, was used. Still, there could be informative censoring that the model did not capture, with, for example, participants showing greater improvements from baseline being more likely to respond to the follow-up questionnaire. A sensitivity analysis for the changes from baseline was therefore performed in which all missing data were replaced with participants' baseline values and the statistical analysis repeated. The results from the sensitivity analysis can be seen in Figure S1.

Table 1. Characteristics of Individuals Aged 80 and Older Undergoing Transcatheter Aortic Valve Implantation (TAVI) or Surgical Aortic Valve Replacement (SAVR) Who Did and Did Not Develop Delirium (N = 136)

Characteristic	Total	SAVR			TAVI		
		No Delirium, n = 25	Delirium, n = 48	*P*-Value	No Delirium, n = 35	Delirium, n = 28	*P*-Value
Age, mean ± SD	83.5 ± 2.7	81.6 ± 1.4	82.7 ± 2.3	.01	84.7 ± 2.8	84.9 ± 2.8	.74
Female, n (%)	76 (56)	12 (48)	24 (50)	.87	25 (71)	15 (54)	.14
Married, n (%)	73 (54)	16 (64)	27 (56)	.52	15 (43)	15 (54)	.40
Activity of daily living function, mean ± SD (range 0–20)	18.9 ± 1.5	19.5 ± 1.0	18.9 ± 1.5	.06	18.9 ± 1.5	18.5 ± 1.4	.28
Instrumental activity of daily living function, mean ± SD (range 0–66)	54.2 ± 10.1	57.1 ± 8.7	57.5 ± 7.9	.87	52.4 ± 10.9	48.6 ± 11.1	.21
Mini-Mental State Examination score, mean ± SD (range 0–30)	27.2 ± 2.9	27.9 ± 2.2	27.8 ± 2.8	.86	27.4 ± 2.4	25.4 ± 3.6	.01
Medical Outcomes Study 12-Item Short Form Survey score, mean ± SD (range 0–100)							
Physical Component Summary	33.9 ± 10.6	38.4 ± 8.8	36.2 ± 10.4	.40	30.5 ± 10.0	30.9 ± 11.3	.88
Mental Component Summary	48.7 ± 10.8	50.3 ± 10.6	50.1 ± 10.4	.94	47.0 ± 8.3	47.1 ± 14.1	.95
Charlson Comorbidity Index, mean ± SD	2.1 ± 1.2	1.8 ± 1.0	1.8 ± 0.9	.78	2.3 ± 1.3	2.7 ± 1.3	.20
Logistic European System for Cardiac Operative Risk Evaluation I, mean ± SD[a]	14.0 ± 9.2	9.9 ± 3.8	8.8 ± 3.1	.31	19.4 ± 1.0	19.8 ± 11.6	.86
New York Heart Association class							
I + II	47 (35)	13 (54)	24 (54)	.98	6 (19)	4 (18)	.96
III + IV	75 (55)	11 (46)	20 (45)	.98	26 (81)	18 (81)	.96
Left ventricular ejection fraction, %	56.6 ± 10.2	57.2 ± 12.0	57.3 ± 9.4	.97	55.9 ± 10.4	55.6 ± 10.3	.89
Maximum aortic gradient, mmHg	79.5 ± 23.9	86.2 ± 26.7	82.1 ± 23.8	.54	73.4 ± 23.7	76.9 ± 20.9	.54
Mean aortic gradient, mmHg	48.3 ± 16.1	51.6 ± 16.8	50.1 ± 16.2	.72	45.6 ± 16.0	45.9 ± 15.2	.93
Aortic valve area, cm^2/m^2	0.4 ± 0.2	0.4 ± 0.1	0.4 ± 0.2	.29	0.4 ± 0.1	0.4 ± 0.07	.40
American Society of Anesthesiologists classification, n (%)							
3	114 (84)	25 (100)	46 (96)	.30	23 (66)	20 (71)	.63
4	22 (16)	0 (0)	2 (4)	.30	12 (34)	8 (29)	.63

SD = standard deviation.

[a]*P*-value based on log-transformed values.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and approved by the Regional Committee for Ethics in Medical Research in Norway (REK Vest 2010/2936–6). Special consideration was given to signs of participant exhaustion during data collection. Whenever these signs were present, data collection was stopped and later resumed.

