Role of novel predictive factors on clinical outcome after transcatheter aortic valve replacement

Rol van nieuwe voorspellende factoren op de klinische uitkomsten na transcathetergebonden aortaklepimplantatie

Masieh Abawi

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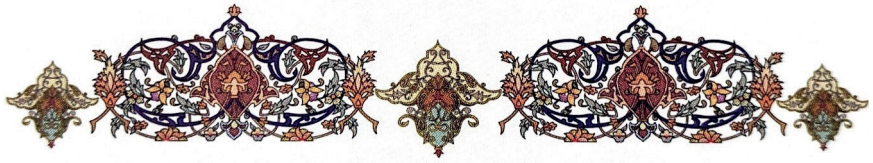
تقدیم برای مادر گرامی ام

Dedicated to my dearest mother

هـرگز دل مـن ز عـلم مـحروم نشـد کـم مـاند ز اسـرار کـه مـعلوم نشـد
هفتاد و دو سال فکـر کـردم شب وروز مـعلومم شـد کـه هـیچ مـعلوم نشـد



Never my heart ever deprived of knowledge
Few secrets were not divulged
For seventy two years I pondered day and night
Only to know that I know nothing

Omar Khayyam (Perzisch: عمر خیّام); 18 May 1048 – 4 December 1131

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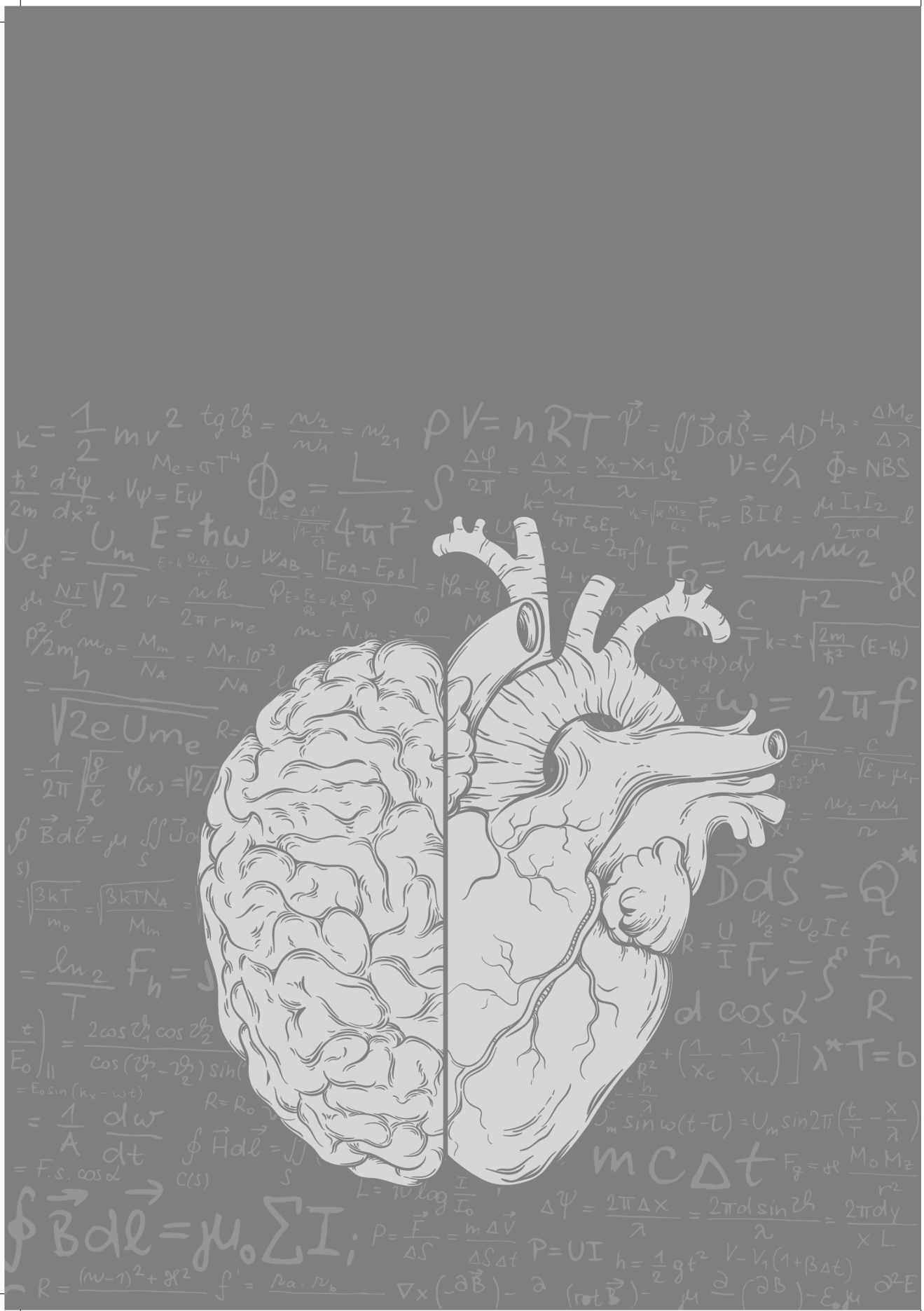

Chapter 1

General Introduction and outlines

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GENERAL INTRODUCTION AND OUTLINES

The native aortic valve contains three semi-lunar shaped leaflets or cusps which are located between the aorta and left ventricle (LV). In about 2% of the community it is found to congenitally have two cusps (1). During the ventricular systole when the pressure in the LV rises and overcomes the pressure in the aorta, these leaflets open to allow blood flow to the rest of the body (Figure 1). Narrowing of these valve leaflets, the so called aortic valve stenosis (AS) leads to blood flow resistance (2). According to population-based studies, 12.4% of the individuals >75 years suffer from AS, and 3.4% from severe AS (3). The global burden of AS is not only a health issue but an economic challenge to healthcare systems that is expected to grow with the aging population (3).

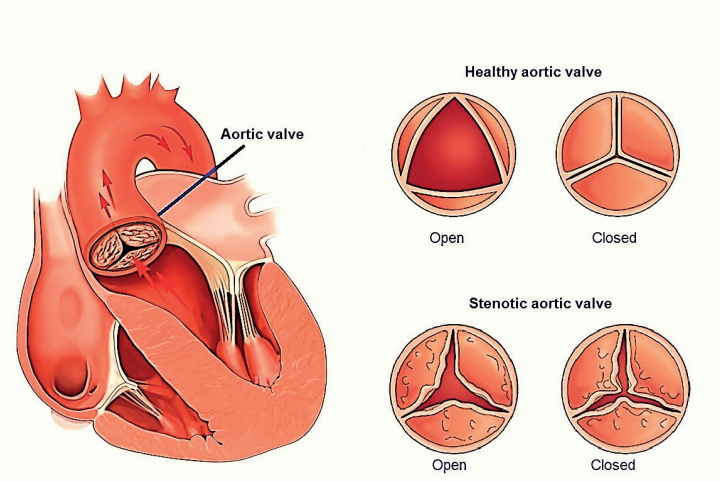

Figure 1. Aortic valve.

According to the American College of Cardiology/American Heart Association guidelines (ACC/AHA), severe AS is defined by using Doppler techniques as an aortic velocity ≥4 m per second or mean pressure gradient ≥40 mm Hg (4). In the presence of high velocity/gradient and immobile or calcified valve cusps, calculation of the aortic valve area (AVA) is supportive but not always necessary as the majority of patients with severe AS may have AVA ≤1.0 cm^2 or an indexed AVA ≤0.6 cm^2/m^2 (4). However, AVA calculations are necessary among patients with low velocity/gradient as these patients often have LV systolic dysfunction (2, 4).

Common causes of AS include congenital, degenerative, or rheumatic processes. In developed countries degenerative calcific disease of native aortic valve is the most common etiology of AS among the elderly (5, 6). Degenerative AS is characterized by progressive valvular fibrosis, leaflet thickening, stiffening and restricting of the motion of the leaflets leading to gradual orifice obstruction, increased afterload, and in the long run to LV hypertrophy (3, 5, 6). Although the exact mechanism of degenerative AS remain unknown, observational data suggest that degenerative AS and atherosclerosis may share common pathways and risk factors (7, 8). For instance, histopathological data show similar active cellular process between degenerative AS and atherosclerosis, involving inflammation, lipid deposition, fibrotic changes and osteopontin production (7, 9, 10).

Management strategies

Classic symptoms of AS include angina, syncope, and dyspnea (3, 5, 6, 11). The age at which severe AS becomes symptomatic depends on the cause. For instance, individuals with degenerative tricuspid AS become symptomatic in their eighties, whereas individuals with congenital bicuspid AS develop symptoms in their fifties, as a bicuspid valve seems more prone to develop stenosis. Although timing of intervention among individuals with severe asymptomatic AS remain controversial (12), however, onset of symptoms dramatically worsens survival, with mean survival of 45±13 months after development of angina, 27±15 months after syncope, and 11±10 months after LV heart failure (5, 11, 13).

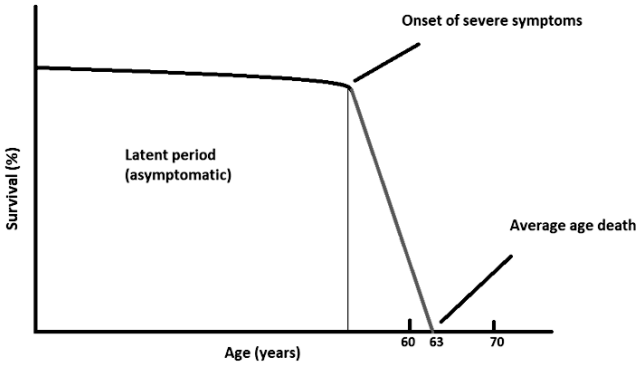

Figure 2. Natural history of untreated aortic valve as described by Ross and Braunwald.

To date, no medical treatment exist to reduce or reverse the progression of degenerative AS. Surgical aortic valve replacement (SAVR) is the standard treatment strategy to replace stenotic native aortic valve in order to remove blood flow resistance (2, 4).

Nearly one-third of all individuals with severe symptomatic AS are at high risk for surgery or even inoperable due to older age, LV dysfunction, and other comorbid conditions (14). Nonsurgical patients who are medically managed have a poor prognosis with an estimated 1-year and 5-year mortality of 50% and 90%, respectively (3, 6, 15) (Figure 2). Since the first introduction in 2002 by Cribier et al., transcatheter aortic valve replacement (TAVR) revolutionized the management of severe symptomatic AS among elderly irrespective of baseline surgical risk (i.e., from high-risk- or inoperable to intermediate or lower surgical risk) (16, 17). Compared with SAVR, TAVR is a less invasive treatment strategy that is performed on a beating heart without involvement of cardiopulmonary bypass or sternotomy (18). Moreover, patients after TAVR are usually discharged shortly after the procedure without long-term recovery period compared with SAVR (19).

Based on the results of the multicenter, randomized PARTNER trial, TAVR is strongly recommended for patients with severe AS who are not suitable for surgery in order to improve survival and functional status (2, 4). According to the results of the PARTNER trial (**cohort B**) among inoperable patients, transfemoral TAVR showed superiority over medical therapy (medical management with or without balloon aortic valvuloplasty) in terms of all-cause mortality, cardiovascular mortality, and rate of repeat hospitalization (20). Even at

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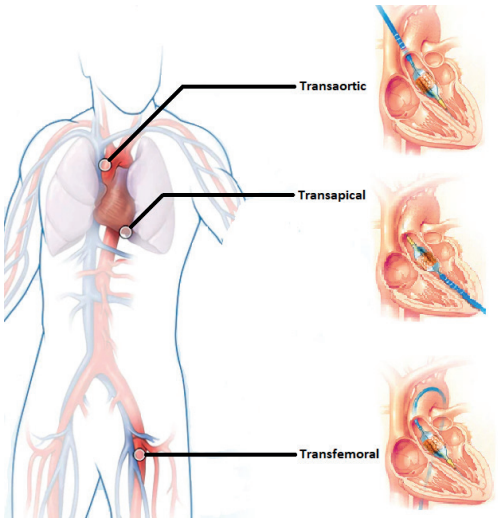

Figure 3. Transcatheter aortic valve replacement, according to the access site.

5 years follow-up TAVR compared with medical treatment was associated with lower all-cause mortality (71.8% vs. 93.6%, p<0.001), cardiovascular mortality (57.5% vs. 85.9%, p<0.001), and risk of repeat hospital admission (47.6% vs. 87.3%, p<0.001) (15). In the PARTNER trial (**cohort A**) among high-risk patients, compared with SAVR, TAVR was non-inferior to SAVR and showed even similar outcome for up to 5-years of follow-up (19, 21, 22). According to the available data among intermediate-risk patients, TAVR was both non-inferior and even superior to SAVR when transfemoral access was performed in terms of all-cause mortality and disabling stroke (23-25). According to the PARTNER-2 trial among intermediate-risk patients with severe, symptomatic AS, TAVR compared to SAVR have similar clinical outcome regarding the incidence of death or disabling stroke for up to 5 years (26). Recently, TAVR showed encouraging results compared with SAVR for lower-risk patients and it has been approved even for this subset of patients (27, 28). Interestingly, an updated meta-analysis of randomized controlled trails (RCT) comparing TAVR versus SAVR showed even lower all-cause mortality and stroke after TAVR for up to 2-years of follow-up, irrespective of baseline surgical risk and transcatheter valve type (17).

However, despite improved techniques, and favorable outcomes, TAVR is associated with several different types of peri-procedural and post-procedural complications, such as ischemic stroke and postoperative delirium (POD) (29-31). Although the etiologies of delirium and peri-procedural cerebral ischemic lesions following TAVR are multifactorial, some patients may be more prone to develop POD and suffer more often from peri-procedural ischemic lesions following TAVR.

To date several risk stratification models have been developed and some are frequently used in daily clinical practice among patients undergoing cardiac surgery (2, 4). These models allow clinicians to calculate risk of mortality following the procedure, before the procedure is undertaken. Moreover, it can also be used for patient information to weight the risk versus benefits for shared-decision making, and for center-based quality control. Among patients undergoing TAVR, EuroSCORE-I (European System for Cardiac Operative Risk Evaluation)

which allows the calculation of in-hospital mortality risk after TAVR, is a frequently used model in Europe. It contains 17 variables, including age, gender, comorbidities, pre-operative state, cardiac and operation-related factors (32, 33). An updated version (EuroSCORE-II) has been announced at the EACTS meeting in Lisbon in 2011. However, this risk model does not account for other potentially relevant prognostic factors such as baseline obesity or smoking status on outcomes after TAVR. Furthermore, the Valve Academic Research Consortium (VARC)-2 classification, which is frequently used for endpoint definitions after TAVR, is also limited because it does not include neurocognitive endpoints such as cerebral ischemic lesions detected with diffusion weighted magnetic resonance imaging (DWI-lesions), and POD after TAVR (34).

With the increasing number of TAVR, and expanding indications towards patients with lower surgical risk, understanding the role of additional prognostic factors that are not included in the EuroSCORE (i.e., smoking status, body mass index), and a broad definition of endpoints after TAVR are crucial. Optimized patient selection based on appropriate risk stratification models and accurate endpoint definitions after TAVR may reduce the risk of mortality from severe comorbidities related to TAVR and maximize the benefit of this treatment. In this case, there is a need for further expansion and optimization of current risk models and endpoint definitions among patients undergoing TAVR.

Thesis outlines

Aims of this thesis was to evaluate the prognostic effect of patient-based and peri-procedural factors on clinical outcomes such as smoking status, body mass index, and delirium after TAVR. **Chapter 2** will evaluate the incidence and prognostic effect of POD after TAVR and give details on the predictive factors on delirium following TAVR. **Chapter 3** gives a comprehensive review and meta-analysis of the literature on the incidence of POD after TAVR, and pools the effect of possible predictive factors. **Chapter 4** will give more insight on the association between cerebral ischemic lesions detect with diffusion weighted magnetic resonance imaging (DWI-MRI) and POD after TAVR. **Chapter 5** evaluates the short-term and long-term cognitive function after TAVR. **Chapter 6** and **7** assesses the prognostic effect of body mass index and smoking status on outcome after TAVR, respectively. Finally, practical recommendations are made in order to guide clinicians in patient selection and to reduce burden of delirium after TAVR.

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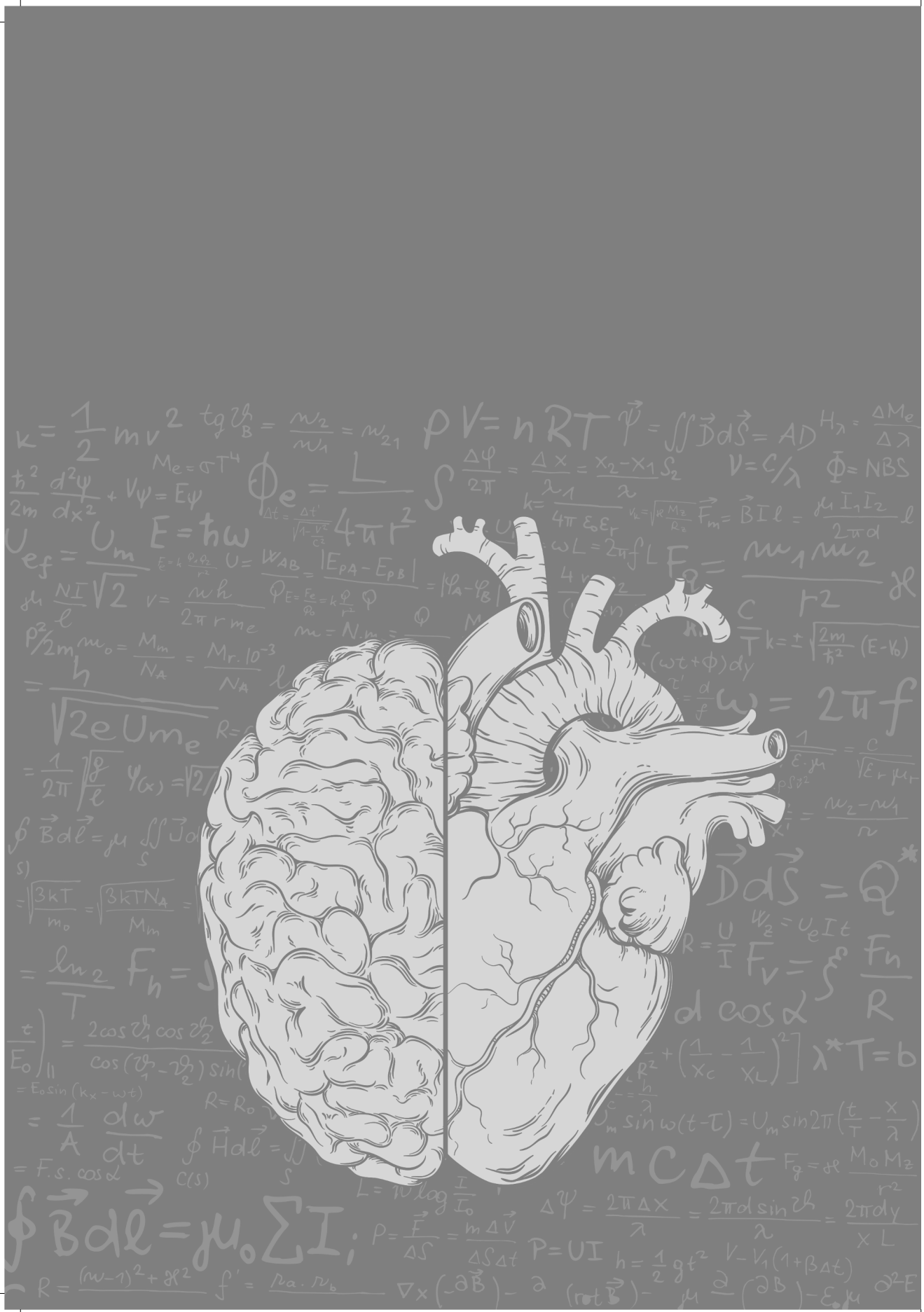

Chapter 2

Incidence, Predictive Factors, and Effect of Delirium After Transcatheter Aortic Valve Replacement

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PERSPECTIVES

WHAT IS KNOWN? In cardiac surgery, postoperative delirium (POD) complicates the post-operative course with prolonged in-hospital stay and increased long-term mortality. Despite the potential effect of delirium on outcomes after TAVR and the susceptibility of these patients, little is known regarding POD after TAVR.

WHAT IS NEW? The incidence of POD is 13.4% in this cohort, which is 5-fold higher in nontransfemoral TAVR (45% vs. 8%). The baseline independent predictors of POD are nontransfemoral TAVR, age, carotid artery disease, current smoking, and atrial fibrillation. The occurrence of POD was associated with prolonged inhospital stay regardless of complications, and remained an independent predictor of mortality in a transfemoral TAVR but not in nontransfemoral TAVR when adjusted for age, sex, logistic EuroSCORE, and the occurrence of complications.

WHAT IS NEXT? The predictors identified in this study can aid the identification of TAVR patients who are at higher risk for developing POD and who will benefit most from intensified surveillance and targeted prevention.

ABSTRACT

Aims: The purpose of this study was to investigate the incidence, predictive factors and effect of postoperative delirium (POD) among patients treated by transcatheter aortic valve replacement (TAVR).

Background: Patients undergoing operations that involves valve replacement appear at higher risk of POD than patients subjected to coronary artery bypass surgery alone. In patients with severe aortic stenosis undergoing TAVR, little is known regarding the potential effect of POD on the clinical outcomes.

Methods: A retrospective observational cohort study of 268 consecutive patients who underwent TAVR at our institute was conducted. Delirium was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorder, 4rd Edition criteria. Primary outcome of this study was the presence of in-hospital POD after TAVR.

Results: The incidence of POD after TAVI was 13.4% (n=36). Of these cases, 18 were associated with post-procedural complications, including major vascular complications/ bleeding (n=4), stroke (n=3), acute kidney injury (n=3), atrial fibrillation (n=4) and infectious disease (n=4). POD was most frequently diagnosed on the second day after TAVI (IQR: 1-5) and was associated with prolonged in-hospital stay regardless of complications (in uncomplicated TAVI: 6 [5-10] vs. 5 [4-5] days, p<0.001; and in complicated TAVI: 9 [8-15] vs. 6 [5-9] days, p<0.001). Predictors of POD were non- transfemoral (transapical/transaortic) access (Odds Radio [OR] 7.74; 95% confidence interval [CI] 3.26-18.1), current smoking (OR 3.99; 95% CI 1.25-12.8), carotid artery disease (OR 3.88; 95% CI 1.50-10.1), atrial fibrillation (OR 2.74; 95% CI1.17-6.37) and age (OR 1.08; 95% CI 1.00-1.17, per year increase). After a median follow-up of 16 [6-27] months, POD remained an independent predictor of mortality in patients undergoing transfemoral TAVI compared to the non-transfemoral TAVI (Hazard Ratio: 2.81; 95% CI 1.16-6.83 vs. 0.43; 95% Cl 0.10-1.76), adjusted for possible confounders in a time-dependent Cox-regression model (i.e., age, sex, Logistic EuroSCORE and the occurrence of complications).

Conclusions: POD after TAVI has an incidence of around 13% and occurs early in the postoperative course. Non-transfemoral access is strongly associated with the occurrence of POD. Patients who develop POD show prolonged in-hospital stay and impaired long term survival.

BACKGROUND

Delirium is an acute organic brain syndrome that often complicates the post-operative course of cardiac surgery (1,2). The incidence of post-operative delirium (POD) after cardiac surgery ranges between 8% and 31% (3–7), increasing with age to 25% to 52% in patients age ≥60 years (8–10) and 31% to 66% in patients age ≥70 years (11–13). Differences in study design and diagnostic criteria are likely responsible for the variance in the reported incidence of POD, as delirium is a clinical diagnosis easily overlooked. A hallmark of delirium is the acute onset and fluctuating course of symptoms related to cognitive dysfunction, including decreased consciousness, inattention, disorientation, and impaired memory (1). Depending on the presence of psychomotor disturbances, delirium can be classified as either hyperactive, hypoactive, or mixed (14). The etiology of delirium involves a complex interaction among predisposing factors (e.g., advanced age, pre-existing cognitive impairment, and previous stroke) and precipitating factors (e.g., surgery, medication changes, and hospitalization) (1).

Although mostly transient, delirium is not a benign cognitive disorder. After cardiac surgery, delirium prolongs mechanical ventilation time (14,15), and intensive care unit and hospital stay (7,15–17), and is associated with sepsis (18) and increased perioperative mortality (13,15). Furthermore, it negatively affects early functional and cognitive performance (6,19,20) and is related to increased mortality for up to 10 years (6,17,21). Moreover, delirium in general is linked to an elevated risk of dementia (22) and dramatically accelerates cognitive decline in Alzheimer disease (23). Whether delirium itself can induce dementia remains controversial, although there is evidence supporting this theory (24).

Nonpharmacological strategies have shown effectiveness in the prevention of delirium in surgical patients, reducing the incidence by 30% to 40%, resulting in less morbidity, shorter length of stay, and reduced medical costs (25). Knowledge of the predictive factors of POD is crucial to identify patients who are at increased risk, and most likely to benefit from preventive measures and intensified post-operative monitoring. Numerous predictors of POD after cardiac surgery have been identified, of which higher age (3–5,7,11,15,26), cognitive impairment (3,4,7,8,10,13), active depression (4,7,10,14), atrial fibrillation (4,5,7), and cardiopulmonary bypass time (3,5,13,14) are most consistently reported.

Patients undergoing operations that involve valve replacement appear at higher risk of POD than patients subjected to coronary artery bypass surgery alone (8,27–29). Nowadays, transcatheter aortic valve replacement (TAVR) is used as an alternative to surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis (AS) who are deemed to be inoperable or at high surgical risk (30). Characterized by advanced age, frailty, and extensive comorbidities, patients undergoing TAVR seem particularly prone to develop POD. Despite the potential effect of delirium on outcomes and the vulnerability of typical candidates for the procedure, little is known regarding POD after TAVR. By means of this retrospective, descriptive study, we sought to investigate the incidence, predictive factors, and effect of POD among patients treated with TAVR.

METHODS

This is a retrospective single-center study. All patients who underwent TAVR for severe native AS at the University Medical Center Utrecht were identified in our institutional database and included in the study. Eligibility for TAVR was discussed by the heart team and required the consensus of at least 1 interventional cardiologist and 1 cardiac surgeon. Motivations to refuse SAVR in patients were high operative risk (as assessed by logistic EuroSCORE >15%) or the presence of contraindications to cardiac surgery (e.g., porcelain aorta, frailty, or patent grafts in proximity of the sternum). Frailty was subjectively measured before allocating TAVR by an interventional cardiologist and/or cardiothoracic surgeon on the basis of the informal "eyeball test" (including cognition function, physical weakness, and walk speed). Patients previously diagnosed with pre-cognitive impairment were excluded. All patients gave informed consent for the procedure, and due to the retrospective nature of the study design, ethics committee approval was waived.

Study Endpoints

The primary outcome of this study was the presence of delirium on any day during the inhospital stay after TAVR. In case of suspected delirium observed by the nurse or attending physician, a delirium observational score (DOS) was used for further assessment. The DOS combines an assessment of the patient's level of consciousness with an evaluation of mental status, inattention, and disorganized thinking. When scoring >3 points, a trained geriatrician was consulted to establish or exclude the diagnosis of delirium on the basis of Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria (Table 1). If the diagnosis of delirium was established, a standardized work-up to exclude precipitating factors was set up (31). Other clinical outcomes were adjudicated in compliance with the Valve Academic Research Consortium-2 criteria (32). Vascular complications were documented for all procedural "access sites," defined as any location traversed by a guidewire, a catheter, or a sheath during the procedure, including arteries, veins, left ventricular apex, and the aorta. Post-discharge survival status was established by contacting the Municipal Civil Registries.

Implantation Procedure

Patients were admitted 1 day before the procedure at our institution (if they were not already admitted because of clinical instability). Valve implantation was performed per the transfemoral, transapical, or transaortic approach, in order of our institutional preference, depending on the presence of suitable access sites. Common access techniques were used. All transfemoral procedures involved a fully percutaneous technique. Conscious sedation was the default anesthetic method in transfemoral procedures; in nontransfemoral TAVR, general anesthesia was instituted. For the transfemoral approach, conscious sedation was established by intravenous infusion of the sedative propofol and the analgesic remifentanil. Sedation was assessed according to the Ramsay sedation scale and was maintained between 3 and 5. Local anesthesia of the access sites was performed by lidocaine infiltration. After the procedure, transfemoral patients were transferred directly to the ward, avoiding any intensive care stay (including the coronary care unit). Nontransfemoral patients stayed for at least 1 night in the intensive care unit, followed by the surgical medium care unit and thereafter the ward.

Statistical Analysis

Categorical variables are expressed as frequencies and percentages and were compared with the chi-square or Fisher exact test. Continuous variables are expressed as mean and SD if normally distributed or as median (interquartile range [IQR]) if skewed and compared with the Student t test or its nonparametric equivalents, respectively.

Univariable variables with p values <0.10 were entered in the backward stepwise multivariable logistic regression to identify the pre-procedural risk factors of POD. Collinearity diagnostics were evaluated for all variables considered for multivariable analysis. In case of multicollinearity, the variable with the higher odds ratio (OR) was incorporated into the model. The association between POD and mortality was analyzed using Kaplan-Meier survival estimates and the log-rank test. To isolate the association of POD with all-cause mortality, a Cox regression model was developed including possible confounders (i.e., age, sex, any post-procedural complication, and logistic EuroSCORE). The proportional hazards assumption was tested for each variable by visual inspection of the log-minus-log plots. Non-proportionality was accounted for by incorporation of time-dependent covariates. Results are reported as ORs or hazard ratios (HRs), where appropriate, with 95% confidence intervals (CIs). All tests were 2-tailed, and a p value ≤0.05 was considered statistically significant. All statistical analyses were carried out using the IBM Statistical Package for Social Science for Windows, version 21.0 (IBM Corp., Armonk, New York) and GraphPad Prism, version 6 (GraphPad Software, La Jolla, California).

RESULTS

Between November 2011 and December 2014, 270 patients underwent TAVR because of severe symptomatic AS at the University Medical Center Utrecht. Two patients (0.7%) were excluded because of known Alzheimer disease, leaving 268 patients for further analysis. There were no cases of delirium observed before the procedure. The overall incidence of POD diagnosed in accordance with DSM-IV criteria was 13.4% (n= 36). Baseline characteristics and procedural and hospital outcomes of the study population stratified according to the occurrence of POD are summarized in Tables 2 to 4.

Table 1. Diagnostic Criteria for Delirium according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.

I	Disturbance of consciousness (i.e. reduced clarity of awareness of the environment, with reduced ability to focus, sustain, or shift attention).
II	A change in cognition (such as memory deficit, disorientation, language disturbance) or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
III	The disturbance is developed over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
IV	Delirium is caused by the direct physiologic consequences of a general medical condition (further criteria for specific forms of delirium caused by substance intoxication or withdrawal).

Pre-operatively, the POD versus non-POD groups differed significantly in the rates of carotid disease (33% vs. 9%; p <0.001), peripheral artery disease (50% vs. 9%; p <0.001), and current smoking habit (22% vs. 18%; p = 0.013). Regarding procedural features, patients who developed POD more frequently underwent nontransfemoral procedures (50% vs. 10%; p <0.001), more frequently received general anesthesia (50% vs. 15%; p <0.001), and underwent longer procedures (140 min vs. 124 min; p = 0.014). Concerning clinical outcomes, stroke (8% vs. 1%; p = 0.034), cardiac tamponade (11% vs. 2%; p = 0.013), post-operative atrial fibrillation (11% vs. 0%; p < 0.001), infectious disease (11% vs. 0.4%; p = 0.001), and acute kidney injury (8% vs. 2%; p = 0.053) were more prevalent in the POD group. Of the 36 POD cases, 18 were associated with at least 1 post-procedural complication, including major vascular complications/bleeding (n = 4), stroke (n = 3), acute kidney injury (n = 3), atrial fibrillation (n = 4), and infectious disease (n = 4).

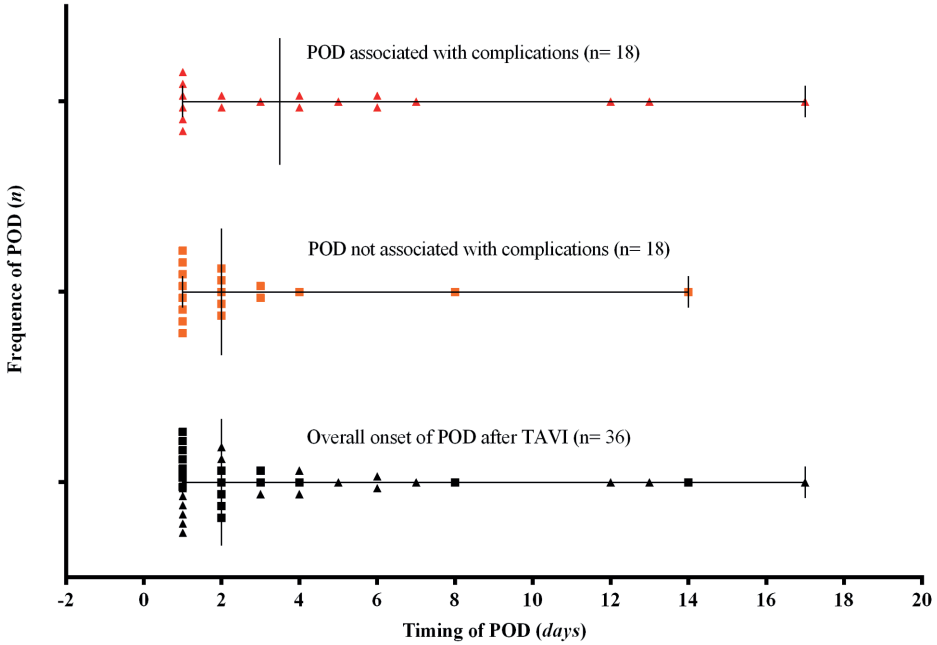

Figure 1. Time to Onset of POD After Transcatheter Aortic Valve Replacement.

Delirium was most frequently diagnosed on day 2 (IQR: 1 to 5 days) after TAVR (Figure 1) and was associated with prolonged in-hospital stay regardless of complications (in uncomplicated TAVR: 6 days [IQR: 5 to 10 days] vs. 5 days [IQR: 4 to 5 days]; p < 0.001; and in complicated TAVR: 9 days [IQR: 8 to 15 days] vs. 6 days [IQR: 5 to 9 days]; p < 0.001) (Figure 2).

Multivariable logistic regression analysis showed that nontransfemoral access (OR: 7.74; 95% CI: 3.26 to 18.10), current smoking (OR: 3.99; 95% CI: 1.25 to 12.80), carotid artery disease (OR: 3.88; 95% CI: 1.50 to 10.10), atrial fibrillation (OR: 2.74; 95% CI: 1.17 to 6.37), and age (OR: 1.08; 95% CI: 1.00 to 1.17) were independent predictors of POD (Table 5). General anesthesia was not incorporated in the model because of multicollinearity with nontransfemoral access.

Table 2. Baseline clinical characteristics of the total study population.

		Delirium		
	Overall (n=268) [*n* (%)]	**Yes (n=36)** [*n* (%)]	**No (n=232)** [*n* (%)]	**p**
Age, years	80±7	82±5	80±8	0.094
Gender, male	123 (46)	17 (47)	106 (46)	0.864
BMI, Kg/m^2	26±4	26±4	26±4	0.830
BSA, m^2	1.83±0.20	1.79 ±0.18	1.84±0.20	0.443
Logistic EuroSCORE	18±9	20±10	17±9	0.814
NYHA class III-IV	154 (60)	24 (69)	130 (58)	0.238
Recent decompensation	50 (19)	11 (31)	39 (17)	0.050
Diabetes mellitus	82 (31)	11 (31)	71 (31)	0.995
Dialyses	4 (2)	2 (6)	2 (1)	0.088
Hypertension	154 (58)	26 (72)	128 (55)	0.054
Dyslipidemia	88 (33)	15 (42)	73 (32)	0.225
Smoking status				
Never smoker	180 (67)	19 (53)	161 (69)	0.048
Prior smoker	62 (23)	9 (25)	53 (23)	0.775
Current smoker	26 (10)	8 (22)	18 (8)	0.013
COPD	57 (21)	8 (22)	49 (21)	0.881
Estimated GFR, ml/min	57±22	51±24	58±21	0.571
Syncope	36 (14)	6 (17)	30 (13)	0.439
Carotid artery disease*	33 (12)	12 (33)	21 (9)	0.000
Prior stroke	35 (13)	5 (14)	30 (13)	0.795
Peripheral artery disease	62 (23)	18 (50)	44 (19)	0.000
Coronary artery disease	144 (54)	20 (56)	124 (53)	0.813
Prior myocardial infarction	49 (18)	9 (25)	40 (17)	0.262
Prior PCI	109 (41)	15 (42)	94 (41)	0.896
Prior CABG	49 (18)	6 (17)	43 (19)	0.787
Prior BAV	8 (3)	0	8 (3)	0.603
Atrial fibrillation	92 (34)	17 (47)	75 (32)	0.080
Prior pacemaker implantation	21 (8)	2 (6)	19 (8)	0.749
Pulmonary hypertension	12 (5)	2 (6)	10 (4)	0.667
Active malignancy	16 (6)	1 (3)	15 (7)	0.704
Liver disease	5 (2)	1 (3)	4 (2)	0.517
Frailty	63 (24)	9 (25)	54 (23)	0.820

Abbreviations. Values are mean ±SD or n (%). *Prior or planned carotid artery intervention and/or ≥50% diameter stenosis of the common carotid artery evaluated by computed tomography angiography or Duplex investigation.

BAV = balloon aortic valvuloplasty; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; GFR = glomerular filtration rate; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

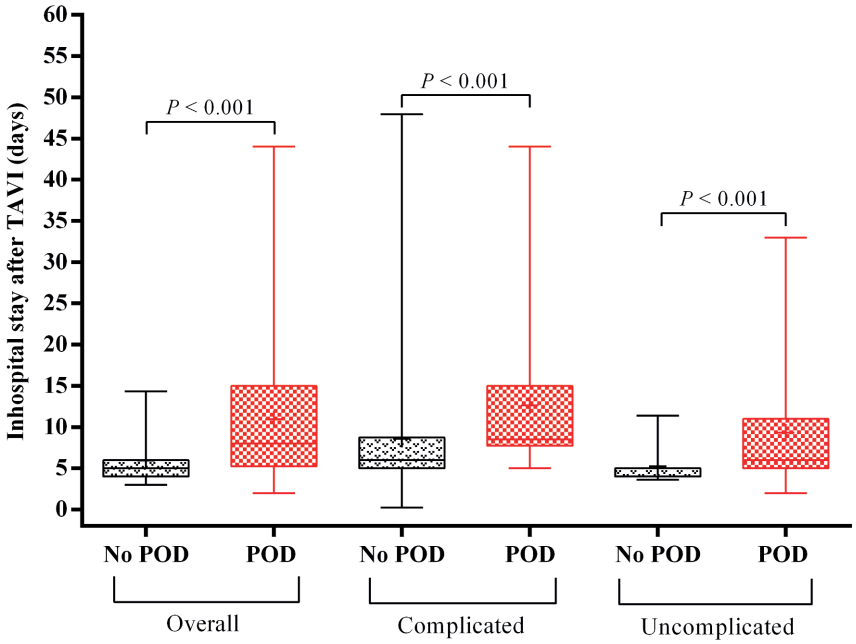

Figure 2. Post-Operative In-Hospital Stay.

Table 3. Procedural features.

		Delirium		p
	Overall (n=268) [*n* (%)]	**Yes (n=36)** [*n* (%)]	**No (n=232)** [*n* (%)]	
Procedural approach				0.000
TF	228 (85)	18 (50)	210 (91)	0.000
TF with general anesthesia	12 (5)	0	12 (6)	0.379
Non transfemoral access *	40 (15)	18 (50)	22 (10)	0.000
General anesthesia	52 (19)	18 (50)	34 (15)	0.000
Balloon-expandable valve	174 (65)	27 (75)	147 (63)	0.173
Postdilatation	55 (21)	4 (11)	51 (22)	0.133
Conversion to surgery	1 (0.4)	0	1 (0.4)	1.000
Intra-procedural death	1 (0.4)	0	1 (0.4)	1.000
Radiation, mGy	683[390-1021]	701[408-975]	694[392-1165]	0.244
Contrast volume, ml	159±51	159±59	160±50	0.847
Procedural time, min	124[112-145]	140[122-159]	124[110-144]	0.014
Interventional time, min	85[73-105]	90[76-110]	85[74-104]	0.330

Values are n (%), median (interquartile range), or mean ±SD. *Transapical/transaortic.
TF = transfemoral approach.

Table 4. Inhospital clinical outcome.

		Delirium		p
	Overall (n=268) [*n* (%)]	Yes (n=36) [*n* (%)]	No (n=232) [*n* (%)]	
Permanent pacemaker implantation	29 (11)	6 (17)	23 (10)	0.247
Stroke	6 (2)	3 (8)	3 (1)	0.034
Myocardial infarction	3 (1)	1 (3)	2 (1)	0.352
Cardiac tamponade	8 (3)	4 (11)	4 (2)	0.013
Atrium fibrillation	4 (2)	4 (11)	0	0.000
Infection	5 (1.9)	4 (11.1)	1 (0.4)	0.001
Any acute kidney injury	29 (11)	5 (14)	24 (10)	0.563
Acute kidney injury stage II/III	7 (3)	3 (8)	4 (2)	0.053
Major vascular complication	20 (8)	4 (11)	16 (7)	0.323
Bleeding(any)	80 (30)	14 (39)	66 (28)	0.240
Major or life-threatening bleeding	21 (8)	4 (11)	17 (7)	0.500
All-cause mortality	7 (3)	1 (3)	6 (3)	1.000

Values are n (%).

Table 5. Baseline and procedural predictors for POD in univariable and multivariable analysis.

	Univariable	p	Multivariable	p
	OR (95% CI)		OR (95% CI)	
Age	1.04 (0.98-1.10)	0.160	1.08 (1.00-1.17)	0.041
Atrial fibrillation	1.87 (0.92-3.81)	0.083	2.74 (1.17-6.37)	0.020
Carotid artery disease	5.02 (2.20-11.5)	0.000	3.88 (1.50-10.1)	0.005
Current smoker	3.39 (1.35-8.53)	0.009	3.99 (1.25-12.8)	0.020
Peripheral artery disease	4.27 (2.06-8.87)	0.000	-	-
Hypertension	2.11 (0.97-4.58)	0.058	-	-
Non transfemoral access*	9.55 (4.34-21.0)	0.000	7.74 (3.26-18.1)	0.000
General anaesthesia	5.82 (2.75-12.3)	0.000	-	-

Values are odds ratio (95% confidence interval). *Transapical or transaortic transcatheter aortic valve replacement approach.

After a median follow-up of 16 months (IQR: 6 to 27 months), overall mortality was 18%. Patients who developed POD demonstrated higher mortality in transfemoral TAVR (39% vs. 13%; p = 0.003) but not in nontransfemoral TAVR (33% vs. 36%; p = 0.841). POD remained a significant predictor of mortality in transfemoral TAVR (HR: 2.81; 95% CI: 1.16 to 6.83), but not in nontransfemoral TAVR (HR: 0.43; 95% CI: 0.10 to 1.76), independent of age, sex, logistic EuroSCORE, and the occurrence of complications (Table 6, Figures 3 and 4).

Table 6. Adapted guidelines for prevention of delirium in at-risk adults from National Institute for Health and Care Excellence (NICE).

Preoperative assessment	
1	Avoid moving persons within and between wards or rooms unless absolutely necessary.
2	Give a tailored, multicomponent intervention package based on the risk factors for delirium.
Postoperative care	
3	Reorient the patient at risk by providing appropriate lighting and clear signage, ensuring that a clock (consider providing a 24-hour clock in the critical care unit) and a calendar are easily visible
4	Address dehydration and constipation by ensuring adequate fluid intake
5	Assess for hypoxia and optimize oxygen saturation, if necessary, as clinically appropriate
6	Treat infections and avoid unnecessary catheterization
7	Promote mobility
8	Address and assessing for pain
9	Carry out a medication review for persons receiving several drugs, taking into account both the type and the number of medications
10	Address poor nutrition by following the advice given in the nutrition support in adults section in the NICE clinical guideline
11	Screen and address sensory impairment by providing hearing and visual aids
12	Promote good sleep patterns

DISCUSSION

In the present study, we investigated the incidence, predictors, and effect of POD after TAVR. The incidence of POD (on the basis of DSM-IV criteria) was 13.4% in this cohort. Nontransfemoral TAVR, increased age, carotid artery disease, current smoking habit, and AF were independent predictors of POD. The occurrence of POD was associated with prolonged in-hospital stay regardless of complications and remained an independent predictor of mortality in transfemoral TAVR but not in nontransfemoral TAVR when adjusted for age, sex, logistic EuroSCORE, and the occurrence of complications.

Post-operative delirium is an outcome that certainly deserves attention in TAVR, as the typical target TAVR patient and several procedural aspects of TAVR designate this intervention as "high risk" of being complicated by delirium. Advanced age and significant comorbidities may predispose all TAVR candidates to POD. Moreover, ischemic brain injury, 1 of the mechanisms suspected to cause POD through alteration of cerebral acetylcholine levels (33), is commonly encountered in TAVR. In cardiac surgery, a higher microembolic load (34), elevated biomarkers of brain tissue damage (35), and clinical cerebrovascular events (5,10,26) have been associated with POD. In response to brain injury, increased microglia activity induced by neuroinflammation in the brain has been hypothesized to be 1 of the mechanisms that may contribute to POD (36). Brain injury related to TAVR most often involves (micro)infarctions caused by cerebral embolization of aortic plaque or valve particles dislodged during prosthesis positioning and deployment (37). Rapid ventricular

pacing may also contribute to ischemic brain injury by causing episodic hypotension and cerebral hypoperfusion (38).