RESULTS

Characteristics of the Study Population

Clinical and sociodemographic characteristics of included participants are presented in Table 1. Fifty-seven percent of the participants were female, and TAVI was performed in 46% of the study population. Participants in the TAVI group were older ($P < .001$) and had more comorbidities ($P < .001$), a higher Logistic EuroSCORE I ($P < .001$), poorer IADL function ($P < .001$), lower MMSE scores ($P = .007$), lower SF-12 PCS scores ($P = .002$), and lower SF-12 MCS scores ($P = .09$).

Participants without delirium were not different from those with delirium in terms of sex ($P > .14$), comorbidity index ($P > .20$), or logistic EuroSCORE ($P > .31$), but participants treated using SAVR developed delirium more often than participants treated with TAVI ($P = .01$).

Postoperative Delirium

An earlier article[12] presented the incidence of delirium in the studied population. Delirium was identified in 66% of participants in the SAVR group and 44% of those in the TAVI group.[12]

ADLs–SAVR Group

ADL scores of participants treated with SAVR were similar to baseline scores at 1- and 6-month follow-up regardless of the presence of delirium (all $P > .05$) (Figure 1). Delirium did not predict performance well when adjusted for baseline or baseline and other risk factors (Table 2).

ADLs–TAVI Group

At 1-month follow-up, participants in the TAVI group with delirium had much worse mean ADL scores than at baseline. After 6 months, ADL scores for the TAVI group with delirium had improved and were no longer statistically significantly different from baseline scores ($P = .06$). The 1- and 6-month follow-up scores of participants undergoing TAVI who did not develop delirium were similar to their baseline scores (Figure 1). The regression models showed that delirium predicted performance well at 1-month follow-up, even when baseline ADL function was included as a linear predictor in the models (Table 2).