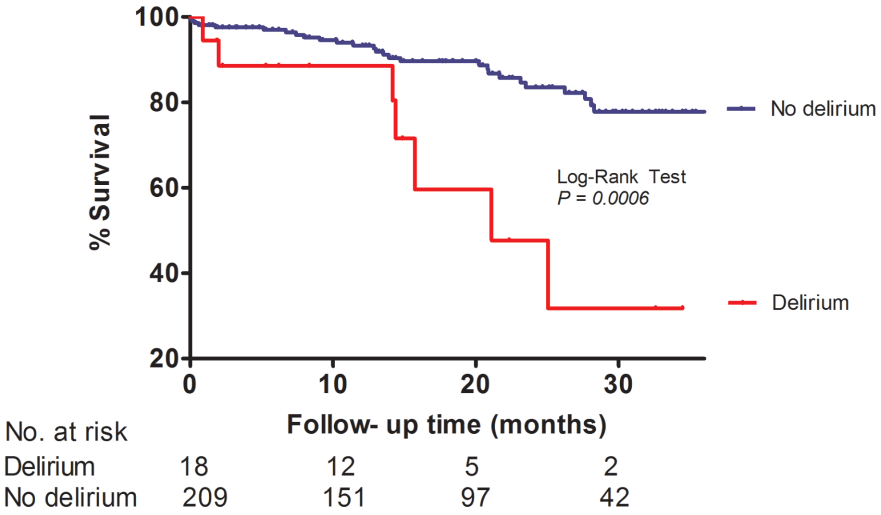

Figure 3. Kaplan-Meier Survival Curves of the Association Between POD After Transfemoral TAVR and Mortality.

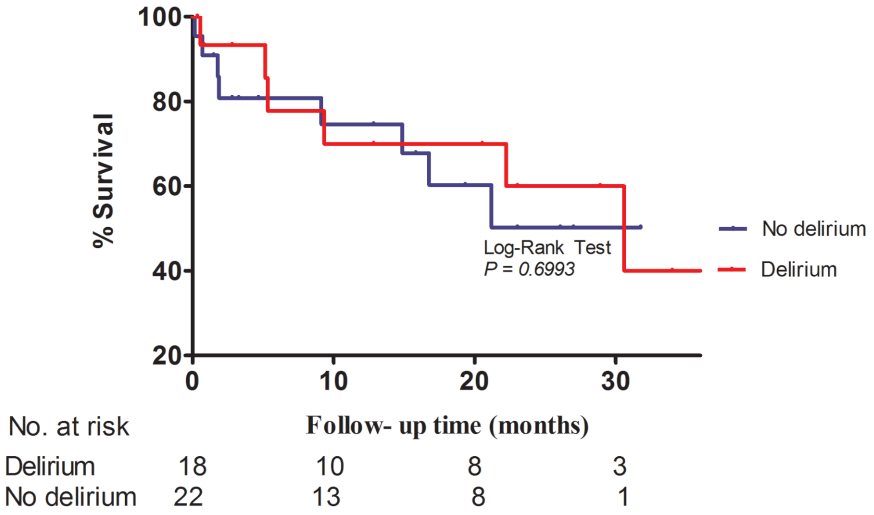

Figure 4. Kaplan-Meier Survival Curves of the Association Between POD After Nontransfemoral TAVR and Mortality.

Data on the incidence of delirium after TAVR are scarce, as the present study is 1 of the first on this topic. A previous small cohort study (including patients treated in 2008 and 2009, n=122) reported a 12% incidence of POD after transfemoral TAVR and 53% after transapical TAVR (39). This is in line with the 8% and 45% POD rate after transfemoral and nontransfemoral TAVR in our analysis. Despite extensive comorbidities, POD appears

to occur substantially less often after transfemoral TAVR (<10%) than after SAVR in elderly patients (31% to 66%), whereas the incidence of POD after nontransfemoral TAVR (~50%) seems to approach that of SAVR (8,12). Recently, a nonrandomized prospective study investigating POD in octogenarians after TAVR and SAVR reported SAVR as a risk factor for POD, with a 22% higher incidence compared with TAVR (12). The reported 44% rate of POD after TAVR in this study is difficult to interpret, however, due to the absence of data on procedural access and the use of a different diagnostic tool (confusion assessment method) for delirium.

Similar to previous data, nontransfemoral access was identified as the strongest predictor of POD in the present analysis (39). A distinct feature of patients with nontransfemoral access is the presence of advanced vascular disease, which may be indicative of coexisting cerebrovascular disease, creating increased potential for intraprocedural cerebral ischemia and POD. Otherwise, nontransfemoral procedures involve a stronger noxious stimulus than transfemoral TAVR, due to the need for general anesthesia, the intensive care stay, and the disorienting effect of the frequent change of environment, and is therefore more likely to precipitate delirium. Nontransfemoral access also comes with post-operative pain, increased opioid use, and post-operative inflammation, all factors capable of triggering POD. Although significantly associated with POD in the univariable analysis, the independent effect of general anesthesia could not be assessed in the present study because of multicollinearity with nontransfemoral TAVR. General anesthesia has been linked to post-operative cognitive dysfunction, as general anesthetics exert an anticholinergic effect and interfere with many neural processes, involving intracellular calcium signaling, receptor functioning, and gene transcription (40). Clinical data on the relevance of anesthetic technique (general anesthesia vs. local anesthesia sedation) in provoking delirium are inconclusive. However, considering the many procedural aspects that may promote delirium, it seems implausible that anesthetic technique is solely causative for the higher rate of POD in nontransfemoral TAVR.

All remaining predictors found in this study, including older age (3–5,7,11,15,26), carotid artery disease (5,26,41), atrial fibrillation (4,5,7), and current smoking (42), have been previously related to POD in cardiac surgery. The common denominator of these factors may be their involvement in the causative chain of ischemic brain injury through an association with (cerebral) atherosclerosis or thromboembolism. Older age is also a risk factor of POD due to an age-dependent decrease in neurotransmitter release and overtime accumulation of cerebral tissue damage that aggravate susceptibly to brain dysfunction (1,43). Besides promoting atherosclerosis, active smoking has been hypothesized to contribute to POD by abrupt cessation during hospitalization, because nicotine withdrawal involves acetylcholine disturbances similar to POD (44). Pre-operative AF not only is postulated to predispose to POD by inflicting thromboembolic brain damage, but may additionally provoke periods of hypotension causing cerebral hypoperfusion (45).

Analogous to observations in conventional cardiac surgery, POD after TAVR was related to an adverse outcome in the present analysis, characterized by prolonged in-hospital stay, and, in case of transfemoral TAVR, elevated follow-up mortality. Stratification according to the presence of post-operative complications (other than delirium) demonstrated that POD in itself leads to prolonged hospitalization after TAVR. To what extent increased morbidity and mortality can be truly attributed to POD is difficult to establish (46). Rather than being

causally related to adverse events, POD may reflect a patient's decreased resilience against noxious stimuli (i.e., fragility), merely identifying those individuals already predisposed to worse treatment outcomes. Along similar lines, the occurrence of POD after less physically demanding transfemoral procedures may identify extremely frail patients, which may explain the higher mortality rate. Uncertainty regarding the sequence of events also clouds the perception of the true effect of POD; for example, prolonged mechanical ventilation has been reported as both a predictor as well as a consequence of delirium, and the same holds true for cognitive impairment (7,9,14,15). Nevertheless, in view of the magnitude of evidence reporting unfavorable outcomes and increased medical costs in POD, it certainly seems like an entity to be avoided, especially in the elderly.

Primary prevention and early recognition of delirium have demonstrated effectiveness in reducing delirium incidence and falls. Moreover, prevention may decrease the length of in-hospital stay, reduce the need for institutionalization, and ultimately reduce medical costs (1,25). The predictors identified in this study can aid in the identification of TAVR patients who are at higher risk for developing POD and who will benefit most from intensified surveillance and targeted prevention. Although many predisposing and precipitating factors of delirium are non-modifiable, several nonpharmacological measures can be taken to prevent POD in susceptible patients, as summarized in Table 6 (47). Specifically, in the TAVR setting, it seems advisable to avoid nontransfemoral access whenever justified. To date, there is no consensus on the efficacy of pharmacological therapy in the prevention and treatment of delirium (1). Whether a reduction of embolic burden by cerebral protection devices may positively affect the rate of POD in TAVR seems speculative considering the multifactorial nature of this cognitive disorder.

Study Limitations

The main limitations of this study are related to its retrospective, single-center design. The retrospective assessment of delirium may have led to underestimation of the incidence of delirium, as symptoms can be subtle, especially in the case of the hypoactive form. Furthermore, we were unable to reliably quantify in retrospect the presence of pre-operative cognitive impairment and active depression, important predictors of POD in cardiac surgery. Finally, the relatively small sample size (transfemoral and nontransfemoral groups) did not allow for exhaustive multivariable analysis to fully isolate the independent effect of delirium on follow-up mortality.

Conclusions

Despite their apparent susceptibility, only 1 in 8 TAVR patients develops delirium during the post-operative course. The incidence of POD heavily depends on procedural access, with a 5-fold higher rate in nontransfemoral compared with transfemoral TAVR. Besides procedural access, older age; carotid artery disease; current smoking; and pre-operative AF were identified as independent predictors of POD. Postoperative delirium after TAVR was associated with prolonged in-hospital stay and increased all-cause mortality during follow-up. Early recognition and prevention strategies may decrease the incidence of POD and improve outcomes in TAVR patients. Future large prospective studies are needed to confirm these first findings on POD after TAVR.

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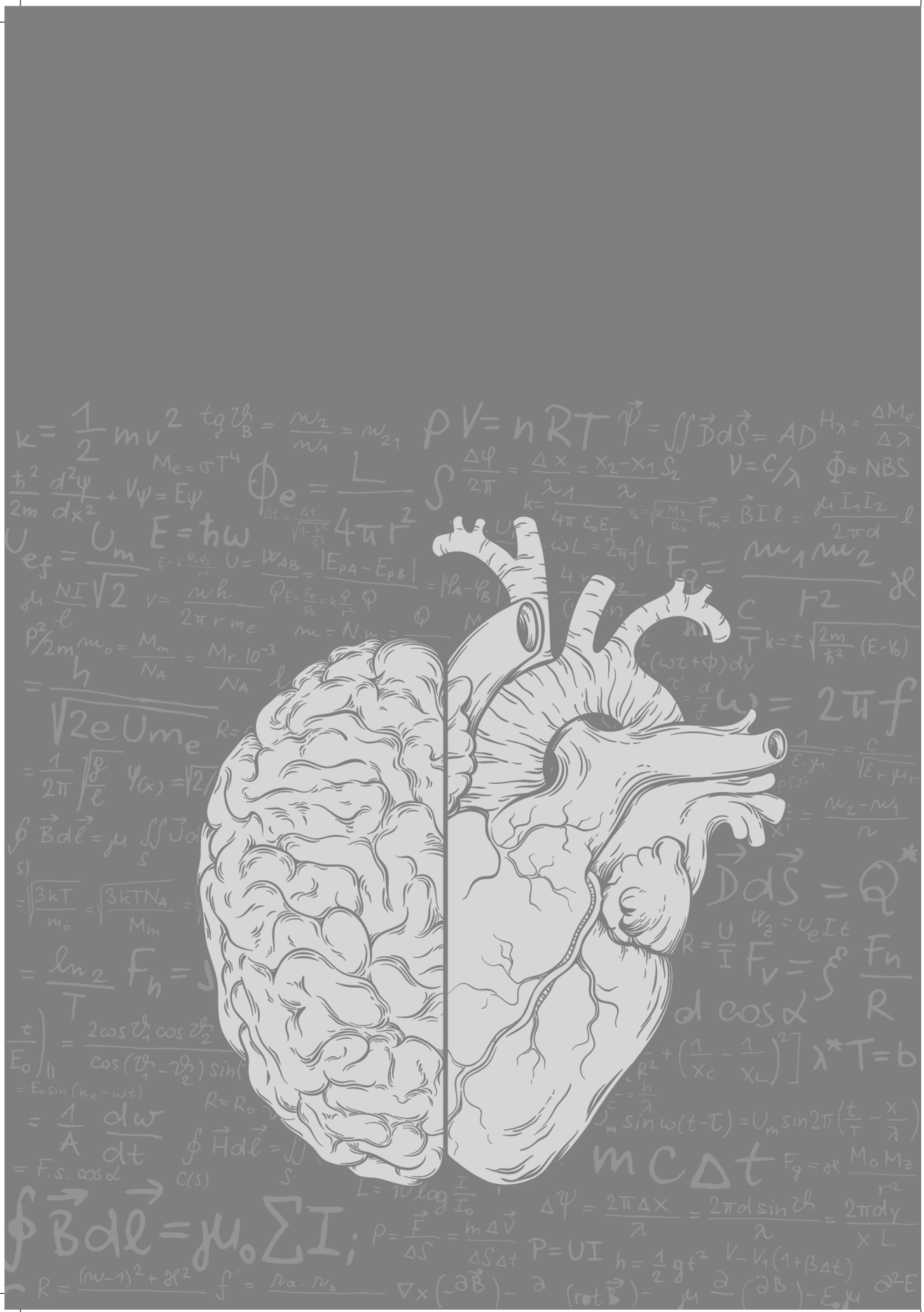

Chapter 3

Postoperative Delirium in Individuals Undergoing Transcatheter Aortic Valve Replacement: *A Systematic Review and Meta-Analysis*

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ABSTRACT

Objectives: To evaluate the incidence of in-hospital postoperative delirium (IHPOD) after transcatheter aortic valve replacement (TAVR).

Design: Systematic review and meta-analysis.

Setting: Elective procedures.

Participants: Individuals undergoing TAVR.

Measurements: A literature search was conducted in PubMed, Embase, BioMedCentral, Google Scholar, and the Cochrane Central Register of Controlled Trials (up to December 2017). All observational studies reporting the incidence of IHPOD after TAVR (sample size > 25) were included in our meta-analysis. The reported incidence rates were weighted to obtain a pooled estimate rate with 95% confidence interval (CI).

Results: Of 96 potentially relevant articles, 31 with a total of 32,389 individuals who underwent TAVR were included in the meta-analysis. The crude incidence of IHPOD after TAVR ranged from 0% to 44.6% in included studies, with a pooled estimate rate of 8.1% (95% CI=6.7–9.4%); heterogeneity was high (Q = 449; I2 = 93%; P heterogeneity < .001). The pooled estimate rate of IHPOD was 7.2% (95% CI=5.4–9.1%) after transfemoral (TF) TAVR and 21.4% (95% CI=10.3–32.5%) after non- TF TAVR.

Conclusion: Delirium occurs frequently after TAVR and is more common after non-TF than TF procedures. Recommendations are made with the aim of standardizing future research to reduce heterogeneity between studies on this important healthcare problem.

BACKGROUND

Individuals with severe aortic valve stenosis (AS) have a significantly more-limited prognosis than those with other valvular heart diseases, with a prevalence of 12% in individuals aged 75 and older.[1] When left untreated, 2- and 5-year overall survival for symptomatic severe AS are 50% and 20%, respectively.[1] Transcatheter aortic valve replacement (TAVR) has emerged as a valuable option to treat severe symptomatic AS in older adults considered to be at high risk of surgical aortic valve replacement (SAVR).[2,3] Studies have generally shown no change in cognition or cognitive improvement at 3 to 6 months follow-up after TAVR.[4–7] According to other studies, inhospital postoperative delirium (IHPOD) is frequently observed early after TAVR[8,9] and is associated with prolonged hospital stay, readmission, and mortality after TAVR, thus being an important clinical concern.[8,10,11]

Delirium is an acute confusional state, characterized by disturbed consciousness, altered cognition, and inattention.[12] Unlike chronic age-related cognitive dysfunction such as dementia, delirium develops over a short period of time (e.g., hours to days or months), represents a change from baseline, and tends to fluctuate during the course of the day and night.[12] Because postoperative complications (i.e., infection, cerebral ischaemic stroke, paravalvular aortic regurgitation, cardiac conduction abnormalities, atrial fibrillation, vascular or bleeding complications) are commonly observed in individuals with IHPOD after TAVR, it is unclear whether delirium affects mortality after TAVR irrespective of postoperative complications. In other settings, such as elective major orthopedic, vascular, or abdominal surgery, postoperative complications and IHPOD were separately associated with prolonged hospital stay, institutional discharge, and rehospitalization within 30 days of discharge.[13] Because 30% to 40% of delirium cases are preventable,[12] early recognition of delirium and treatment of its underlying precipitating factors are essential to improve outcomes.

Table 1. Differential diagnosis of delirium.

	Delirium	Dementia	Depression	Schizophrenia
Onset	Acute	Insidious	Variable	Variable
Course	Fluctuating	Steady progression	Diurnal variation	Variable
Consciousness and orientation	Clouded; disoriented	Clear until late stages	Generally unimpaired	Unimpaired but patient may be perplexed in acute stages
Attention and memory	Poor short term memory; inattention	Poor short term memory without marked attention	Poor attention but memory intact	Poor attention but memory intact
Psychosis present?	Common	Less common	Less common	Frequent
Electroencephalogram	Abnormal in 80-90%, generalised diffuse slowing in 80%	Abnormal in 80-90%; generalised disuse slowing in 80%	Generally normal	Generally normal

The incidence and prevalence of delirium varies depending on individual characteristics, setting of care, and sensitivity of the detection method. The overall prevalence of delirium in the community-dwelling population is 1% to 2%, although it rises to 14% in those aged 85 and older and 14% to 24% in individuals admitted to the hospital.[14] The incidence of delirium increases with hospitalization: greater than 50% in the intensive care unit, 60% in nursing homes and post-acute care, and 83% at the end of life.[14,15] Reports of the incidence of IHPOD in individuals undergoing TAVR vary widely, limiting their usefulness. According to the literature, the incidence of IHPOD after TAVR ranges from 0% to 44%, with the highest incidence rate in individuals undergoing nontransfemoral (non-TF) TAVR,[16,17] but there have been no systematic reviews or meta-analyses of reports of IHPOD incidence after TAVR. This knowledge is needed for several reasons. In routine clinical settings, it is important to identify subgroups of individuals at risk of delirium to guide preventive strategies. In research settings, accurate estimation of the incidence of delirium after TAVR can be used to calculate the minimum sample size required in intervention trials. Therefore, we performed a systematic review and meta-analysis to evaluate the incidence of POD after TAVR and predictors of POD according to the published literature.

METHODS

Search Strategy and Study Selection

Search strategy, study selection, data extraction, and statistical analysis were performed in accordance with the Meta-analysis of Observational Studies in Epidemiology checklist.[18] Using the terms "TAVR" or "TAVI" or "transcatheter aortic valve implantation" or "transcatheter aortic valve replacement" and "delirium" or "cognition" or "acute confusional state" or "acute brain failure" or "acute brain dysfunction" or "encephalopathy", a comprehensive search of the English-language medical literature was performed. Two authors (MA, CD) independently searched PubMed, Embase, BioMedCentral, Google Scholar, and the Cochrane Central Register of Controlled Trials for articles published between January 1, 2002, and December 1, 2017. We chose 2002 because that was the year that Dr. Cribier in Ruen, France, performed the first TAVR in a human.[19]

All observational prospective or retrospective studies reporting the incidence of IHPOD after TAVR were evaluated for inclusion in our meta-analysis. Studies with fewer than 25 participants and studies with overlapping populations were excluded. Backward snowballing was used (check of reference lists from included studies and pertinent reviews to identify additional citations).

Data Extraction

Two authors (MA, RJ) independently evaluated studies for possible inclusion. Nonrelevant articles were excluded based on title and abstract. Two authors (MA, CD) independently extracted data on study design, participant characteristics, and outcomes. Conflicts about data extraction were discussed and resolved with another author (MP). In case of studies with overlapping populations, the most relevant article or the article with the largest sample size was included. Data were collected on authors, year of publication, study design, sample size, baseline participant clinical characteristics, and observed event rates.

Table 2. Patients study characteristics.

First author	Year	Design	n	Age, mean (SD)	Male (%)	LES, %	TF access	Diagnostic method	Frequency examined (n)	Time period	Incidence of POD (%)
Walther[22]	2010	Propensity matched	100	82.7±5	23	29.4±13.0	0	NA	NA	NA	3
Abdel-Wahab[23]	2011	Prospective	690	81.4±6.3	44	20.4±13.1	638	NA	NA	NA	9.3
Erdoes[17]	2011	Prospective	44	78.6±6	55	28.0±15.0	32	CAM	NA	prior to TAVI, post-procedural days 1 and 4-6	0
Wilbring[40]	2013	Propensity matched	53	77.8±4.5	65	29.9±14.0	0	NA	NA	NA	11.5
Sherif[37]	2014	Prospective	1432	female: 82.8±5.8; male: 80.3±6.4	42.2	NA	1256	NA	NA	NA	9.2
Tse[38]	2014	Retrospective	117	81±8	50.4	NA	74	Physician diagnosis; DSM-IV-TR	NA	NA	27
Santarpino[36]	2015	Propensity matched	102	80±4	41	17.0±14.0	NA	Na	NA	NA	2
Bestehorn[25]	2015	Propensity matched	763	78.8±6	56.5	13.5	763	Physician diagnosis	NA	NA	3.8
Eide[30]	2015	Prospective	65	84.8±2.8	37.0	19.6	NA	CAM	Daily	5 days	44.6
Egerod[28]	2015	Prospective	54	79±7.3	51.9	NA	52	CAM-ICU	2	NA	0
Gauthier[31]	2015	Retrospective	176	84-86	52	NA	117	NA	NA	NA	26.1
Jagielak[33]	2015	Prospective,	32	80.9±5.2	46.9	2.8	0	NA	NA	NA	6.5
Adrie[24]	2015	Propensity matched	26	86 (83-89)	57	32.0	26	CAM-ICU	NA	NA	0

First author	Year	Design	n	Age, mean (SD)	Male (%)	LES, %	TF access	Diagnostic method	Frequency examined (n)	Time period	Incidence of POD (%)
Van Mieghem[39]	2016	Randomized control trial	65	82 (78-85)	52	NA	65	MMSE and MoCA	NA	One day before and 5-7 days after TAVI	9
Neijenhuis[35]	2016	Prospective	591	80.2±8.4	42	NA	337	NA	NA	NA	7.1
Chu[27]	2016	Prospective	30	85±5.5	36.7	NA	0	NA	NA	3	3.3
Eggebrecht[29]	2016	Prospective	17919	81.2±6.1	45	21.1±15.4	17919	NA	NA	NA	3.8
Huded[32]	2016	Retrospective	294	84.3±6.5	53	NA	205	CAM and clinician diagnosis	Twice daily	NA	20.7
Maniar[34]	2016	Retrospective	168	81±8	45	NA	57	CAM-ICU	Every 12 hours	NA	29.2
Abawi[8]	2016	Retrospective	268	80±7	46	18.0±9.0	228	DOS	At the end of every shift	Up to discharge	13.4
Fanning[47]	2016	Prospective	40	81.7±6.9	40	NA	20	CAM and MoCa	3±1 days post procedure	6 months	2.5
Schoenenberger[6]	2016	Prospective	229	83.4±5.5	44.1	17.6±15.8	213	Physician diagnosis	NA	3 months before TAVI, 6 months after	0.9
Serletis-Bizios[44]	2016	Prospective	130	84.7±5.4	52	15.3±8.5	130	NA	NA	NA	4.6
Assmann[11]	2016	Retrospective	89	80.4±6.3	43	15.9±9.8	89	DOS	Daily	During hospital stay	28
Soundhar[45]	2017	Retrospective	7566	81	50.7	NA	NA	ICD-9-CM	NA	NA	4.6
Frerker[42]	2017	Propensity matched	805	77.5±4.4	39.6	NA	805	NA	NA	NA	2.5
Boureau[26]	2017	Prospective	150	83.7±4.6	56	17.0±8.1	NA	NA	NA	NA	12
van Mourik[46]	2017	Retrospective	114	79.6±8.7	32.5	17.6±11.4	114	NA	NA	NA	4.4

First author	Year	Design	n	Age, mean (SD)	Male (%)	LES, %	TF access	Diagnostic method	Frequency examined (n)	Time period	Incidence of POD (%)
Giuseffi[43]	2017	Retrospective	105	79.9±9.5	52	NA	105	CAM-ICU	Every 12 hours	3 days post procedural or up to discharge	19
Bagienski[9]	2017	Retrospective	141	82.0 (77.5–85.0)	36.9	14.0	113	Chart-based	NA	First four days after index procedure	20.6
Fanning[41]	2017	Prospective	31	82.4±7.7	35	16.7±13.2	31	CAM	Daily	During hospital stay	3.2

Abbreviations. CAM = Confusion Assessment Method; DOS = Delirium Observational Scale; ICU = intensive care unit; LES = logistic EuroSCORE; MoCA = Montreal Cognitive Assessment; NA = not available; TAVI = transcatheter aortic valve implantation.

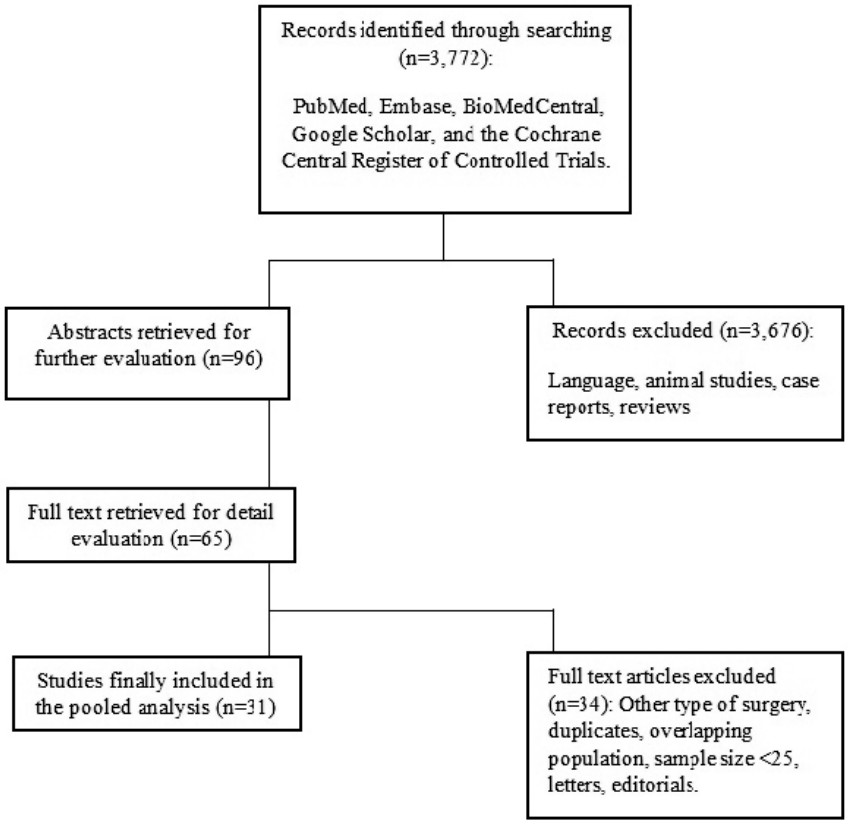


Figure 1. Study flow-chart.

Outcomes

The primary endpoint was the crude IHPOD after TAVR. IHPOD was defined as the presence of delirium during hospital stay after aortic stenosis treatment. Secondary outcomes of interest were incidence of IHPOD as defined using a specific diagnostic tool (e.g., Confusion Assessment Method (CAM)) and the incidence of IHPOD according to procedure (TF TAVR vs non-TF TAVR). The effect of baseline characteristics (age, TF approach, Logistic EuroSCORE) on incidence of IHPOD after TAVR was also assessed. Because of lack of data, we could not compare the effect of general anesthesia with that of local anesthesia of a cerebral protection device on the incidence of IHPOD after TAVR.

Statistical Analysis

A weighted meta-analysis of single-arm studies reporting incidence of IHPOD after TAVR was performed. Cumulative event rates were obtained from included studies and reported. Pooled estimate rates and 95% confidence intervals (CIs) were calculated using a binary random-effects model.[20] Heterogeneity across studies was assessed using Cochrane Q statistics and I^2 values. (Heterogeneity p≤.1 was considered significant) I^2 values of less than 25% indicated low heterogeneity, 25% to 50% moderate heterogeneity, and greater than 50% high heterogeneity. Subgroup analysis was performed to assess the incidence of IHPOD

in studies using the CAM for its definition. A subsequent subgroup analysis was performed to evaluate the incidence of IHPOD in individuals treated with different vascular accesses (TF, non-TF); studies with participants treated using only TF or non-TF approaches and studies clearly reporting the rate of IHPOD according to TF or non-TF approaches were included in this subgroup analysis. A weighted meta-regression analysis with a random-effects model was also performed to evaluate the effect of age, proportion of participants treated using the TF approach, and logistic EuroSCORE on incidence of IHPOD after TAVR.[21] These variables were also considered together to assess their influence on heterogeneity across studies. Statistical analyses were conducted using Meta-Analyst Beta 3.13 (Tufts Evidence-based Practice Center, Boston, MA) and Stata version 14.1 (Stata Corp., College Station, TX).

RESULTS

In a search using key words, 3,772 reports were identified and reviewed at title and abstract level (Figure 1). Initial evaluation identified 96 publications that were further evaluated. When inclusion and exclusion criteria were applied, 31 publications remained for assessment.[6,8,9,11,17,22–46] Most included studies were observational (14 prospective,[6,17,23,26–30,33,35,37,41,44,47], 6 propensity matched,[22,24,25,36,40,42] 10 retrospective [8,9,11,31,32,34,38,43,45,46]), with only one randomized controlled trial.[39] Differences in the differential diagnosis between POD and other comparable cognitive disorders, including dementia, depression, and schizophrenia, are summarized in Table 1. All studies included in the analysis were published between 2010 and 2017 (Table 2). Analysis was performed on 32,389 participants. The crude incidence of IHPOD after TAVR ranged from 0% to 44.6% across included studies, with a pooled estimate rate of 8.1% (95% CI=6.7–9.4%) (Figure 2). Heterogeneity among studies was high (Q = 449; I2 = 93%; p heterogeneity < .001). Seven studies reported IHPOD according to the CAM, for a total of 682 patients (Figure 3).[17,24,28,30,32,34,41] The pooled estimate rate of CAM-defined IHPOD was 13.5% (95% CI=4.9–22.1%), with evidence of high interstudy heterogeneity (Q = 151; I2 = 96%; p heterogeneity <.001). Thirteen studies (total 20,537 participants) clearly reported the occurrence of IHPOD in individuals undergoing TF-TAVR. The pooled estimate rate of IHPOD after TF-TAVR was 7.2% (95% CI=5.4–9.1%), with evidence of high heterogeneity among studies (Q = 95; I2 = 87%; p heterogeneity < .001) (Supplementary Figure 1).

Eight studies (total 468 participants) clearly reported incidence of IHPOD after non-TF TAVR. The pooled estimate rate of IHPOD after non-TF TAVR was 21.4% (95%CI=10.3–32.5%), with the lower bound of the 95% CI higher than the upper bound of 95% CI estimated for IHPOD after non-TF TAVR (Supplementary Figure 2). Heterogeneity among studies was high for TF and non-TF TAVR (Q = 95; I2 = 87%; p heterogeneity < .001 for TF TAVR; Q = 111; I2 = 94%; p heterogeneity < .001 for non-TF TAVR). No significant relationships were observed in meta-regression analyses between mean age (p = .55), logistic EuroSCORE (p = .51), or percentage of participants treated using the TF approach (p =.27) (Supplementary Figure 3A–C). Residual heterogeneity remained high even considering these variables together (residual I^2 = 92.2%), suggesting that other features influenced the observed interstudy heterogeneity.

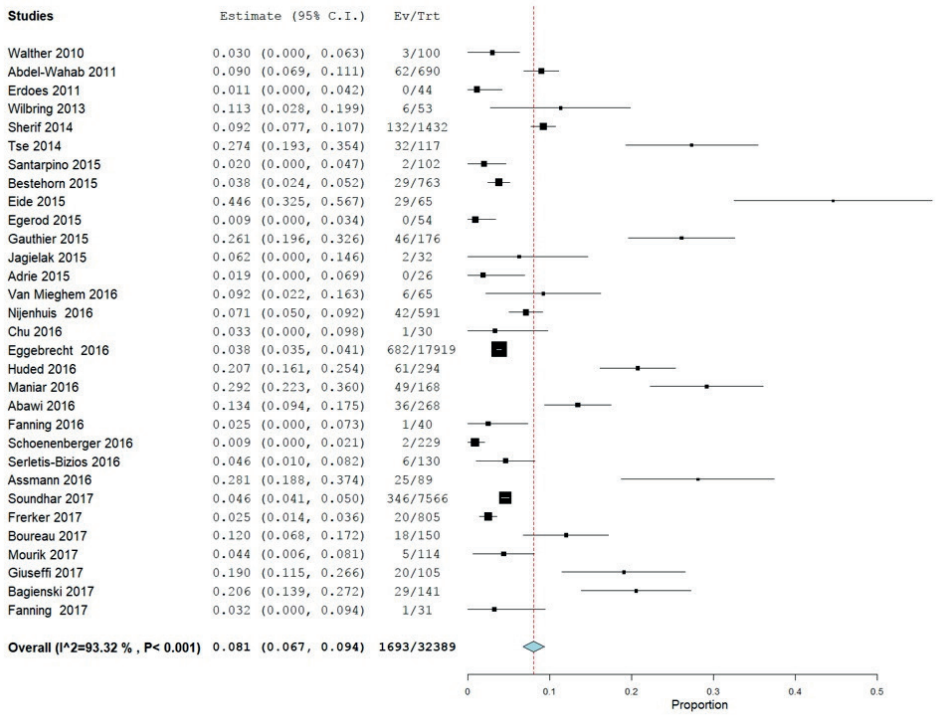


Figure 2. Forest plot showing individual and pooled event rates for in-hospital postoperative delirium after transcatheter aortic valve replacement from included studies.

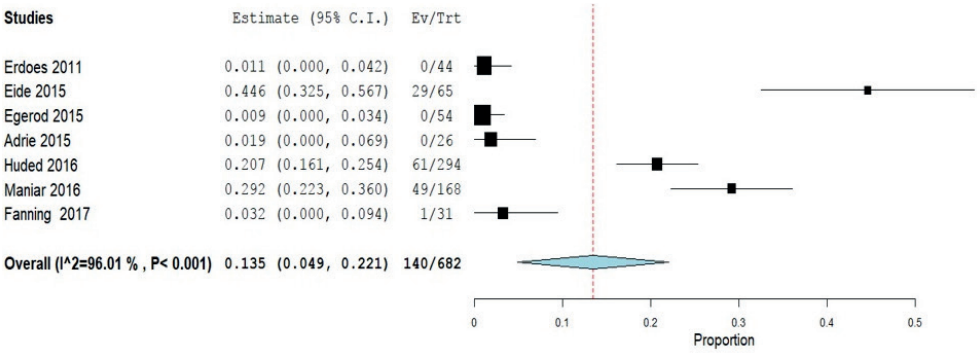
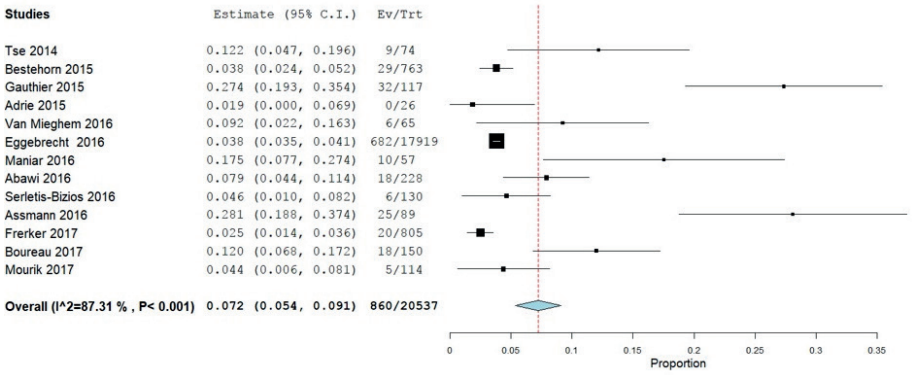
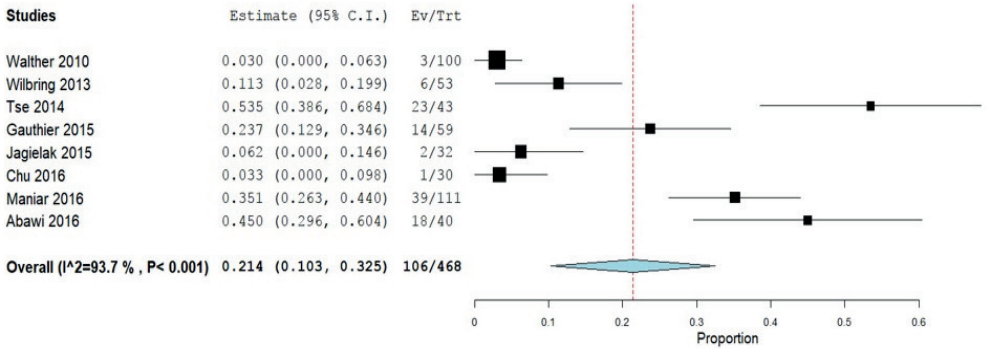


Figure 3. Forest plot showing incidence of in-hospital postoperative delirium after transcatheter aortic valve replacement defined using Confusion Assessment Method.



Supplemental Figure 1. Incidence of inhospital postoperative delirium after TF-TAVR.



Supplemental Figure 2. Incidence of inhospital postoperative delirium after non-TF TAVR.

DISCUSSION

The results of this study confirm that IHPOD is frequently observed after TAVR. The main results of our meta-analysis of 31 studies comprising 32,389 participants are as follows: overall, the pooled incidence of IHPOD after TAVR was 8.1% (95% CI=6.7–9.4%); using a specific measure for classifying delirium, such as the CAM, appeared to identify an even higher rate of POD after TAVR (13.5%, 95% CI=4.9–22.1%); the pooled incidence of IHPOD after non-TF TAVR (21.4%, 95% CI=10.3–32.5%) was 3 times as high as with TF-TAVR (7.2%, 95% CI=5.4–9.1%); and no significant relationships were observed on meta-regression analyses between incidence of IHPOD after TAVR and mean age, percentage of participants treated using TF access, and logistic EuroSCORE.

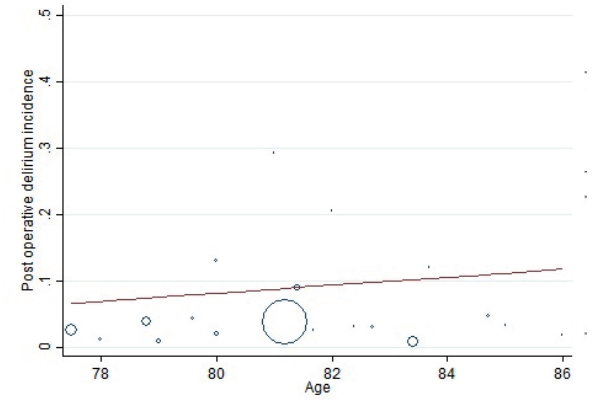
To the best of our knowledge, this is the first large meta-analysis reporting the pooled incidence of IHPOD in individuals undergoing TAVR. We found that 8.1% of individuals undergoing TAVR developed IHPOD. Delirium in older adults is unrecognized in 60% of all clinical cases because of difficulty in detecting its hypoactive subtype and screening tools with lower sensitivity for detection of delirium.[12] Therefore, our findings could be an underestimation of the true incidence of delirium after TAVR. According to our findings,

using the CAM showed an even higher incidence of IHPOD after TAVR, underscoring the importance of such a validated tool in screening for delirium in older adults. The CAM is a validated tool for identifying delirium with high sensitivity (94%) and specificity (89%) in research settings,[48] although there is little information regarding the usefulness of this method for identifying IHPOD in routine clinical settings. Future studies, including an ongoing trail (Clinical Trial.gov, NCT02585128), may shed more light on the efficiency of this method for identifying delirium after TAVR in routine clinical practice.

The pooled incidence of IHPOD was 3 times as high in individuals undergoing non-TF TAVR (21.4%) than in those with TF TAVR (7.2%). TF access is the preferred TAVR approach because it is less invasive, whereas non-TF approaches are used when TF access is not possible because the peripheral vessels are severely atherosclerotic. Several factors could explain the higher incidence of IHPOD in individuals undergoing non-TF TAVR than in those undergoing TF TAVR, including different patient profile, the more invasive nature of non-TF TAVR, use of general anesthesia, postoperative pain and opioid use, spending 1 or more days in the intensive care unit, prolonged hospital stay, late mobilization, and postoperative systemic inflammation.[12] Future studies are needed to investigate whether avoiding these factors could influence the incidence of IHPOD after TAVR.

The majority of participants included in our meta-analysis were derived from 2 large prospective registries, with the lack of information regarding delirium diagnostic criteria and timing of the delirium screening.[29,45] Interestingly, while these 2 large studies reported lower incidence of IHPOD after TAVR (e.g., 3.8% and 4.6%), small studies included in our analysis report higher incidence of IHPOD after TAVR.[6,8,9,11,17,22–28,30–44,46,47] Several participant- and procedural-related factors, including age at admission, comorbid condition, TAVR access, and hospital complication rate, could explain the differences in the incidence of IHPOD between these studies. Larger studies are needed to identify clinical and procedural predictors of change in cognitive status early after TAVR, and to evaluate nonpharmacological strategies to reduce the incidence of IHPOD after TAVR.

According to the Diagnostic and Statistical Manual of Mental Disorders, 5th Ed delirium could be subclassified as following: 1) delirium due to substance intoxication; 2) alcohol/or drug withdrawal delirium; 3) drug induced delirium; 4) delirium due to general medical/somatic condition; 5) delirium due to multiple aetiologies; 6) delirium not otherwise specified. Although the etiopathogenesis of delirium is unknown, it is a multifactorial disorder that usually reflects the complex interaction between heterogeneous predisposing factors (e.g., age, preexisting cognitive impairment, cerebrovascular disease) and exposure to precipitating risk factors (e.g., major surgery, transcatheter valvular interventions, infectious disease, polypharmacy, psychoactive drugs, metabolic alterations).[8,14] Predisposing factors are generally classified as non-modifiable and characterize a person's susceptibility to develop delirium. Precipitating factors are potentially modifiable factors that trigger onset of delirium. To that end, individuals who are vulnerable to delirium may require only a minor precipitating factor for delirium to develop, whereas non-vulnerable individuals will require a series of precipitating factors or strong alterations to develop delirium.[12] Specifically in the TAVR setting, several peri- or postprocedural factors seem to precipitate delirium, including stroke, cardiac tamponade, atrial fibrillation, and infections.[8]



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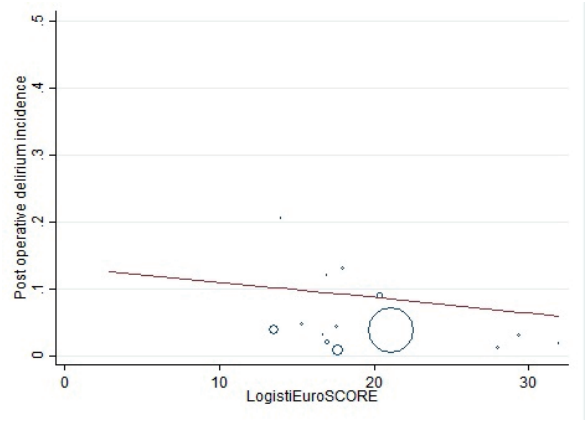

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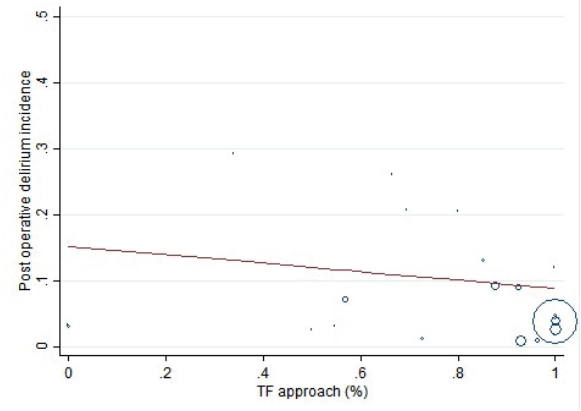

C

Supplemental Figure 3. Meta-regression analysis: impact of age (A), Logistic EuroSCORE (B), TF approach (C) on inhospital postoperative delirium after TAVR.

Several hypotheses have been postulated, including neurotransmitter imbalances, inflammatory processes, and physiologic stress. Advanced age and multiple comorbidities are also known risk factors for development of delirium[8,10,32,34,38] although we could not find associations between incidence of IHPOD after TAVR and mean age, percentage of participants treated with non-TF access, and logistic EuroSCORE. Our meta-regression was performed at the study level, with lack of participant-level data; thus, considering the mean values of tested variables (and not individual data) from included studies; such limitations may have reduced the power of our meta-regression to find similar associations. Residual heterogeneity remained high even considering these variables together, suggesting that other features influenced the observed between-study heterogeneity.