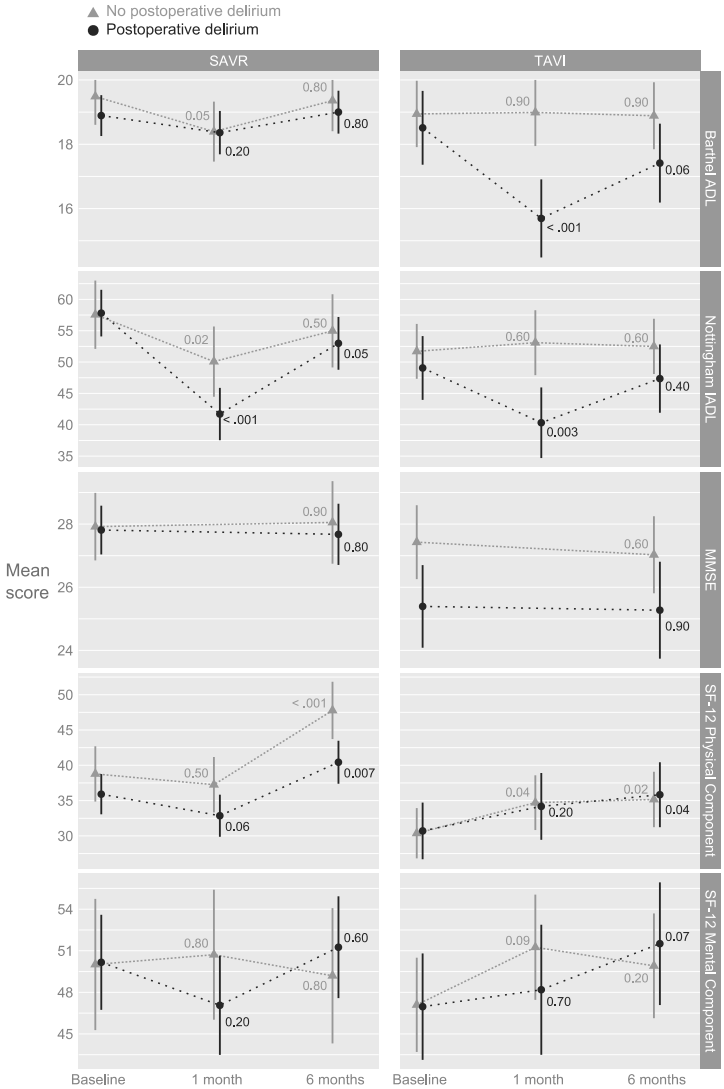

Figure 1. Model-based estimated means for activities of daily living (ADLs; possible range of scores 0–20), instrumental activities of daily living (IADLs; possible range of scores 0–66), Mini-Mental State Examination (MMSE; possible range of scores 0–30), and Medical Outcomes Study 12-item Short Form Survey scores ((SF-12) possible range of scores 0–100) (with 95% confidence intervals) at baseline and 1- and 6-month follow-up. Organized according to treatment (surgical aortic valve replacement (SAVR), transcatheter aortic valve implantation (TAVI)) and presence or absence of delirium (circles and triangles, respectively) (N = 136). The result of testing for change from baseline, based on longitudinal models, is shown as *P*-values at each time point. See Table 2 for information on the number of observations used to estimate each outcome.

This analysis also showed that participants who developed delirium had mean baseline-adjusted scores 3.1 points lower (worse) than those who did not ($P = .002$). This effect also persisted when adjusting for other risk and comorbidity factors (sex, Charlson Comorbidity Index, baseline logistic EuroSCORE I) ($P = .001$). At 6-month follow-up, presence of delirium in the first 5 days after surgery no longer predicted ADL performance.

IADLs–SAVR Group

IADL scores at 1-month follow-up were lower than at baseline for participants who did not develop delirium ($P = .02$) and even lower for those who did ($P < .001$). There were no or minor differences from baseline at 6-month follow-up ($P = .50$ for participants without delirium, $P = .05$ for SAVR participants with delirium). The

Table 2. Effect of Experiencing Delirium on Physical and Cognitive Function and Self-Reported Health, Adjusted for Baseline Values, at 1- and 6-Month Follow-Up, for Individuals Aged 80 and Older with Severe Aortic Stenosis

	Surgical Aortic Valve Replacement					Transcatheter Aortic Valve Implantation				
		Estimated,[c] *P*-Value					Estimated,[c] *P*-Value			
		Baseline Adjusted[a]		Baseline and Risk Adjusted[b]			Baseline Adjusted[a]		Baseline and Risk Adjusted[b]	
Assessment	n*	1 Month	6 Months	1 Month	6 Months	n*	1 Month	6 Months	1 Month	6 Months
Activity of daily living function	67	0.3, .60	0.1, .90	0.0, >.99	−0.3, .70	60	−3.1, .002	−1.5, .10	−3.1, .001	−1.6, .10
Instrumental activity of daily living function	47	−8.1, .07	−1.8, .70	−9.4, .06	−3.0, .60	48	−10.6, .004	−3.0, .40	−10.5, .005	−2.3, .50
Mini-Mental State Examination	45		−0.3, .70		−0.6, .50	52		−1.1, .40		−1.4, .20
Medical Outcomes Study 12-Item Short Form Survey										
Physical Component Summary	52	−2.9, .20	−4.1, .10	−4.0, .10	−4.9, .05	44	−0.6, .80	0.9, .80	−0.6, .80	1.1, .70
Mental Component Summary	52	−5.1, .10	5.1, .10	−6.3, .06	4.3, .20	44	−4.0, .20	2.4, .40	−3.6, .20	3.0, .30

[a]Adjusted for baseline score.

[b]Adjusted for sex and baseline score, Charlson Comorbidity Index, and Logistic European System for Cardiac Operative Risk Evaluation I.

[c]Estimated difference in mean score between an individual experiencing delirium and an individual not experiencing delirium based on a linear longitudinal model with the mean score of the individual experiencing delirium modeled as a linear function of experiencing delirium and baseline value/baseline value and other risk factors.

*Number of patients included in the models, i.e., with at least one measurement (baseline, 1 month and/or 6 month).

regression models showed no predictive power of delirium at 6 months but suggest a possible moderate to large effect size at 1 month (not statistically significant) (Table 2).