Subclinical cerebral ischemic lesions detected on diffusion weighted magnetic resonance imaging (DWI lesions) appear to affect more than 70% of individuals undergoing TAVR.[49] Analogous to observations in cardiac surgery, these lesions may play an important role in the pathophysiology of delirium after TAVR.[50,51] Whether cerebral embolic protection devices reduce the incidence of IHPOD remains unclear because of the multifactorial nature of this cognitive disorder, although a recent study investigating the use of a filter-based cerebral embolic protection device during TAVR found less IHPOD in individuals in the filter group (3%) than in those without a filter (15%).[39] Moreover, the prospective, randomized evaluation of the TriGuard HDH Embolic Deflection Device During TAVR (DEFLECT III) trial showed 40% to 50% reduction of new cerebral DWI lesions after TAVR and better neurocognitive performance at discharge and 30 days.[52]

Our findings have important implications for routine clinical practice for individuals undergoing TAVR. Older age, preoperative cognitive status, frailty, and comorbid conditions are non-modifiable risk factors for delirium, although several nonpharmacological measures can be taken to prevent delirium in vulnerable individuals undergoing TAVR, for instance, avoiding non-TF TAVR or general anesthesia whenever possible. Furthermore, there appears to be a role for an embolic protection device during TAVR, because cerebral DWI lesions have been associated with IHPOD. Furthermore, as the Neurologic Academic Research Consortium recommends, a systematic neurocognitive assessment of individuals undergoing TAVR is fundamental to better evaluating the safety and effectiveness of the procedure, including different delirium assessment tools.[53] Avoiding psychoactive drugs whenever possible; managing sleep, anxiety, and agitation; involving family members in care, particularly for reorientation and prevention of self-harm; encouraging mobility and self-care; assessing for and addressing pain; ensuring that patients have glasses, hearing aids, and dentures; normalizing electrolytes; and treating infections are other steps that can be taken.[12,14] To that end, a multidisciplinary collaboration with better participant selection will promote progressive, safe application of this promising technique.

Study Limitations

Our review has several limitations. First, this study used a study-level pooled analysis, so a major limitation is lack of individual-level data. Second, although we used a comprehensive search strategy of the existing literature and state of- the-art methods for the analysis, our analysis was not necessarily definitively accurate. Third, there was significant interstudy heterogeneity, because assessment of delirium varied widely between included studies. Studies included heterogeneous populations (age, comorbid condition, surgical risk scores,

approach), which may have contributed to the high heterogeneity observed in delirium incidence rate. Fourth, we measured the effect only of age, access site, and Logistic EuroSCORE on incidence of IHPOD after TAVR; because of lack of data, we could not assess the effect of other factors, such as general versus local anaesthesia, cerebral embolic protection device, and postoperative complications. Therefore, our results should be interpreted as hypothesis generating. Fifth, use of cerebral embolic protection has been associated with better cognitive outcome after TAVR, however, due to the lack of data regarding the overall treatment effect of cerebral protection on delirium incidence we did not exclude studies using cerebral protection devices during TAVR, which possibly influenced our results. Future studies are needed to investigate whether use of cerebral protection during TAVR affects the incidence of IHPOD after TAVR.

Conclusions

In conclusion, IHPOD is frequently observed after TAVR (~8% of individuals, ~13.5% using the dedicated CAM), and its incidence is 3 times as high after non-TF TAVR as with TF TAVR. Future studies are needed to evaluate possible risk factors and better understand the etiology of delirium after TAVR so as to be able to implement preventive and therapeutic strategies.

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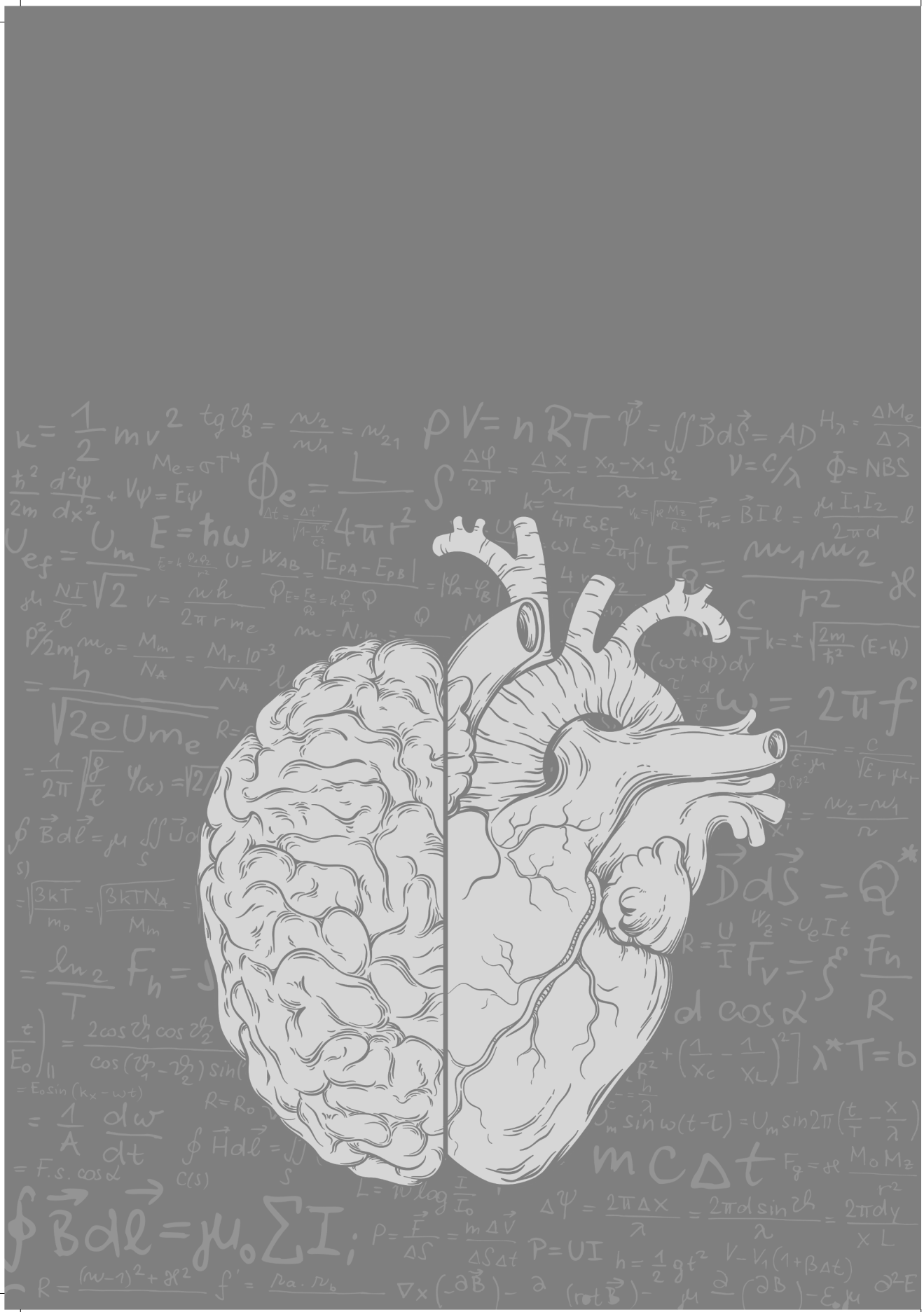

Chapter 4

Effect of New Cerebral Ischemic Lesions on the Delirium Occurrence after Transcatheter Aortic Valve Replacement

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ABSTRACT

Background: New cerebral lesions are frequently detected with diffusion weighted magnetic resonance imaging (DWI-MRI) after transcatheter aortic valve replacement (TAVR). Recent literature has shown that postoperative delirium (POD) occurs frequently after TAVR. Aim of this study is to investigate the association between new cerebral DWI-lesions and delirium occurrence following TAVR.

Methods: Consecutive patients who underwent TAVR with postprocedural MRI were included. All periprocedural, clinical and imaging data were prospectively collected. Cerebral DWI was performed within 5 days after TAVR. The occurrence of POD was assessed using the Delirium Observational Scale based on Diagnostic and Statistical Manual of Mental Disorder, 4rd Edition criteria.

Results: Post-procedural cerebral DWI was performed in 103 patients (80±8 years, logistic EuroSCORE 17±9%). Higher number of new cerebral DWI-lesions were observed among patients with delirium compared with patients without delirium after TAVR (8[5-15] vs.4 [2-7], p=0.023). After controlling for possible confounding factors (i.e., global cortical atrophy, white matter abnormalities, logistic EuroSCORE, access site), the number of new cerebral DWI-lesions remained significantly associated with POD (Odds Ratio 1.08; 95% confidence interval 1.10-1.16, per number of DWI-lesions increase).

Conclusions: Higher number of new cerebral ischemic lesions detected with DWI-MRI after TAVR were associated with incidence of POD following TAVR.

BACKGROUND

Transcatheter aortic valve replacement (TAVR) has emerged as a valuable option to treat symptomatic severe aortic valve stenosis (AS) in patients considered to be inoperable or at high risk for surgical aortic valve replacement (SAVR) (1, 2). While TAVR has evolved markedly (3-5), the randomized PARTNER trial raised safety concerns regarding the higher incidence of neurological events after TAVR compared with medical therapy or SAVR (6). According to an updated meta-analysis (n=29,043), the incidence of 30-days perioperative clinical stroke among patients undergoing TAVR was 3.1% (7). In addition, these patients have fourfold higher rate of mortality compared with patients without clinical stroke after TAVR (7, 8).

Among patients with sclerotic aortic valve, cerebral ischemic lesions have been observed with even minimal trauma such as valve passage with the use of small-bore diagnostic pigtail catheters for hemodynamic assessment (9). To that end, patient with symptomatic severe AS undergoing TAVR are at increased risk for cerebral ischemic lesions during TAVR. Recently, both imaging and histopathological studies revealed cerebral microembolic particles during TAVR (10-12). For instance, studies using Doppler during TAVR have observed cerebral microemboli among all patients during TAVR, specifically during manipulation of the aortic arc/root/valve by guidewires and catheters, balloon dilatation of the native aortic valve, and expansion of the valve prosthesis (10, 11). Accordingly, Reinsfelt et al. found a positive correlation between higher number of these cerebral microembolic particles and postprocedural serologic release of S100B that is a marker of astroglial injury in the brain (11). Likewise, Van Mieghem et al. captured debris in 86% of all patients during TAVR using dual filter-based cerebral protection device that was placed in the brachiocephalic trunk and left common carotid artery (12). The majority of these captured debris were originated from the native aortic valve leaflets, aortic wall, and ventricular myocardium (12), possibly due to the procedural-related features such as aggressive manipulations on the aortic arch and calcified annulus during positioning and deployment of the prostheses valve.

Cerebral embolic particles are suggested to cause cytotoxic edema following arterial occlusion, leading to prompt reduction of membrane proton-diffusion capacity (13). By addition of a strong magnetic-field gradient pulse, this reduced proton-diffusion capacity is detectable as a “bright” area against dark background of normal brain tissue (13, 14). Currently, diffusion weighted magnetic resonance imaging (DWI-MRI) has been applied frequently after TAVR to assess new cerebral lesions (DWI-lesions) (15). Studies using DWI-MRI revealed new cerebral ischemic lesions in all patients following TAVR, irrespective of the access strategy (16-18). The clinical effect of these cerebral DWI-lesions after TAVR remain unknown. However, according to the literature, these lesions may negatively affect cognitive and functional performances, and may increase the risk for future clinical stroke (19, 20).

Among patients undergoing off-pomp coronary artery bypass grafting (CABG) number of new cerebral DWI-lesions have been associated with postoperative delirium (POD) (21). Another study by Fanning et al. observed an association between number of DWI-lesions and early cognitive decline following TAVR (22). Previously, we identified several risk-factors associated with delirium following TAVR (23), however, with respect to so-called “silent”

new cerebral DWI-lesions limited data exist regarding the association between cerebral DWI-lesions and POD after TAVR. Therefore, we aimed to investigate the association between new cerebral DWI-lesions and delirium occurrence among patients with severe symptomatic AS undergoing TAVR.

METHODS

Study design

Patients who underwent TAVR with postprocedural cerebral MRI at the University Medical Center Utrecht between January 2010 and April 2015 were included in this study. Majority of these patients were participated in the previously prospective studies investigating cerebral lesions after TAVR (24-27). All data were prospectively collected and retrospectively pooled and analysed. All patients gave informed consent for the procedure, and because of the retrospective nature of this study collecting known data requirement of a new ethical committee approval was waived.

TAVR procedure

All patients had been judged inoperable or at high operative risk by the Heart Team consisting of at least one interventional cardiologist and one cardiac surgeon. All patients underwent electrocardiogram and transthoracic echocardiography before and after the procedure to detect underlying causes of embolism (atrial fibrillation, left ventricular thrombus) as part of standard clinical care. Based on the measurements of pre-procedural multislice computed tomography scan for the evaluation of access site valve implantation was performed either via the transfemoral or non-transfemoral approach (transapical/direct aortic). General anesthesia or conscious sedation was used according to the access site.

MRI-brain lesion assessment

Patients were imaged within 5 days after TAVR. The MRI scan included a DWI sequence for detection of new cerebral ischemic injury determined with maximum contrast between lesion and normal tissue signal (Figure-1). Pre-existing brain abnormalities (e.g., microangiopathy, infarctions, or atrophy) and the appearance of new lesions in DWI on postoperative scans were assessed by two trained observers blinded to neurocognitive outcomes (stroke/TIA or POD). Cerebral lesions were subsequently defined according to Valve Academic Research Consortium (VARC-2) criteria (28) as following: (1) silent lesions in absence of clinical symptoms and/or (2) clinically apparent stroke if there was an acute episode of focal or global neurological dysfunction caused by the brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Location, number of lesions, and lesions volume of all focal diffusion abnormalities (left –or right hemisphere and cerebellum), were documented and included in this analysis. Localization of new cerebral DWI-lesions was performed according to the vascular territories as anterior cerebral artery(ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), and vertebrobasilar artery (VBA). DWI- lesion-volume measurements were performed by manually outlining the lesions area on the DWI images multiplied by the slice thickness.

Fluid-attenuated inversion recovery (FLAIR) sequences on MRI were used to diagnose white matter disease and global cortical atrophy. White matter disease was diagnosed by White Matter Hyperintensity (WMH) grading and divided into four levels (grade 0 to 3) according

Table 1. Baseline and clinical characteristics of the study patients (n=103).

	Study patients	Delirium		
	(n=103) [n (%)]	Yes (n=15) [n (%)]	No (n=88) [n (%)]	p
Age, years	80±8	83±4	79±8	0.084
Gender, male	50 (49)	7 (47)	43 (49)	0.875
Logistic EuroSCORE, %	17±9	21±11	16±9	0.043
BMI, Kg/m^2	27±5	26±6	27±5	0.552
Carotid artery disease*	10 (10)	3 (20)	7 (8)	0.159
Procedural aspects				
General anesthesia	26 (25)	5 (33)	21 (24)	0.521
Non transfemoral ‡	7 (7)	3 (20)	4 (5)	0.062
Cerebral protection device	39 (38)	6 (39)	33 (39)	0.870
SMT device	13 (13)	2 (13)	11 (13)	
Embrella device	13 (13)	2 (13)	11 (13)	
TriGuard device	13 (13)	2 (13)	11 (13)	
Balloon-expandable valve	67 (65)	10 (67)	57 (64)	0.887
In-hospital clinical outcome				
Ischemic cerebrovascular events (stroke/TIA)	6 (6)	1 (7)	5 (6)	1.000
Permanent pacemaker implantation*	4 (4)	1 (7)	3 (3)	0.473
New onset atrial fibrillation (any)	11 (11)	3 (20)	8 (9)	0.199
Major vascular complication	8 (8)	1 (7)	7 (8)	1.000
Major or life-threatening bleeding	7 (7)	0 (0)	7 (8)	0.590
AKI stage 2 or 3	2 (2)	1 (7)	1 (1)	0.271

Abbreviations. BMI = Body Mass Index; TIA = transient ischemic attack; NOAF = New Onset Atrial Fibrillation; AKI = Acute Kidney Injury.

*Prior or planned carotid artery intervention and/or ≥50% diameter stenosis of the common carotid artery evaluated by computed tomography angiography or Duplex investigation.

‡ = transapical/transaortic

to its severity which was rated by Fazekas visual rating scale: grade 0: no WMH; grade 1: punctuate WMH; grade 2: beginning confluent WMH, and grade 3: confluent WMH (29). Global cortical atrophy (GCA) scale is the mean score for cortical atrophy throughout the complete cerebrum divided into four levels (grade 0 to 3) according to its severity: grade 0: no cortical atrophy; grade 1: mild atrophy; grade 2: moderate atrophy; and grade 3: severe/end-stage atrophy.

Study endpoints

The primary outcome was delirium occurrence after TAVR. For the evaluation of delirium by the nurse or attending physician, a Delirium Observational Screening Score (DOS) was rated at the end of every shift, according to the local protocol (30). When the results of DOS score

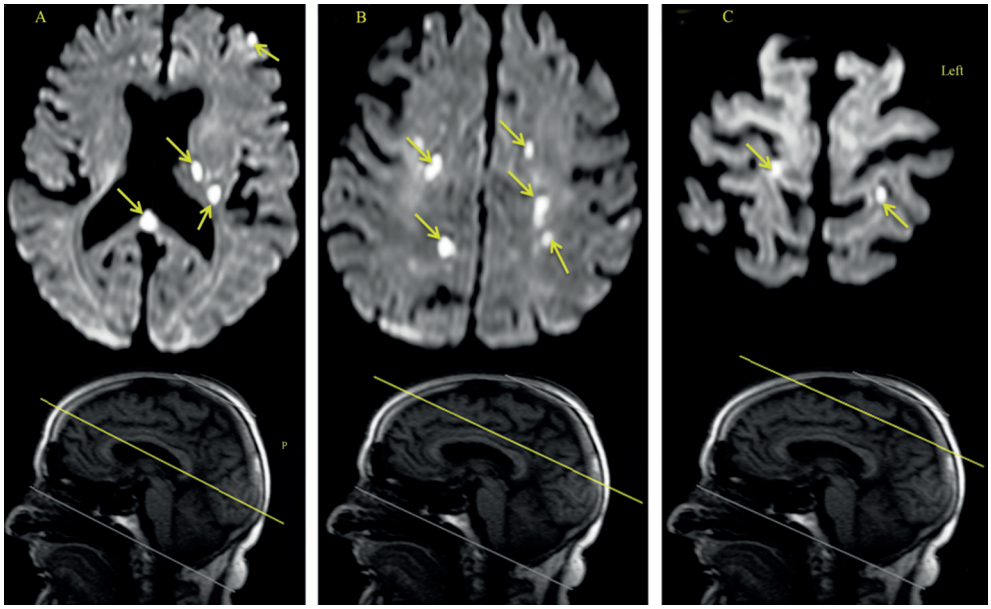

Figure 1. Periprocedural lesion detected on post- TAVR MRI. The lesion typically appears brighter on DWI sequence.

was >3, the Geriatrician was consulted to confirm or refute the diagnosis delirium conform the Diagnostic and Statistical Manual of Mental Disorder, Fourth Revision (DSM-IV).

Other clinical outcomes were adjudicated in compliance with the VARC-2 criteria (28). Vascular complications were documented for all procedural access sites, defined as any location traversed by a guide-wire, a catheter or a sheath during the procedure, including arteries, veins, left ventricular apex and the aorta.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and compared with the Chi-square or Fisher's Exact test. Continuous variables were expressed as mean and standard deviation if normally distributed or as median [interquartile range: IQR] if skewed and compared with the Student's t-test or the Mann-Whitney U test, respectively. Sub-analysis were performed with data stratification according to the periprocedural complications including at least one of the following complications: need for permanent pacemaker implantation, and/OR new atrial fibrillation (NOAF), and/ OR acute kidney injury (AKI) stage-II/III, and/OR major vascular complications, and/ OR major/life-threatening bleeding.

Multivariable logistic regression was performed including possible confounders for delirium (i.e., Logistic EuroSCORE, global cortical atrophy, white matter disease, non-transfemoral access, number of new cerebral DWI-lesions) to assess the impact of DWI-lesions on the occurrence of POD. Results were reported as odds ratios (ORs) with 95% confidence intervals (CI). All tests were two-tailed and a p-value <0.05 was considered statistically significant. All statistical analyses were carried out using the IBM Statistical Package for Social Science for

Table 2. Individual characteristics and clinical outcomes of patients (n=15) with postoperative delirium after TAVR.

Baseline						Periprocedural outcomes					
N	Gender	Age	Fazekas scale	GCA grading	LES	TAVR approach	Type of anesthesia	Complications	Total number of lesions	Total volume of lesions (µL)	Mean volume of lesions (µL)
1	F	84	3	2	16.81	TF	CS	PM	7	479.04	68.43
2	M	80	2	1	48.71	TF	CS	AKI-II/III	3	39.44	13.15
3	F	85	2	1	21.82	TF	CS	NOAF	1	45.24	45.24
4	M	85	3	2	25.10	Non-TF	GA	-	7	621.35	62.14
5	M	79	1	2	7.62	TF	CS	-	9	177.48	19.72
6	F	82	3	2	18.60	TF	GA	-	26	950.72	33.95
7	F	89	3	2	18.26	TF	GA	-	42	3335.05	74.11
8	F	83	1	2	13.80	TF	CS	-	22	1760.65	70.43
9	M	79	2	2	11.17	TF	CS	-	1	110.36	110.36
10	F	89	3	3	12.80	Non-TF	GA	CVE	8	2377.10	216.10
11	F	81	2	1	16.58	TF	CS	-	20	417.92	20.90
12	F	89	3	1	43.55	TF	CS	NOAF	9	156.84	15.68
13	M	81	1	2	15.62	TF	CS	MVC, NOAF	1	37.72	37.72
14	M	80	3	2	26.28	Non-TF	GA	-	7	453.64	64.81
15	M	82	2	1	20.43	TF	CS	-	8	343	38

Abbreviations. F=female; M=male; LES=logistic EuroSCORE; GCA=Global Cortical Atrophy; TF=transfemoral; non-transfemoral=transapical or transaortic; CS=conscious sedation; GA=general anesthesia; MVC=major vascular complication; PM=pacemaker implantation; AKI=acute kidney injury stage- II/III; NOAF=new onset atrial fibrillation; CVE=cerebrovascular event (stroke/TIA).

Windows, version 21.0 (IBM Corp., Armonk, New York, USA) and GraphPad Prism, version 6 (GraphPad Software, La Jolla, Callifornia, USA).

RESULTS

Patient characteristics

From 377 consecutive patients who underwent TAVR 103 were included with a post TAVR MRI. All patients baseline and clinical characteristics are presented in Table-1. Individual characteristics of patients with POD are presented in Table-2. Imaging findings are presented in Table-3. We observed higher number of cerebral DWI-lesions among patients with POD. After correction for possible confounders (i.e., logistic EuroSCORE, global cortical atrophy, white matter disease, access site) number of new cerebral DWI-lesions remained significantly associated with POD following TAVR (OR 1.08, 95% CI 1.01-1.16). The majority of these lesions were located in the left hemisphere and cerebellum. Higher number of new cerebral

DWI-lesions were observed in the ACA territories among patients with POD than without POD after TAVR (Figure-2). There were no significant between-group differences (POD vs. non-POD) in DWI-lesion size. We observed higher number of DWI-lesions among patients who underwent uncomplicated TAVR compared with complicated TAVR (9 [7-22] vs.4 [2-7], p=0.002) (Figure-3).

Table 3. Characteristics of DWI-MRI according to delirium status.