IADLs–TAVI Group

At 1-month follow-up, IADL scores did not differ from baseline in participants who did not develop delirium ($P = .60$) but were lower than at baseline for those who did ($P = .003$). There were no differences in scores from baseline to 6-month follow-up independent of delirium (without delirium, $P = .60$; with delirium, $P = .40$) (Figure 1). The regression models showed that, for participants undergoing TAVI, delirium predicted performance well at 1-month follow-up, even after adjusting for baseline IADL function. According to this analysis, participants who developed delirium had mean baseline-adjusted scores that were approximately 10 points lower (worse) than scores of those who did not ($P = .005$). This was also the case when adjusted for other risk and comorbidity factors (Table 2).

MMSE–SAVR Group

There were no differences in cognitive function between baseline and 6-month follow-up in participants who did and did not develop delirium (Figure 1). For participants undergoing SAVR, the regression models showed no significant improvement in prediction when including delirium as a predictor in the analysis (Table 2).

MMSE–TAVI Group

Although individuals undergoing TAVI who developed delirium had lower overall scores than those who did not (even at baseline), no differences in cognitive function were found 6 months after treatment (Table 2). Taking into account baseline MMSE score and other risk factors, including information on the presence or absence of delirium did not improve predictions (Table 2).

SF-12 PCS–SAVR Group

There were minor, statistically nonsignificant changes in SF-12 PCS score after 1 month. Participants who did and did not develop delirium had a major increase in scores at 6-month follow-up ($P \leq .007$) (Figure 1). The regression models found no improvements in prediction when taking the presence of delirium into account, except for a significant ($P = .05$) effect after 6 months (Table 2).

SF-12 PCS–TAVI Group

At 1-month follow-up, only participants who did not develop delirium had a statistically significant improvement in self-reported physical health ($P = .04$). Six months later, there were improvements in all participants (Figure 1). The regression models showed no improvement in prediction when taking the presence of delirium into account (Table 2).

SF-12 MCS–SAVR Group

There were no statistically significant differences on the SF-12 MCS at 1- or 6-month follow-up (Figure 1). The regression model revealed no improvement in prediction when taking the presence of delirium into account (Table 2).

SF-12 MCS–TAVI Group

No statistically significant changes were found in participants who did or did not develop delirium at 1- or 6-month follow-up (Figure 1). For participants undergoing TAVI, there was no effect of delirium at 1- or at 6-month follow-up (Table 2).

Sensitivity Analysis

The results from the sensitivity analysis showed only minor changes in the estimated effects, so the findings seem robust. All changes from baseline with $P \leq .04$ (in Figure 1) remained statistically significant. The results from the sensitivity analysis are presented in Figure S1. This supplement is organized like Figure 1, but all estimates and *P*-values are based on the sensitivity analysis model described.

DISCUSSION

To the best of the knowledge of the authors, this is the first study to examine delirium as a predictor of ADL, IADL, and cognitive function and self-reported health in individuals aged 80 and older after TAVI. This work demonstrates how delirium affects individuals aged 80 and older after SAVR or TAVI, the latter being a less-invasive treatment.

Previous studies found an association between delirium and functional decline after hip fracture[8] and cardiac surgery.[9,11] It has been suggested that functional impairment is an important end point after cardiac surgery in older adults.[33,34] The current study shows that, at 1-month follow-up, participants who underwent TAVI and developed delirium had a major decrease in ADL scores. This effect persisted after adjusting for baseline ADL score and other risk factors. The same level of decrease was not present in individuals aged 80 and older undergoing the more-invasive SAVR. One could argue that individuals aged 80 and older scheduled for TAVI are more vulnerable than those undergoing SAVR. ADL scores in participants undergoing TAVI and not developing delirium remained constant from baseline to follow-up.

IADL function has been linked to cognition.[35] In the current study, participants with delirium scored lower on the IADL scale at 1-month follow-up than those without delirium: 16 points for participants undergoing SAVR and 9 points for participants undergoing TAVI. Diminished IADL performance might be expected, especially after SAVR, which requires full sternotomy, aortic cross-clamping, and extracorporeal bypass circulation. Furthermore, electrocardiography devices, temporal pacemakers, and catheters limit mobility during the immediate postoperative period. After 6 months, the IADL scores of individuals who underwent TAVI and SAVR had increased and did not significantly differ from baseline.

Important differences in cognitive function were identified. MMSE scores at baseline and 6-month follow-up of individuals who underwent TAVI and developed delirium were approximately 2 points lower than scores of participants undergoing TAVI who did not develop delirium, although the cognitive changes from baseline to 6-month follow-up in all participants treated with TAVI were not significant. No differences were observed in MMSE scores of participants who underwent SAVR, regardless of development of delirium. Even though diminished cognitive function has been reported 6 months after hip fracture in individuals with delirium,[36] and delirium has been shown to be associated with persistent cognitive impairment and prolonged recovery up to 1 year after cardiac surgery,[31] a decrease in cognitive scores 6 months after SAVR or TAVI was not observed. These encouraging results compare favorably with findings from other studies[30] and provide further knowledge in the area of delirium by including individuals undergoing cardiac surgery aged 80 and older treated with a novel aortic valve therapy. The study measured cognitive function only at baseline and 6-month follow-up, and it was not possible to explore possible fluctuations that could have occurred during the intermediate postoperative period. It also cannot be determined whether some participants developed cognitive impairment after 6 months.

The SF-12 has been used to measure self-reported health status after SAVR and TAVI.[37–39] To the authors' knowledge, the self-reported health of individuals aged 80 and older undergoing TAVI who develop delirium has not been established. The PCS score of individuals who underwent SAVR and developed delirium was lower (nonsignificantly) at 1-month follow-up than at baseline but improved significantly at 6 months. The scores of individuals who underwent SAVR and did not develop delirium remained constant at 1-month follow-up and improved greatly after 6 months, supporting observations from the Placement of AoRTic TraNscathetER Valve Trial.[39] In the current study, participants treated with TAVI had the lowest PCS scores at baseline. Differences in scores between the TAVI and SAVR groups became more accentuated 6 months after treatment, suggesting that individuals who underwent TAVI were frail at baseline and remained frail after treatment.

MCS scores of the SAVR and TAVI groups had a different pattern than others have reported.[37,39] There was no statistically significant difference in these scores from baseline to 1- and 6-month follow-up. The utility of the SF-12 for detecting changes over time in individuals with heart failure has been questioned.[40] Similarly, the SF-12 MCS may not be sufficiently sensitive to detect changes in delirium. It is also possible that participants in the SAVR group had higher expectations for the procedure than the frailer group that underwent TAVI and developed delirium. Nevertheless, it is surprising that cognitive, ADL, and IADL function were well preserved in the SAVR cohort, because these participants did not receive as much screening as those in the TAVI group regarding general atherosclerosis and aortic calcification. This indicates that the selection and quality of surgery and perioperative treatment of participants were good, because participants who underwent TAVI were older and had a higher EuroSCORE and more comorbidities. It also shows that SAVR may be performed safely in individuals aged 80 and older with reasonably good physical and mental health. With new technology (widespread use of intraoperative, epiaortic ultrasound to detect aortic atheroma and thereby avoid cerebral embolization; recently developed rapid

deployment aortic valve prostheses to reduce extracorporeal bypass circulation time in elderly adults undergoing open surgery for aortic stenosis), SAVR may potentially be performed with even less risk of cerebral complications.[41,42]

This study has several strengths, including its prospective design with consecutive inclusion of individuals and its use of valid and reliable instruments. Furthermore, the study hospital performs all TAVI and SAVR in western Norway, allowing the inclusion of a representative group of individuals aged 80 and older with severe aortic stenosis from the entire region. The fact that the participants were more homogeneous in terms of age, diagnosis, and treatment received than in other studies[9,11,30,31] can explain the high incidence of delirium in the current study. Screening with CAM was performed in a thorough manner at bedside for 5 days postoperatively, starting on the first postoperative day. Participants were also assessed on weekends and holidays. Meetings with health professionals in contact with participants and close examination of their reports were performed before the CAM was scored.

A limitation of the study is that it was not designed as a randomized controlled trial. Randomization to compare treatment modalities was not possible, because TAVI and SAVR are used to treat distinctly different target groups.[6] Because of this, the results were analyzed stratified according to treatment. Another limitation was the modest size of the studied cohort. The results warrant future studies with larger samples. There was also the risk of type 1 errors due to use of multiple testing. The high ADL, IADL, and cognitive functioning of the cohort may limit the applicability of the results to other populations and might indicate that subject selection bias was present before participants were referred to the university hospital. It is also a limitation that cognitive function at 6-month follow-up was not measured in the 22 participants who did not attend their consultation, but the consequences of missing MMSE data at 6 months were investigated in a sensitivity analysis and showed only minor changes in the estimated effects. Other tools could have been added to complement the cognitive evaluation done with the MMSE.[43] Six months may be considered a short follow-up period for evaluating the long-term consequences of delirium. This warrants further study with longer follow-up.