	Study patients	Delirium		
	(*n*=103) [*IQR*]	Yes (n=15)	No (n=88)	p
Fazekas score 2 or 3	72 (70)	12 (80)	60 (68)	0.544
Global cortical atrophy, scale 2 or 3	47 (46)	10 (67)	37 (42)	0.077
Number of lesions per patient				
Total	5[2-8]	8[5-15]	4[2-7]	0.023
Left hemisphere and cerebellum	2[1-4]	4[2-6]	2[1-3]	0.012
Right hemisphere and cerebellum	2[1-5]	5[2-6]	2[1-4]	0.065
Volume of lesions per patient, (μL)				
Total	231[64-626]	418[134-786]	212[59-577]	0.231
Mean	45[22-75]	45[27-69]	44[21-76]	0.783
Left hemisphere and cerebellum	91[37-236]	110[62-487]	72[23-206]	0.078
Right hemisphere and cerebellum	79[9-294]	138[30-352]	74[9-228]	0.277
Minimum	19[9-42]	22[10-38]	19[9-43]	0.940
Maximum	78[44-128]	104[56-146]	77[42-128]	0.331

DISCUSSION

In the present study we aimed to assess the effect of new cerebral DWI-lesions on the delirium occurrence following TAVR. We observed an association between the number of new cerebral DWI-lesions and delirium occurrence after TAVR. Moreover, ACA was frequently affected in patients with delirium. After stratifying according to periprocedural complications, new cerebral DWI-lesions were more observed among patients with POD after uncomplicated procedures compared with patients with POD after complicated procedures.

To date no study addressed neuroimaging-based risk factors for delirium following TAVR, as the present study is to the best of our knowledge one of the first to investigate this topic (31). It has been suggested that the majority of new cerebral DWI-lesions following TAVR may be clinically silent and do not appear to cause any noticeable neurocognitive abnormalities (32). Some researchers have failed to show any association between cerebral DWI-lesions and cognitive performance after TAVR (33). Interestingly, we observed an association between these new cerebral lesions and delirium after TAVR, which is in line with cardiac surgery (21). Also Fanning et al. observed an association between new cerebral DWI-lesions and early postoperative cognitive decline among intermediate-risk patients undergoing TAVR (22).

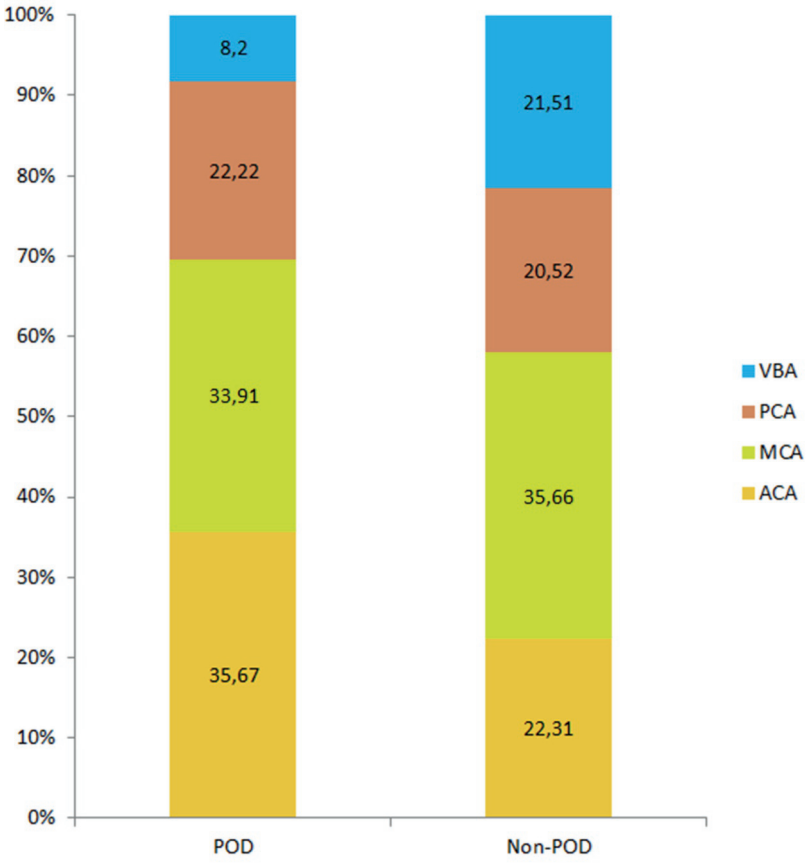

Figure 2. Distribution of new microembolic lesions on postprocedural Diffusion-Weighted Magnetic Resonance Imaging according to postoperative delirium (POD) status.

Abbreviations. ACA=Anterior cerebral artery; MCA=Middle cerebral artery; PCA=Posterior cerebral artery; VBA=Vertebrobasliary artery.

Lesions in brain areas supplied by ACA are linked with social impairment, lack of social judgment, and deficiencies in executive control (34). It is likely that lesion localization is crucial in determining the probability of generating neurocognitive symptoms such as delirium (13, 35). Although the exact relationship of cerebral vascularization and damage on the occurrence of delirium are unknown, we observed higher number of new cerebral DWI-lesions in the brain areas supplied by ACA among patients with delirium after TAVR. However, future larger studies are needed to unravel the association between affected brain areas and delirium after TAVR.

Since postprocedural complications are commonly observed in patients with delirium after TAVR, it is unclear to what extent new cerebral DWI-lesions contributes to the delirium occurrence after TAVR (31, 36). We observed higher number of new cerebral DWI-lesions in patients who developed POD after uncomplicated TAVR, suggesting a possible contribution of these lesions to the pathophysiology and onset of delirium after TAVR. Since POD

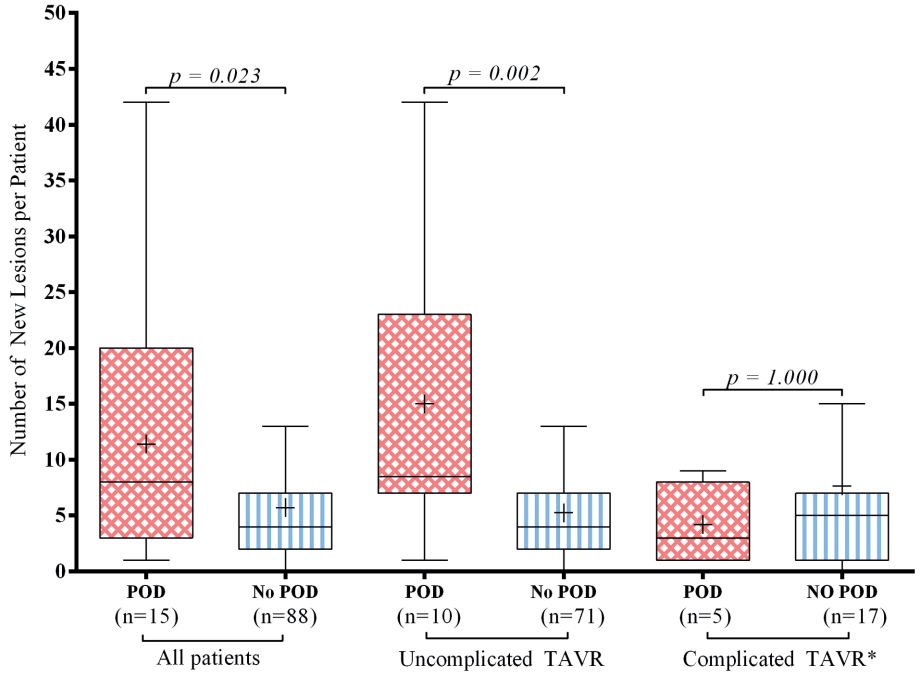

Figure 3. Number of DWI-lesions stratified according to postoperative complication*.

* at least one or more peri-procedural complication: need for permanent pacemaker implantation OR new atrial fibrillation OR Acute kidney injury stage- II/III OR major vascular complication OR major or life-threatening bleeding.

negatively affects postoperative course irrespective of postoperative complications (37), therefore, techniques should be continuously improved to accomplish a non- ischemic event rate procedure in order to minimize the incidence of POD following TAVR.

Several mechanisms have been hypothesized by which new cerebral ischemic lesions could lead to delirium. For instance, cerebral ischemic lesions could lead to delirium through alteration of cerebral acetylcholine levels (38), and in response to this, neuro-inflammation has been recognized as trigger for episodes of delirium (39). Use of cerebral embolic protection device (EPD) during TAVR may decrease the amount of new cerebral DWI-lesions after TAVR and it may contribute to an improved cognitive performance following TAVR compared with patients without EPD during TAVR (40). Recently, data from randomized trials investigating the use of EPD showed promising results after TAVR (41-43). New cerebral DWI-lesions were reduced by 40-50% in patients receiving cerebral embolic protection device (EPD) in DEFLECT III-trial (42). Moreover, there were less neurologic deficits (3.1 vs. 15.4%) and these patients were improved in their cognitive performance at discharge and 30 days compared with patients without EPD during TAVR. However, although the use of EPD is feasible, the embolization of some debris appears to be an unavoidable consequence of the TAVR procedure itself. Therefore, understanding the mechanism and the clinical impact of subclinical ischemic lesions following TAVR are crucial in the understanding of delirium occurrence after TAVR.

Limitations

Important limitations of this study are its small sample size and single center design. Its retrospective design may have led to underestimation of the incidence of delirium and inaccurate measurement of potential confounders. Therefore, future studies are needed to asses clinical impact of these so called "silent" lesions and neurocognitive performance after TAVR.

Conclusions

Periprocedural cerebral ischemic lesions detected with DWI-MRI after TAVR are associated with delirium occurrence after TAVR. Patients with delirium suffer more from cerebral DWI-lesions in the brain areas supplied by ACA, suggesting a possible vascular etiology of delirium after TAVR.

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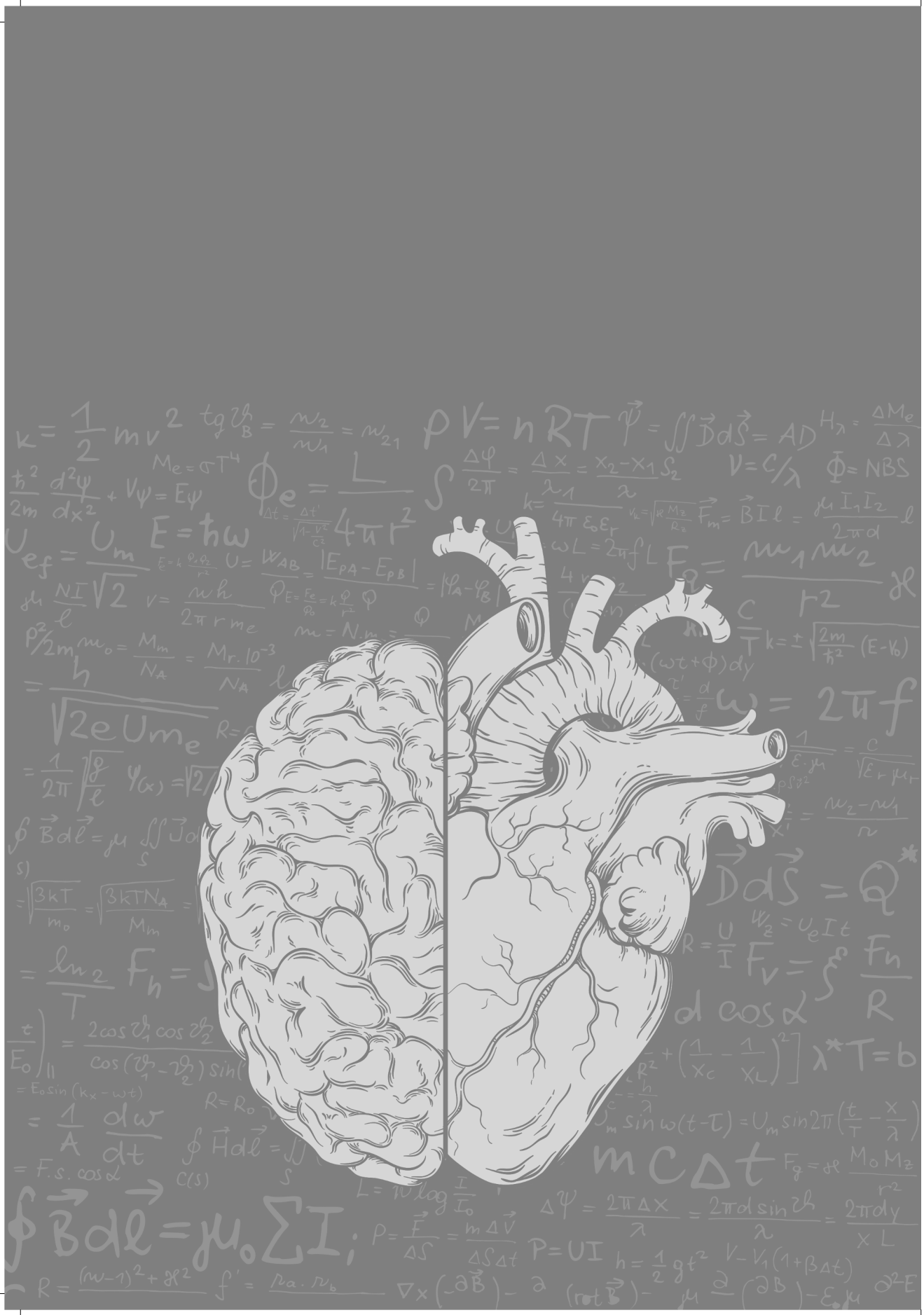

Chapter 5

Evaluation of Cognitive Function Following Transcatheter Aortic Valve Replacement

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ABSTRACT

Background: Transcatheter aortic valve replacement (TAVR) is associated with procedural-related neurological events and acute cognitive decline. However, data on the effect of TAVR on mid-term cognitive outcome are scarce. Therefore, we aimed to assess the impact of TAVR on mid-term cognitive outcome using different neurocognitive test batteries.

Methods: Patients with severe aortic valve stenosis scheduled for TAVR were enrolled. Cognitive assessment was performed at baseline and 4 months post- TAVR using 8-word verbal-learning test ("Immediate Recall Memory Test" [IRMT], "Delayed Recall Memory Test" [DRMT], "Recognition of Verbal Information Test" [RVIT]), global cognitive function ("Mini Mental State Examination" [MMSE]),and executive function ("Trail Making Test" [TMT], "Clock-Drawing Test" [CDT]).

Results: A total of 30 patients (age: 81±6 years, logistic EuroSCORE: 19±10%) completed the follow-up cognitive assessments. Postoperatively, 17% (n= 5) developed delirium, 13% (n= 4) received permanent pacemaker, and there were no cerebrovascular events. Mean hospital duration time was 5±2 days. Patients (n=22) who did not complete the follow-up cognitive assessments had comparable baseline, procedural and hospital outcome. At follow-up there was a significant improvement in IRMT (27±5 vs. 30±4, p=0.016), with a trend toward improved DRMT (4±2 vs. 5±2, p=0.079). Moreover, patients with lower baseline MMSE and IRMT improved significantly during the follow-up.

Conclusions: TAVR was associated with an improved IRMT during follow-up. Both MMSE and IRMT were significantly improved among those with lower baseline scores.

INTRODUCTION

Structural heart disease, including aortic valve stenosis (AS), chronic valvular regurgitation, left ventricular hypertrophy, wall motion abnormalities, and ventricular filling defects, result in reduced ejection fraction and cerebral hypoperfusion (1). In the general population cerebral hypoperfusion is associated with accelerated cognitive decline and increased risk for developing dementia (2). Currently, transcatheter aortic valve replacement (TAVR) has emerged as a valuable option to treat severe AS in elderly patients considered to be inoperable or at high risk for surgical aortic valve replacement (SAVR) (3, 4). However, despite improved techniques, patients undergoing TAVR are at increased risk for developing acute cerebral hypoperfusion during balloon aortic-valvuloplasty/valve deployment, and early cerebrovascular events (CVEs) immediately after, or in the first few hours, following the procedure (5, 6).

Clinical CVEs affect only 1-11% (median 4%) of the patients undergoing TAVR, however, diffusion weighted magnetic resonance imaging (DWI) revealed new cerebral DWI-lesions among >70% of patients after TAVR, regardless of valve type or implantation strategy (7-9). Although the exact mechanism underlying cognitive changes after TAVR remain unclear, new cerebral DWI-lesions could contribute to the cognitive decline early after TAVR (10, 11). As a consequence, patients undergoing TAVR are therefore often predisposed to develop vascular cognitive complications (9, 10, 12). Currently, cerebral protection devices are frequently used during TAVR, which could reduce the amount of cerebral damage, and therefore protect the brain (13-15). However, the role of hemodynamic changes and cerebral oxygenation on the cognitive changes after TAVR are still unclear (6, 16).

Furthermore, some studies show acute cognitive decline after TAVR, while others show preserved or even improved cognitive function during follow-up, more pronounced among individuals with cognitive impairment pre-TAVR (17-19). To that end, a more comprehensive cognitive test battery is required to assess vascular and executive cognitive function following TAVR. To date, studies evaluating specific cognitive domains with the use of a comprehensive neurocognitive test battery among patients undergoing TAVR are scarce, with some showing conflicting results (20). Moreover, neurovascular disease affects a variety of cognitive domains, and is therefore challenging to evaluate. Therefore, we aimed to explore and assess the effect of TAVR on cognition at follow-up using comprehensive neurocognitive test batteries.

METHODS

Study design

Patients with AS who were scheduled for a TAVR procedure between June 2012 and February 2014 were evaluated by the department of Geriatrics and included in this pilot study. Baseline, periprocedural and imaging data were prospectively collected. All patients gave informed consent for the procedure. Approval of the Medical Ethics Committee of the University Medical Center Utrecht was not necessary due to the fact that these examinations are part of the standard clinical care.

TAVR procedure

All patients had been judged inoperable or at high operative risk by the Heart Team consisting of at least one interventional cardiologist and one cardiac surgeon. Motivations for TAVR in patients were: 1) logistic EuroSCORE≥15%, or 2) the presence of contra-indications to cardiac surgery (e.g. porcelain aorta, frailty, patent grafts in proximity of the sternum). Frailty was subjectively measured prior to allocating TAVR by an interventional cardiologist and/or cardiothoracic surgeon based on the informal 'eyeball test' (including cognition function, physical weakness and walk speed). Severity of heart failure was evaluated using the classification of the New York Heart Association.

Patients were admitted 1 or 2 days before the procedure at our institution. All patients underwent transthoracic echocardiography before and after the procedure to detect underlying causes of possible embolism (atrial fibrillation, left ventricular thrombus) as part of standard clinical care. Based on the measurements of pre-procedural multislice computed tomography scan for the evaluation of access site valve implantation was performed either via the transfemoral or non-transfemoral approach (transapical/direct aortic). Transfemoral procedures involved a fully percutaneous technique. General anesthesia or conscious sedation was used according to the access site. During the procedure valve prostheses were subsequently deployed as per routine under rapid ventricular pacing (balloon expandable valve – 180 beats/min) or "slow" ventricular pacing (self-expanding system – 120-140 beats/min). Patients were monitored for at least 72 hours and discharged on a regimen of life-long low-dose aspirin (80-100 mg per day) or oral anticoagulant (in case of clinical indication for it) and 3 months clopidogrel (75 mg per day). All in-hospital data (i.e., complications) were recorded according to Valve Academic Research Consortium-2 (VARC-2) criteria.

Neurocognitive assessment

After the patients were considered eligible for a TAVR, they visited the department of Geriatrics. Cognitive assessment was performed at baseline, and 4 months post- TAVR using 8-word verbal-learning test ("Immediate Recall Memory Test" [IRMT], "Delayed Recall Memory Test" [DRMT], "Recognition of Verbal Information Test" [RVIT]), global cognitive function ("Mini Mental State Examination" [MMSE]),and executive function ("Trail Making Test" [TMT], "Clock-Drawing Test" [CDT]).

As a part of routine care, the risk for postoperative delirium (POD) was evaluated at the end of every shift by the nurse or attending physician using Delirium Observational Screening Score (DOS) (21). The DOS is a time-efficient, easy to use and valid method to measure delirium by nurses (22). It combines an assessment of the patient's level of consciousness in 13 statements or questions, which the observer has to answer with "never" (score=0) or "sometimes or always" (score= 1) if applicable. When the results of DOS score was 3 or more, the Geriatrician was consulted to confirm or refute the diagnosis delirium conform the Diagnostic and Statistical Manual of Mental Disorder, Fourth Revision (DSM-IV).

The verbal-learning test is a subtest of the "Amsterdam Dementia Scale-6" and was used to evaluate verbal memory. Eight words are presented orally 5 times, after each trial the patients have to name as many words as possible (IRMT). After 15 minutes the patients have to recall the words they have learned in the 5 trials before (DRMT). Thereafter, a list of 16 words is orally presented, containing the 8 words which were named before in the list in the 5 trials

and 8 words that were not presented; patients have to indicate whether the words were presented before in the list (RVIT).

MMSE is a validated tool to assess global cognitive function among elderly as a screening test for dementia. It contains a 30 point questionnaire and it measures orientation, attention, verbal memory, language, visuospatial ability and calculation (23).

TMT consist of two parts and they are used to measure executive functions: part A (TMT-A) measures visual search and rate of information processing, and part B (TMT-B) is used to measure mental flexibility and divided attention (24). In the TMT-A the numbers 1 to 25 are circled and presented on a paper, the patient is asked to connect these numbers by drawing a lines in sequential ascending order as fast as possible; in part B circled numbers and letters are presented, now patients have to connect numbers and letters in sequential order, as fast as possible, switching between numbers and letters is required (1-A, 2-B).

CDT requires several cognitive functions: visual perception, visual construction skills and executive functions (25). For this test, the patient is asked to draw a clock that shows the time 10 minutes after 11. CDT is rated on a six-point scale: 2 points for drawing a circle, 2 points for placing the numbers in the circle and 2 points for correct placement of the hands of the clock.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and compared with the Chi-square or Fisher's Exact test. Continuous variables were expressed as mean and standard deviation if normally distributed or as median [interquartile range: IQR] if skewed and compared with the Student's t-test or the Mann-Whitney U test, respectively. A p-value of < 0.05 considered to be statistical significant. All statistical analyses were carried out using the IBM Statistical Package for Social Science for Windows, version 21.0 (IBM Corp., Armonk, New York, USA).

RESULTS

At baseline, 52 patients (81±6 years, logistic EuroSCORE 19±11%) were enrolled. Mean follow-up duration was 4±1 months, and 30 (58%) patients (age: 81±6 years, logistic EuroSCORE: 19±10%) completed the neurocognitive assessments at follow-up. Reasons for not completing the follow-up were: death (n=3), referred to other hospital (n=8), too much effort to come (n=4), language barrier (n=1), and lost to follow-up (n=6).

Baseline, procedural and hospital outcomes data from patients with and without follow-up are presented in **Table-1** and **Table-2.** All baseline, procedural, and hospital outcome were comparable between those who did and did not complete the follow-up, except higher e-GFR rate in patients who did complete the follow-up (63±20 vs. 45±17, p= 0.002). Postoperatively, 17% (n= 5) developed delirium, 13% (n= 4) received permanent pacemaker, and there were no cerebrovascular events (stroke/transient ischemic attack). Mean hospital duration time was 5±2 days.