In conclusion, delirium is an important predictor of lower ADL and IADL function 1 month after invasive treatment for aortic stenosis, even when gentler techniques such as TAVI are used. Lower ADL and IADL scores at 1-month follow-up (Figure 1) in individuals aged 80 and older with postoperative delirium address the importance of prevention and recognition of the condition. This is probably even more relevant in a population in which functional ability is perhaps more appealing than longevity. Close monitoring of individuals at risk of developing delirium, even after less invasive aortic valve therapy, is therefore recommend. Future studies should focus on the effect of delirium on adverse events demanding acute readmission to hospital and nursing home placement in individuals aged 80 and older after SAVR or TAVI.

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REFERENCES

1. Rudolph JL, Jones RN, Levkoff SE et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation 2009;119:229–236.
2. Detroyer E, Dobbels F, Verfaillie E et al. Is preoperative anxiety and depression associated with onset of delirium after cardiac surgery in older patients? A prospective cohort study. J Am Geriatr Soc 2008;56:2278–2284.
3. Bakker RC, Osse RJ, Tulen JH et al. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. Eur J Cardiothorac Surg 2012;41:544–549.
4. Osnabrugge RL, Mylotte D, Head SJ et al. Aortic stenosis in the elderly: Disease prevalence and number of candidates for transcatheter aortic valve replacement: A meta-analysis and modeling study. J Am Coll Cardiol 2013;62:1002–1012.
5. Nkomo VT, Gardin JM, Skelton TN et al. Burden of valvular heart diseases: A population-based study. Lancet 2006;368:1005–1011.
6. Leon MB, Smith CR, Mack M et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–1607.
7. Makkar RR, Fontana GP, Jilaihawi H et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012;366:1696–1704.
8. Krogseth M, Wyller TB, Engedal K et al. Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients. J Psychosom Res 2014;76:68–74.
9. Rudolph JL, Inouye SK, Jones RN et al. Delirium: An independent predictor of functional decline after cardiac surgery. J Am Geriatr Soc 2010;58:643–649.
10. Rudolph JL, Marcantonio ER. Review articles: Postoperative delirium: Acute change with long-term implications. Anesth Analg 2011;112:1202–1211.
11. Koster S, Hensens AG, Schuurmans MJ et al. Consequences of delirium after cardiac operations. Ann Thorac Surg 2012;93:705–711.
12. Eide LS, Ranhoff AH, Fridlund B et al. Comparison of frequency, risk factors, and time course of postoperative delirium in octogenarians after transcatheter aortic valve implantation versus surgical aortic valve replacement. Am J Cardiol 2015;115:802–809.
13. Forman DE, Rich MW, Alexander KP et al. Cardiac care for older adults: Time for a new paradigm. J Am Coll Cardiol 2011;57:1801–1810.
14. Rumsfeld JS, Alexander KP, Goff DC Jr et al. Cardiovascular health: The importance of measuring patient-reported health status: A scientific statement from the American Heart Association. Circulation 2013;127:2233–2249.
15. Elmalem S, Dumonteil N, Marcheix B et al. Health-related quality of life after transcatheter aortic valve implantation in elderly patients with severe aortic stenosis. J Am Med Dir Assoc 2014;15:201–206.

16. Amonn K, Stortecky S, Brinks H et al. Quality of life in high-risk patients: Comparison of transcatheter aortic valve implantation with surgical aortic valve replacement. Eur J Cardiothorac Surg 2013;43:34–41; discussion 41–42.
17. Vahanian A, Alfieri O, Andreotti F et al. Guidelines on the management of valvular heart disease (version 2012). The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:1–44.
18. Inouye S, van Dyck C, Alessi C et al. Clarifying confusion: The Confusion Assessment Method. Ann Intern Med 1990;113:941.
19. Wei LA, Fearing MA, Sternberg EJ et al. The Confusion Assessment Method: A systematic review of current usage. J Am Geriatr Soc 2008;56:823–830.
20. Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. Md State Med J 1965;14:61–65.
21. Sadaria KS, Bohannon RW, Lee N et al. Ratings of physical function obtained by interview are legitimate for patients hospitalized after stroke. J Stroke Cerebrovasc Dis 2001;10:79–84.
22. Gladman JR, Lincoln NB, Adams SA. Use of the extended ADL scale with stroke patients. Age Ageing 1993;22:419–424.
23. Lincoln NB, Gladman JRF. The extended activities of daily living scale: A further validation. Disabil Rehabil 1992;14:41–43.
24. Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
25. Ware J Jr, Kosinski M, Keller S. A 12-Item Short-Form Health survey: Construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–233.
26. Charlson ME, Pompei P, Ales KL et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373–383.
27. Frenkel WJ, Jongerius EJ, Mandjes-van Uitert MJ et al. Validation of the Charlson Comorbidity Index in acutely hospitalized elderly adults: A prospective cohort study. J Am Geriatr Soc 2014;62:342–346.
28. Roques F, Michel P, Goldstone AR et al. The logistic EuroSCORE. Eur Heart J 2003;24:881–882.
29. European System for Cardiac Operative Risk Evaluation [on-line]. Available at www.euroscore.org Accessed December 3, 2014.
30. Rudolph JL, Marcantonio ER, Culley DJ et al. Delirium is associated with early postoperative cognitive dysfunction. Anaesthesia 2008;63:941–947.
31. Saczynski JS, Marcantonio ER, Quach L et al. Cognitive trajectories after postoperative delirium. N Engl J Med 2012;367:30–39.
32. Hardy SE, Allore H, Studenski SA. Missing data: A special challenge in aging research. J Am Geriatr Soc 2009;57:722–729.
33. Malani PN. Functional status assessment in the preoperative evaluation of older adults. JAMA 2009;302:1582–1583.
34. Min L, Mazzurco L, Gure TR et al. Longitudinal functional recovery after geriatric cardiac surgery. J Surg Res 2015;194:25–33.
35. Gold DA. An examination of instrumental activities of daily living assessment in older adults and mild cognitive impairment. J Clin Exp Neuropsychol 2012;34:11–34.
36. Krogseth M, Wyller TB, Engedal K et al. Delirium is an important predictor of incident dementia among elderly hip fracture patients. Dement Geriatr Cogn Disord 2011;31:63–70.
37. Fairbairn TA, Meads DM, Mather AN et al. Serial change in health-related quality of life over 1 year after transcatheter aortic valve implantation: Predictors of health outcomes. J Am Coll Cardiol 2012;59:1672–1680.
38. Chatterjee S, Kumbhani DJ, Sardar P et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: An updated review of literature. Curr Cardiol Rep 2014;16:473.
39. Reynolds MR, Magnuson EA, Wang K et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: Results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). J Am Coll Cardiol 2012;60:548–558.
40. Bennett SJ, Oldridge NB, Eckert GJ et al. Comparison of quality of life measures in heart failure. Nurs Res 2003;52:207–216.
41. Ibrahim KS, Vitale N, Tromsdal A et al. Enhanced intra-operative grading of ascending aorta atheroma by epiaortic ultrasound vs echocardiography. Int J Cardiol 2008;128:218–223.
42. Haverich A, Wahlers TC, Borger MA et al. Three-year hemodynamic performance, left ventricular mass regression, and prosthetic-patient mismatch after rapid deployment aortic valve replacement in 287 patients. J Thorac Cardiovasc Surg 2014;148:2854–2860.
43. Mitchell AJ. A meta-analysis of the accuracy of the Mini-Mental State Examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res 2009;43:411–431.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Sensitivity analysis showing minor changes in estimated effects: activities of daily living (ADLs; possible range of scores 0–20), instrumental activities of daily living (IADLs; possible range of scores 0–66), Mini-Mental State Examination (MMSE; possible range of scores 0–30), and Medical Outcomes Study 12-Item Short Form Survey scores ((SF-12) possible range of scores 0–100) (with 95% confidence intervals) at baseline and 1- and 6-month follow-up.

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