Table 1. Baseline clinical characteristics.

	Study cohort	Follow-up available		
	(n=52) [n (%)]	Yes (n=30) [n (%)]	No (n=22) [n (%)]	p
Age, years	81±6	81±6	80±7	0.353
Gender, female	26 (50)	15 (50)	11 (50)	1.000
Educational level*	9 (17)	7 (23)	2 (9)	0.272
Logistic EuroSCORE, %	19±11	19±10	19±1	0.890
BMI, Kg/m^2	25±4	26±3	24±4	0.146
NYHA class III-IV	34 (65)	21 (70)	13 (59)	0.414
Frailty	14 (27)	6 (20)	8 (36)	0.189
Estimated GFR, ml/min	55±20	63±20	45±17	0.002
Diabetes mellitus	11 (21)	4 (13)	7 (32)	0.169
Hypertension	31 (60)	19 (63)	12 (55)	0.523
Prior CABG	12 (23)	8 (27)	4 (18)	0.473
Carotid artery disease**	6 (12)	3 (10)	3 (14)	0.689
Prior stroke/TIA	10 (19)	5 (17)	5 (23)	0.725
Peripheral artery disease	7 (14)	3 (10)	4 (18)	0.438
Atrial fibrillation (any)	21 (40)	12 (40)	9 (41)	0.947
Current smoking	3 (6)	2 (7)	1 (5)	1.000
Echocardiography data				
LVEF	49±13	48±12	50±15	0.365
PAG, mmHg	65±23	65±22	65±25	0.846
MAG, mmHg	38±15	38±16	36±15	0.611
Procedural data				
General anesthesia	6 (12)	4 (13)	2 (9)	1.000
Non transfemoral ‡	5 (10)	3 (10)	2 (9)	1.000
Balloon-expandable valve	35 (67)	20 (67)	15 (68)	0.908

Abbreviations. EuroSCORE European System for Cardiac Operative Risk Evaluation; *BMI* body mass index; *NYHA* New York Heart Association; *GFR* glomerular filtration rate; *CABG* coronary artery bypass grafting; *TIA* transient ischemic attack, *LVEF* left ventricular ejection fraction, *PAG* peak aortic gradient, *MAG* mean aortic gradient.

*Higher education or University.

**Prior or planned carotid artery intervention and/or ≥50% diameter stenosis of the common carotid artery evaluated by computed tomography angiography or Duplex investigation.

‡ = transapical/transaortic/direct aorta.

Table 2. Inhospital clinical outcome.

	Study cohort	Follow-up available		
	(n=52) [n (%)]	Yes (n=30) [n (%)]	No (n=22) [n (%)]	
Cerebrovascular events (stroke/TIA)	0 (0)	0 (0)	0 (0)	-
Permanent pacemaker implantation	6 (12)	4 (13)	2 (9)	1.000
Vascular complications				
Major	5 (10)	3 (13)	1 (5)	0.381
Minor	15 (29)	10 (33)	5 (23)	0.404
Bleeding complications				
Life-threatening	1 (2)	1 (3)	0 (0)	1.000
Major	4 (8)	3 (10)	1 (5)	0.629
Minor	15 (29)	10 (33)	5 (23)	0.404
Acute Kidney Injury stage 2 or 3†	3 (6)	1 (3)	2 (9)	0.567
Acute postoperative delirium	12 (23)	5 (17)	7 (32)	0.200
In-hospital stay, days	6±3	5±2	7±5	0.351

TIA: transient ischemic attack.

Table 3. Baseline cognitive assessment in patients with cognitive changes at follow-up.

	Patients with decreased cognitive tests	Patients with unchanged/or improved cognitive tests	p
IRMT	30±5 (n=9; 30%)	27±5 (n=21; 30%)	0.036
DRMT	5±2 (n=7; 23%)	4±2 (n=23; 77%)	0.149
RVIT	7.8±0.4 (n=6; 20%)	7.3±1.1 (n=24; 80%)	0.291
MMSE	29±1 (n=9; 30%)	26±1 (n=21; 70%)	0.000
Trail making A	72±30 (n=13; 45%)	56±13 (n=16; 55%)	0.273
Trail making B	171±73 (n=19; 65%)	163±68 (n=10; 35%)	0.890
CDT	6±0 (n=4; 14%)	5±1 (n=24; 86%)	0.153

Abbreviations. *IRMT* immediate recall memory test, *DRMT* delayed recall memory test, *RVIT* recognition of verbal information test, *MMSE* mini mental state examination, *TMT* trail making test, *CDT* clock-drawing test.

Results of the cognitive assessment are presented in **Table-3** and **Figure-1**. During the follow-up there was a significant improvement in IRMT (27±5 vs. 30±4, p=0.016), with a trend toward improved DRMT (4±2 vs. 5±2, p=0.079). Moreover, pronounced improvement in IRMT and MMSE were observed among patients with lower preprocedural scores. Although there were no differences in other cognitive domains among patients with POD, the majority of patients who experienced POD had decreased CDT during the follow-up compared with patients who did not develop POD (60% vs. 4%, p= 0.011).

DISCUSSION

In the current study, we aimed to assess cognitive functions during the follow-up after TAVR using a comprehensive neurocognitive assessment battery. We observed an improved immediate recall memory among patients at 4 months follow-up after TAVR. Moreover, both immediate recall memory and global cognitive function were significantly improved among those with lower preprocedural scores.

The present study adds to the growing body of evidence examining the relationship between TAVR and cognitive function in the elderly. Interestingly, although there were no changes observed in remaining cognitive tests, we observed improved IRMT during the follow-up when compared with baseline. Few studies including a systematic review found unchanged -or even improved cognitive function following TAVR (20). Recently, a study (n=51) by Auffret et al. found an improved short-term global and domain-specific cognitive function, which remained stable at 1 year following TAVR (17). Moreover, another study (n=111) by Ghanem et al. found that cognitive function was preserved among the majority of patients for up to 2 years post-TAVR, with only 9% age-related cognitive deterioration (26). However, we did not define any cutoff for cognitive change after TAVR, as a result, a statistical reliable cognitive change may not necessarily correlate with clinically meaningful change. Moreover, since patients included in our study were assessed only once during the follow-up, a "regression to the mean" phenomenon could not be excluded.

Age and baseline aortic valve area (AVA) have been linked to follow-up cognition after TAVR, however, studies have failed to find any periprocedural predictor of cognitive change after TAVR (18, 26). Therefore, exact mechanism underlying cognitive change following TAVR remain unclear. Factors which possibly could contribute to improvement of memory (i.e. early and late memory) following TAVR, include restoration of cardiac output, improved hemodynamic status which might result in better cerebral blood supply and oxygenation could explain this effect (20, 27). However, a recent study did not find any relationship between cerebral hypo/hyper-perfusion during TAVR and postoperative cognitive change (6). Therefore, future studies are needed to elucidate the effect of hemodynamic changes on cognitive function, including memory and executive function after TAVR.

Although routine cognitive tests are not yet included in the guidelines for TAVR, elderly patients with lower baseline cognitive scores may benefit more from the TAVR procedure. Interestingly, we observed significant improvement in IRMT and MMSE among patients with lower baseline scores. In addition, Auffret et al. observed more cognitive improvement among those with cognitive impairment pre-TAVR. Moreover, Schoenenberger et al. observed that 12.7% patients in the study population had relevant deterioration in de MMSE score, and among the subgroup of 48 patients with impaired baseline cognition, 37.5% patients cognitively improved (18). Moreover, they found that patients who cognitively improved had lower baseline AVA compared with patients in whom cognitive function did not improved at follow-up.

While MMSE test is an unspecific tool to assess cognitive function (23), it is often used to assess global cognitive function after TAVR (20). In line with a recent study by Schoenenberger et al. among 229 patients undergoing TAVR, we did not find overall change in mean

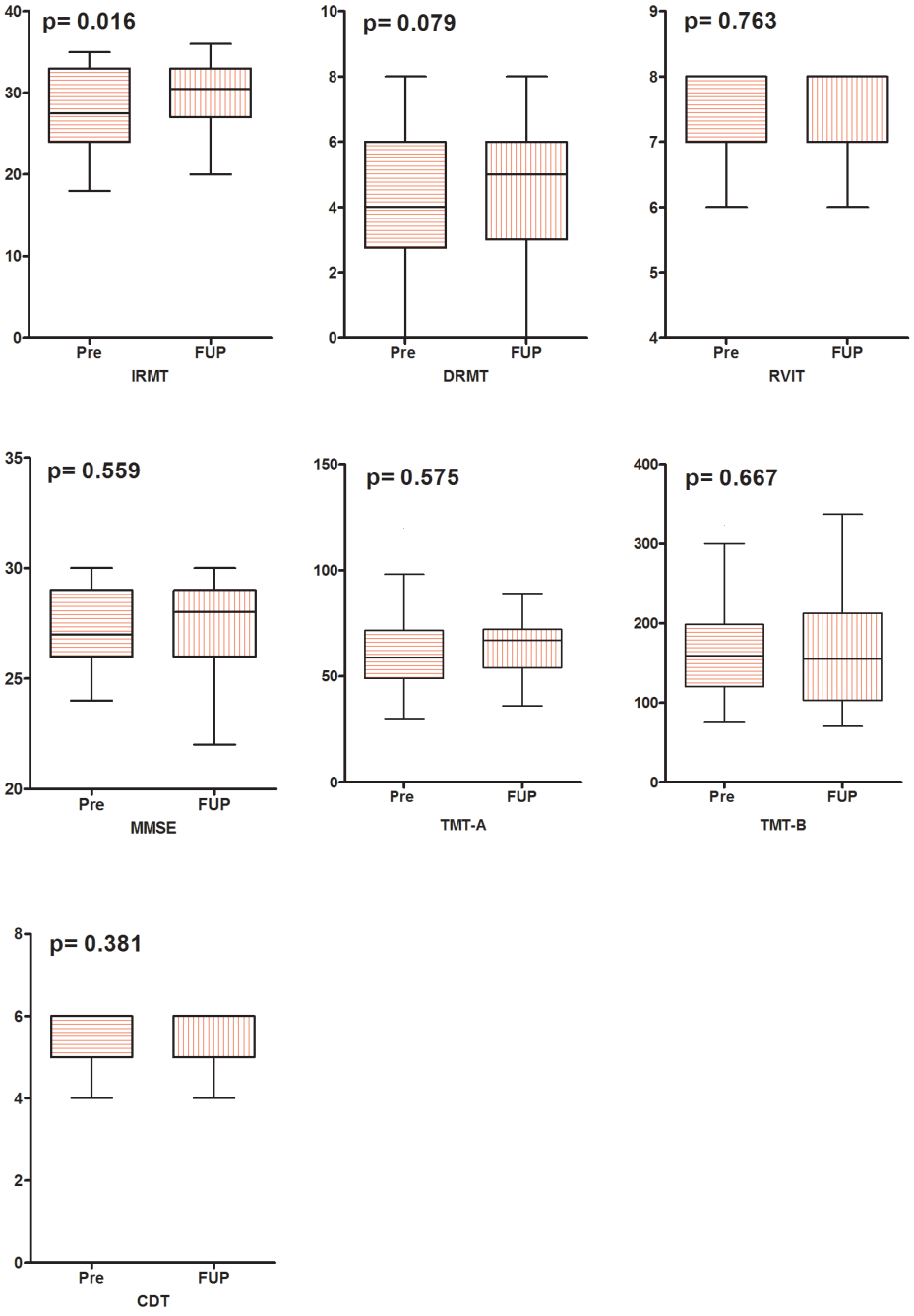

Figure 1. Baseline and follow-up cognitive assessment.

MMSE after TAVR (18). However, a study by Orvin et al. using MMSE for the assessment of global cognitive functions report significant improvement at 30-days following TAVR (28), which could be explained by possible "learning effect" due to the short interval between baseline and follow-up period (29). In our study a possible learning-effect was minimized by performing the follow-up tests at 4 months after TAVR. However, since the majority of the patients in our study had an overall high baseline MMSE score (27±3 vs. 27±2, p= 0.559) and therefore had less potential for change, a possible "ceiling effect" could not be excluded (30). Future studies are needed to assess these effects on cognitive outcome after TAVR.

New cerebral ischemic lesions on MRI are frequently detected among patients undergoing TAVR, which are associated with 2-fold increased risk for developing dementia, and future stroke (31, 32). In cardiac surgery, a decline in postoperative neuropsychological assessment is associated with the "number" of cerebral ischemic lesions on MRI, while there is no association found between cerebral ischemic lesion "load" and neuropsychological impairment after cardiac surgery (33-35). Although there are scarce data exist regarding the relationship between cerebral ischemic lesion and cognitive function after TAVR, the number of new cerebral ischemic lesion might negatively affect early cognitive function following TAVR (10, 11). Cerebral ischemic lesions in anterior cerebral artery territories might negatively affect social judgment and executive functioning (36). Therefore, we expected to observe decreased executive function among patients included in this study, however, our observation did not reveal such an effect which could be explained due to equal topographical distribution of periprocedural DWI-lesions in the brain after TAVR (37).

Previously we observed higher number of cerebral ischemic lesions in anterior cerebral artery territories among patients who developed POD after TAVR (10). Currently, in a sub-analysis, i.e., POD vs. non-POD we observed a decreased executive function (i.e., CDT) among patients with POD during the follow-up. However, patients in the current study had no MRI during the follow-up, therefore, it is unclear whether periprocedural cerebral ischemic lesions could influence executive function during the follow-up. Moreover, delirium is associated accelerated decline in cognitive function during the first year after cardiac surgery (38), suggesting an important role for preventive strategy since 30-40% of the delirium cases are preventable (39).

As TAVR extend to lower-risk population, therefore, use of a comprehensive neurocognitive assessment focused on specific cognitive domains, such as executive function, during longer follow-up may be a better approach to show subtle changes in cognition after TAVR procedure (20). Furthermore, several brain embolic protection devices have been developed in order to reduce the amount of cerebral DWI-lesions after TAVR (14, 15, 40-42). Use of cerebral embolic protection device may improve cognitive outcome during postoperative period, with possible positive effect on long-term follow-up outcome after TAVR (9, 13, 43). However, future studies are needed to assess the effect of new cerebral DWI lesions and the use of protection devices on long-term cognitive outcome after TAVR, since these cerebral lesions negatively affect long-term cognition in other settings.

Limitations

Important limitations of this study are its small sample size and single center design. First, there was lack of comparison with a control group, therefore a natural change in cognitive

function (non-TAVR related) could not be excluded. Second, our results could be confounded by drop out of patients who could not complete the cognitive assessments, due mainly to logistic reasons. However, the clinical characteristics and outcome of patients included in the current study were similar to those not participating in the study, and the selected population was representative of the patients undergoing TAVR at present. Third, as this was an exploratory study with small sample size, we could not perform a multivariate analysis to adjust for possible factors contributing for the cognitive changes at follow-up. Therefore, the results should this be interpreted as exploratory and causality cannot be inferred. Larger studies are needed to investigate factors which may contribute to the cognitive changes at early and long-term follow-up. Fourth, a possible "floor effect" and/or "ceiling effect" could not be excluded, since the majority of the patients in our study had an overall high baseline cognitive test scores, and therefore had less potential for change (30). Finally, although we could not assess the amount of learning effect, future studies are needed to elucidate this effect.

Conclusions

Transcatheter aortic replacement is associated with early -and mid-term cognitive changes. Therefore, larger studies with longer follow-up duration are needed to identify clinical predictors of changes in cognitive status, and to evaluate non-pharmacological strategies in order to prevent cognitive decline after TAVR.

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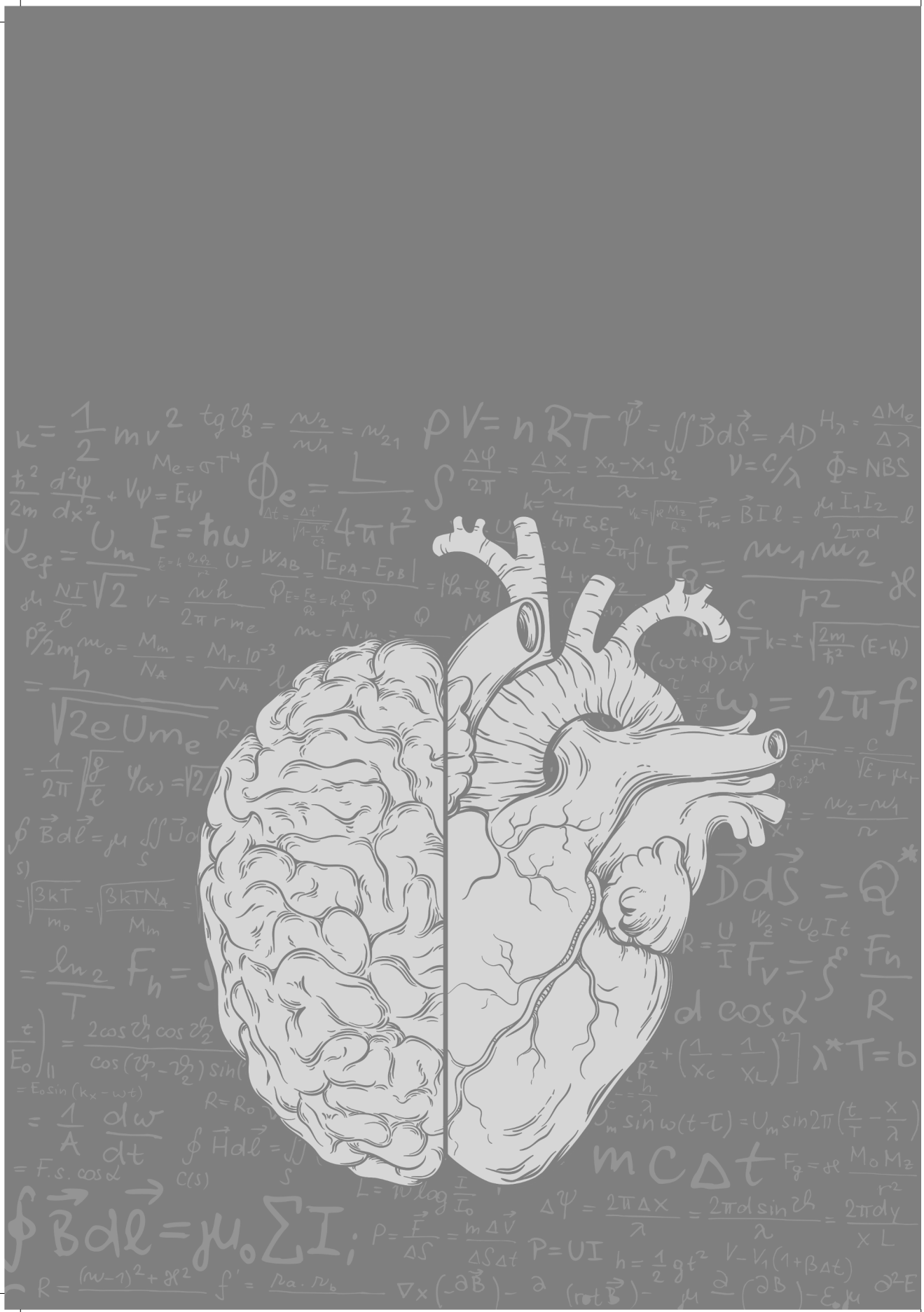

Chapter 6

Effect of body mass index on clinical outcome and all-cause mortality in patients undergoing transcatheter aortic valve implantation

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ABSTRACT

Objectives: To assess the effect of body mass index (BMI) on outcome among patients with severe aortic stenosis (AS) admitted for transcatheter aortic valve implantation (TAVI).

Background: Being overweight or obese is associated with improved outcome following certain medical treatments, suggesting the existence of a BMI paradox. However, the relationship between BMI and mortality after TAVI remains controversial.

Methods: Patients were classified according to World Health Organisation criteria such as normal weight, overweight, or obesity according to their BMI (18.5 to 24.9 kg/m^2, 25.0 to 29.9 kg/m^2, and ≥30.0 kg/m^2, respectively).

Results: A total of 549 consecutive patients (age: 80.2 ±7.5 years; logistic European system for cardiac operative risk evaluation [EuroSCORE]: 17.3 ± 9.9%) who underwent TAVI for AS were included. Of these patients, 43% (*n* = 237) had normal weight, 36% (*n* = 200) were overweight, and 20% (*n* = 112) were obese. There were no differences in peri-operative bleeding or vascular complication rates between the groups. All-cause mortality after 30 days, and 1 year, were higher in normal weight patients compared with overweight and obese patients (7% vs. 5 and 4%, *p*=0.383, and 19% vs. 9 and 10%, *p*=0.006, respectively). After adjustment for several confounding factors, overweight was associated with a decreased 30-day and 1-year all-cause mortality outcome (hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.47–0.99, and HR 0.65; 95% CI 0.45–0.94, respectively).

Conclusions: Despite the well-documented adverse effects of increased body weight on health, being overweight is associated with improved survival following TAVI when compared with normal weight.

INTRODUCTION

Overweight and obesity are the fifth leading modifiable cause of death in the world, accounting nearly 3.4 million deaths annually [1]. The prevalence of obesity, often defined as body mass index (BMI) ≥30.0 kg/m2, has been increasing dramatically [1]. According to available data, more than two-thirds of adults in the United States, and more than 2.1 billion people worldwide, suffer from obesity [1, 2]. Although it has been suggested that obesity occurs because of an energy imbalance between caloric intake and expenditure, the resulting energy excess and associated weight gain reflects a complex interaction between genes, epigenetic markers, environment, and lifestyle [2–4].

According to the Framingham Heart study, conducted among participants (age: 30–49 years) with no cardiovascular disease at baseline, overweight and obesity were associated with a decrease in life expectancy and increased early mortality during the follow-up period of ≥4 years [5]. Accordingly, another population-based cohort reported an increased risk of all-cause mortality among elderly (≥85 years) obese participants [6]. In addition to the risk of mortality, obesity is an underlying promotor of systemic metabolic dysfunction, i. e., dyslipidaemia, decreased insulin sensitivity, hyperinsulinaemia, hyperglycaemia, and hypertension [2, 4].

However, despite the well-documented adverse effects of overweight or obesity on general health status, being overweight or obese is associated with better survival in patients undergoing medical interventions [7], vascular surgery [8], cardiovascular intervention [9], and in patients who are hospitalised for acute decompensated heart failure [10, 11]. These observations led to the concept of reverse epidemiology, also known as the "obesity paradox". The obesity paradox states that a higher BMI may, counter-intuitively, be linked to improved survival in certain patient groups. However, these observations do not support common practice where weight loss is recommended prior to cardiac treatments.

Contradicting data exist regarding the effect of BMI on outcome in patients with severe aortic stenosis (AS). In one study (n = 1664) overweight and obese patients with severe AS were at increased risk for mortality, whereas another study (n = 400) found contradictory results [12, 13]. Although there are few data regarding the effect of BMI on outcome among patients with AS who undergo transcatheter aortic valve implantation (TAVI), several cohort studies showed contradicting or supporting results [14–20]. For instance, a large French Aortic National CoreValve and Edwards (FRANCE-2) registry showed improved survival outcome among overweight and obese individuals undergoing TAVI [14]. Overweight or obesity was associated with improved survival following TAVI in other cohort studies as well [21]. However, a recent study did not find such a paradoxical relationship [19]. Therefore, the current study aimed to assess the effects of body mass index on short and long-term all-cause mortality in patients undergoing TAVI in the current era.

METHODS

We performed a retrospective observational cohort study encompassing all eligible consecutive patients who underwent TAVI between September 2008 and October 2016 at the University Medical Center Utrecht, Utrecht, the Netherlands. All demographic and peri-

procedural data were prospectively collected in our dedicated database and retrospectively analysed in this study. All patients gave informed consent for the procedure and due to the retrospective nature of the study design, ethics committee approval was waived.

Body mass index

BMI was defined as the weight in kilograms divided by the square of the height in meters. The weight and height of all patients were prospectively collected at hospital admission before the TAVI procedure. Baseline and clinical data were stratified by BMI categories according to the World Health Organisation (WHO) criteria as normal weight, overweight, and obese (18.5 to 24.9 kg/m^2, 25.0 to 29.9 kg/m^2, and ≥30.0 kg/m^2, respectively).

TAVI procedure

All patients had been judged inoperable or at high operative risk by the Heart Team and required consensus of at least one interventional cardiologist and one cardiac surgeon. Motivations to refuse surgical aortic valve replacement (SAVR) in patients were: 1) logistic European system for cardiac operative risk evaluation [EuroSCORE] ≥15%, or 2) the presence of contra-indications to cardiac surgery, e. g. porcelain aorta, frailty or patent grafts in proximity of the sternum. Access site was evaluated based on the measurements of pre-procedural multislice computed tomography scan. Valve implantation was performed either via the transfemoral or non-transfemoral approach (transapical or direct aortic). General anaesthesia or conscious sedation was used according to current local practice.

Study endpoints

Main endpoint of this study was all-cause mortality at 30 days and 1 year after TAVI. All clinical outcomes were documented during the hospital stay, in compliance with the Valve Academic Research Consortorium-2 (VARC-2) criteria and compared across all 3 BMI categories [22]. Vascular complications were documented for all procedural 'access sites', defined as any location traversed by a guide-wire, a catheter or a sheath during the procedure, including arteries, veins, left ventricular apex and the aorta. For the evaluation of postoperative delirium (POD) by the nurse or attending physician, a Delirium Observational Screening (DOS) scale score was rated at the end of every shift, according to the local protocol [23].

Statistical analysis

Categorical variables were expressed as frequencies and percentages and compared with the One-way ANOVA, Chisquared test or Fisher's exact test, when appropriate. We applied Bonferroni's correction in case of multiple comparisons. Continuous variables were expressed as mean and standard deviation if normally distributed or as median [interquartile range] if skewed and compared with the Student's t-test or the Mann-Whitney *U* test, respectively. The association between BMI as a categorical variable and all-cause mortality was analysed using Kaplan–Meier survival estimates and the Log-Rank test. We developed a Cox regression model with selected variables with a p-value < 0.10 to isolate the association of BMI with all-cause mortality. All statistical analyses were carried out using the IBM Statistical Package for Social Science for Windows, version 24.0 (IBM Corp., Armonk, New York, USA).

RESULTS

Patient characteristics

We included a total of 562 consecutive patients who underwent TAVI for severe AS in the study. Because of the small sample size, we excluded patients (*n* = 13) with BMI <18.5 kg/m^2, leaving 549 (98%) patients for the final analysis. Patient characteristics of all patients included in this study are given in Table 1.

Table 1. Baseline characteristics stratified according to the BMI categories.

	All patients (n=549) [*n* (%)]	NW (n=237)	OW (n=200)	O (n=112)	p-value, overall	NW vs. OW	NW vs. O	OW vs. O
Age, years	80.2±7.5	80.8±7.5	80.5±7.3	78.4±7.5	0.004	1.000	0.003	0.025
Gender, male	241 (44)	113 (48)	96 (48)	32 (29)	0.001	1.000	0.002	0.003
BMI, Kg/m^2	26.6±4.4	22.8±1.5	27.2±1.4	33.3±2.8	0.000	0.000	0.000	0.000
Logistic EuroSCORE	17.3±9.9	18.1±10.6	16.5±8.5	17.4±10.5	0.417	0.637	1.000	1.000
Frailty	184 (34)	80 (34)	60 (30)	44 (39)	0.248	1.000	0.922	0.289
NYHA class ≥III	305 (58)	131 (58)	100 (52)	74 (67)	0.041	0.740	0.313	0.035
Estimated GFR, ml/min	56.3±22.5	56.4±23.5	57.6±20.3	53.8±24.5	0.460	1.000	0.867	0.702
Porcelain aorta	58 (11)	25 (11)	24 (12)	9 (8)	0.551	1.000	1.000	0.828
Diabetes mellitus	175 (32)	54 (23)	62 (31)	59 (53)	0.000	0.180	0.000	0.000
Hypertension	329 (60)	129 (54)	120 (60)	80 (71)	0.010	0.703	0.007	0.142
Dyslipidemia	185 (34)	63 (27)	77 (39)	45 (40)	0.008	0.025	0.036	1.000
Smoking (current/prior)	178 (32)	81 (34)	67 (34)	30 (27)	0.356	1.000	0.508	0.675
Coronary artery disease	261 (48)	114 (48)	90 (45)	57 (51)	0.591	1.000	1.000	0.956
Prior myocardial Infarction	103 (19)	42 (18)	37 (19)	24 (21)	0.705	1.000	1.000	1.000
Prior PCI	200 (36)	93 (39)	71 (36)	36 (32)	0.412	1.000	0.598	1.000
Prior CABG	90 (16)	33 (14)	36 (18)	21 (19)	0.390	0.758	0.770	1.000
Peripheral artery disease	118 (22)	59 (25)	36 (18)	23 (21)	0.209	0.243	1.000	1.000
Atrial fibrillation	174 (32)	78 (33)	58 (29)	38 (34)	0.580	1.000	1.000	1.000
Active malignancy	60 (11)	27 (11)	25 (13)	8 (7)	0.331	1.000	0.707	0.440
COPD	109 (20)	50 (21)	37 (19)	22 (20)	0.793	1.000	1.000	1.000
Pulmonary hypertension	38 (7)	16 (7)	12 (6)	10 (9)	0.620	1.000	1.000	1.000
Prior TIA or stroke	108 (20)	47 (20)	41 (21)	20 (18)	0.850	1.000	1.000	1.000
Medication use								
Calcium- inhibitors	120 (22)	56 (24)	40 (20)	24 (21)	0.653	1.000	1.000	1.000
Beta-blockers	305 (56)	128 (54)	107 (54)	70 (63)	0.252	1.000	0.410	0.377
Anti-arrhythmias	40 (7)	16 (7)	12 (6)	12 (11)	0.281	1.000	0.553	0.375
Diuretics	345 (63)	137 (58)	128 (64)	80 (71)	0.044	0.543	0.042	0.576

	All patients (n=549) [*n* (%)]	NW (n=237)	OW (n=200)	O (n=112)	p-value, overall	NW vs. OW	NW vs. O	OW vs. O
Angiotensin-II-inhibitors	99 (18)	36 (15)	31 (16)	32 (29)	0.005	1.000	0.007	0.012
Aspirin	298 (54)	135 (57)	102 (51)	61 (55)	0.459	0.641	1.000	1.000
Lipid lowering agents	310 (57)	121 (51)	116 (58)	73 (65)	0.039	0.432	0.039	0.657
Insulin	70 (13)	16 (7)	29 (15)	25 (22)	0.000	0.044	0.000	0.134
Echocardiography data								
LVEF	54.6±17.8	53.1±16.6	52.6±16.7	61.3±20.2	0.000	1.000	0.001	0.000
LVEF ≤30	46 (9)	19 (9)	22 (12)	5 (5)	0.171	0.948	0.838	0.188
Peak aortic gradient, mmHg	66.0±23.3	66.3±24.0	65.3±23.5	66.4±21.5	0.742	1.000	1.000	1.000
Mean aortic gradient, mmHg	40.0±17.1	40.3±17.6	39.8±16.5	39.7±16.5	0.962	1.000	1.000	1.000
Procedural								
General anesthesia	154 (28)	72 (30)	53 (27)	29 (26)	0.567	1.000	1.000	1.000
Non-transfemoral[a]	91 (17)	46 (19)	32 (16)	13 (12)	0.181	1.000	0.230	0.951
PPR, ≥ mild	32 (6)	21 (9)	6 (3)	5 (5)	0.025	0.025	0.310	1.000

Abbreviations. *NW* normal weight (18.5 _ BMI _ 24.9), *OW* overweight (25.0 _ BMI _ 29.9), *O* obese (BMI ≥ 30.0), *BMI* body mass index, *GFR* glomerular filtration rate, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *COPD* chronic obstructive pulmonary disease, *TIA* transient ischaemic attack, *CCBs* calcium channel blockers, *ARB's* angiotensin II receptor blockers, *LVEF* left ventricular ejection fraction, *PPR* peri-prosthetic aortic valve regurgitation.

[a]Transapical/direct aorta.

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According to the BMI categories, 43% (*n* = 237) had normal weight, 36% (*n* = 200) were overweight, and 20% (*n* = 112) were obese. BMI distribution is graphically presented in Fig. 1. Obese patients were relatively younger than normal weight and overweight patients (78.4 ± 7.5 vs. 80.8 ± 7.5 and 80.5 ± 7.3, $p = 0.004$, respectively); were more often female (71% vs. 52 and 52%, $p = 0.001$, respectively); obese patients had, non-surprisingly, a higher prevalence of diabetes mellitus (53% vs. 23 and 31%, $p \leq 0.001$, respectively), hypertension (71% vs. 54 and 60%, $p = 0.010$, respectively), hypercholesterolaemia (40% vs. 27 and 39%, $p = 0.008$, respectively). Obese patients had a higher left ventricular ejection fraction (LVEF) compared with normal weight and overweight patients (61.3 ± 20.2 vs. 53.1 ± 16.6, and 52.6 ± 16.7%, $p \leq 0.001$, respectively). After the procedure, normal weight was associated with mild/or more than mild periprosthetic aortic valve regurgitation (PPR). No differences were observed in procedural features between the groups.

Clinical outcomes

In-hospital outcomes are summarised in Table 2. Median follow-up time was 682 [interquartile range: 328–1270] days, and 33% (*n* = 181) deaths occurred during the follow-up period, with the highest rate among normal weight patients compared with overweight and obese patients (38.4% vs. 27.5% and 31.3%, $p = 0.049$, respectively). At 30-day follow-up, as

Table 2. Clinical outcomes.

	All patients [*n* (%)]	NW	OW	O	p-value, overall	NW vs. OW	NW vs. O	OW vs. O
Bleeding complications								
Life-threatening or major	78 (14)	35 (15)	27 (14)	16 (14)	0.931	1.000	1.000	1.000
Minor	82 (15)	31 (13)	35 (18)	16 (14)	0.424	0.593	1.000	1.000
Vascular complications								
Major	76 (14)	33 (14)	27 (14)	16 (14)	0.980	1.000	1.000	1.000
Minor	74 (14)	29 (12)	30 (15)	15 (13)	0.701	1.000	1.000	1.000
AKI stage ≥2	29 (5)	18 (8)	7 (4)	4 (4)	0.108	0.170	0.350	1.000
Permanent pacemaker implantation	54 (10)	24 (10)	15 (8)	15 (13)	0.246	1.000	1.000	0.292
New onset atrial fibrillation	72 (13)	34 (14)	27 (14)	11 (10)	0.495	1.000	0.731	1.000
TIA -or stroke	22 (4)	8 (3)	8 (4)	6 (5)	0.392	1.000	1.000	1.000
Postoperative delirium	77 (14)	45 (19)	19 (10)	13 (12)	0.012	0.013	0.189	1.000
Infection[a]	38 (7)	19 (8)	13 (7)	6 (5)	0.631	1.000	1.000	1.000
In-hospital stay, day	6.7±5.4	7.3±6.3	6.1±20	6.7±5.8	0.057	0.050	1.000	0.864
In-hospital mortality	22 (4)	12 (5)	6 (3)	4 (4)	0.395	0.823	1.000	1.000

Abbreviations. *NW* normal weight (18.5 _ BMI _ 24.9), *OW* overweight (25.0 _ BMI _ 29.9), *O* obese (BMI ≥ 30.0), *AKI* acute kidney injury, *PPI* permanent pacemaker implantation, *AF* atrial fibrillation, *TIA* transient ischaemic attack, *POD* postoperative delirium.

[a]Infections (Urinary tract, OR access site, OR pneumonia, OR combined).

well as 1-year follow-up, all-cause mortality rates were higher in normal weight patients compared with overweight and obese patients (6.8% vs. 4.5%, and 3.6%, $p = 0.386$; and 18.6% vs. 9.0%, and 9.8%, $p = 0.006$, respectively). There were no differences in in-hospital bleeding or vascular complications between the groups.

Unadjusted survival is presented as a Kaplan–Meier curve in Figures 2 and 3. Estimated survival rates varied significantly among the groups after 30 days ($p = 0.047$, log-rank test) and 1 year ($p = 0.017$, log-rank test). Patients with normal weight with BMI 18.5–24.9 kg/m^2 had the highest mortality risk, whereas overweight patients had the lowest mortality risk. Univariate and multivariate analysis results of the association between BMI and 30-day and 1-year mortality are shown in Table 3.

After adjustment for baseline and periprocedural covariates, i. e., age, gender, New York Heart Association class ≥ III, diabetes mellitus, hypertension, dyslipidaemia, left ventricular ejection fraction, calcium channel blockers, beta blockers, antiarrhythmics, diuretics, angiotensin II receptor antagonists, aspirin, lipid-lowering agents, insulin, PPR ≥ mild, postoperative delirium, and hospital stay, only overweight was associated with a decreased 30-day and 1-year all-cause mortality rate compared with normal weight and obesity

(overweight adjusted model at 30 days: hazard ratio [HR] 0.69; 95% confidence interval [CI] 0.47–0.99; adjusted model at 1 year: HR 0.65; 95% CI 0.45–0.94, respectively). However, there was no association between BMI as a continuous variable and mortality.

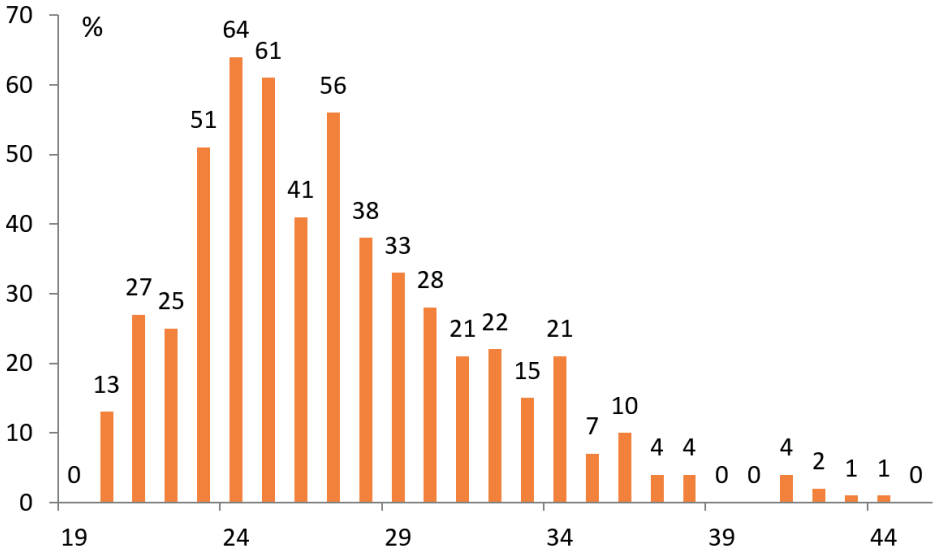

Figure 1. Distribution of body mass index.

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Table 3. Effect of body weight on all-cause mortality during follow-up.

	Univariate HR (95% CI)	p	Multivariate[a] HR (95% CI)	p
At 30-day				
Body mass index[b]	0.98 (0.95-1.01)	0.258	0.98 (0.94-1.02)	0.374
Normal weight vs. Overweight	0.70 (0.50-0.98)	0.038	0.68 (0.45-0.95)	0.027
Normal weight vs. Obese	0.79 (0.54-1.17)	0.237	0.81 (0.50-1.29)	0.370
Overweight vs. Obese	1.13 (0.74-1.72)	0.583	1.18 (0.71-1.96)	0.520
At 1-year				
Body mass index[b]	0.98 (0.94-1.01)	0.189	0.97 (0.94-1.02)	0.217
Normal weight vs. Overweight	0.65 (0.47-0.91)	0.013	0.69 (0.43-0.88)	0.009
Normal weight vs. Obese	0.74 (0.50-1.10)	0.136	0.70 (0.43-1.12)	0.133
Overweight vs. Obese	1.14 (0.75-1.74)	0.547	1.19 (0.72-1.96)	0.497

Abbreviations. HR hazard ratio, *CI* confidence interval

[a]Adjusted for: age, gender, New York Heart Association (NYHA) class ≥ III, diabetes mellitus, hypertension, dyslipidaemia, left ventricular ejection fraction (LVEF), calcium channel blockers, beta blockers, antiarrhythmics, diuretics, angiotensin II receptor blockers, aspirin, lipid-lowering agents, insulin, periprosthetic aortic valve regurgitation (PPR) ≥mild, postoperative delirium, hospital stay.

[b]As a continuous variable.

DISCUSSION

In the present study, we aimed to evaluate the impact of body mass index on all-cause mortality and clinical outcome in patients undergoing TAVI. After adjustment, being overweight was associated with decreased 30-day and 1-year all-cause mortality, while there was no association found between obesity and mortality outcomes following TAVI. Furthermore, there were no differences observed in postoperative bleeding or vascular complications between the BMI categories.

Considering the aging population, the global prevalence of overweight and obesity is expected to rise [12]. AS is the predominant type of valvular heart disease among elderly and associated with poor prognosis [24]. Prevalence of AS is 3%, increasing with age up to 10% in adults ≥80 years [25]. Currently, TAVI has emerged as a valuable option to treat severe AS in elderly patients considered to be inoperable or at high surgical risk for SAVR [26]. However, fewer data exist regarding body weight management in patients undergoing TAVI.

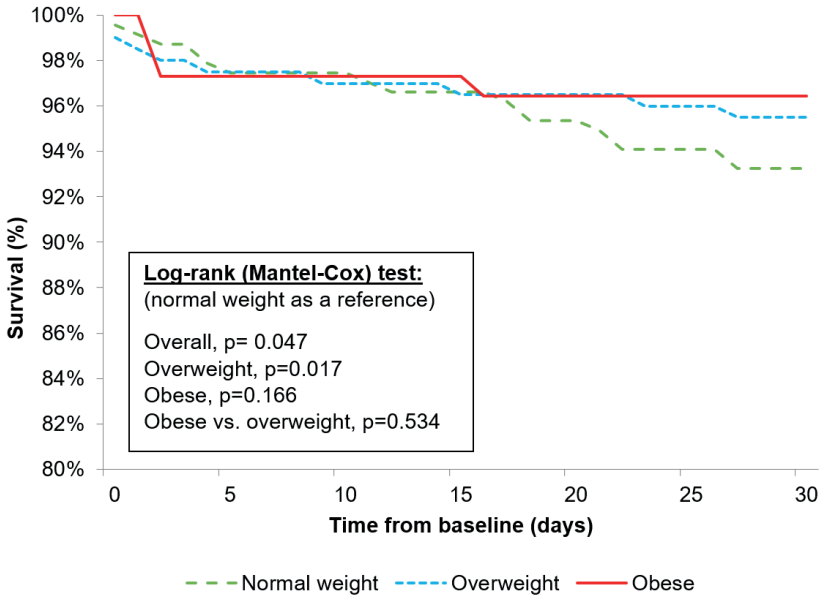

Figure 2. Thirty-day all-cause mortality, graphically presented by Kaplan–Meier survival curves.

Interestingly, we observed decreased short-term and long-term mortality outcomes after TAVI among overweight patients. According to our knowledge, this is the first time such a short-term effect of overweight on mortality outcomes after TAVI has been shown. Our findings are in line with literature findings including patients who were admitted for first-time coronary artery bypass (CABG) or combined CABG/aortic valve replacement surgery, patients after coronary angiography for diagnosis of acute coronary syndrome, and among patients undergoing cardiac surgery [27–29]. While some studies reported no effect of being overweight on mortality outcome after TAVI [15, 19], others reported long-term positive effect of overweight on mortality outcome after TAVI [14, 17, 18]. Although current guidelines are advising weight loss and prevention of overweight and obesity, these counter-intuitive

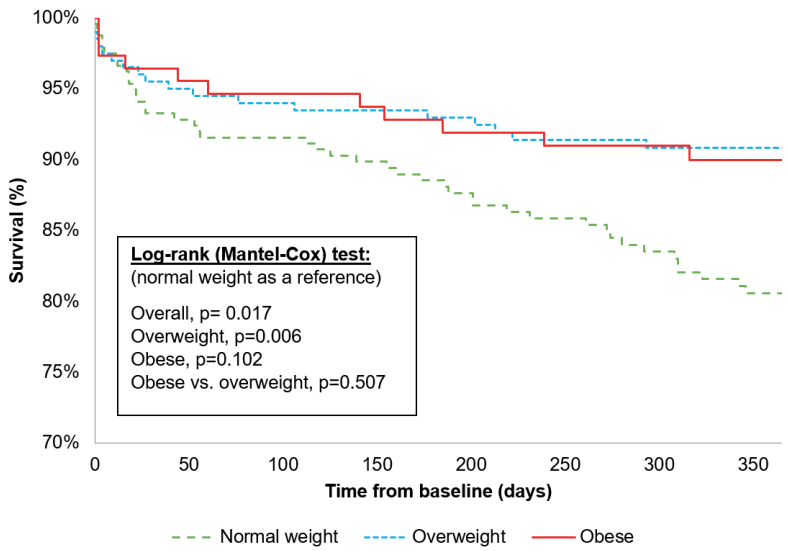

Figure 3. One-year all-cause mortality, graphically presented by Kaplan–Meier survival curves.

findings regarding the positive association between overweight/obesity and mortality may create the impression that an intentional weight loss may not always be favourable.

Generally, obesity has been associated with adverse clinical health status [4], however, we observed no association between obesity and mortality after TAVI. Our results are in line with some previous reports [15, 18, 19], however, several other studies including a meta-analysis, found a beneficial effect of obesity on mortality outcome after TAVI [14, 17, 21]. In addition, inconstancies in these contradictive observations could be explained by unhealthy metabolic profile (i. e., hypertension, dyslipidaemia, diabetes) of obese individuals included in our study that may have influenced the results [30].

Although we observed no association between BMI as a continuous variable and mortality, several other studies reported a gradual reduction in death rate for every increment in BMI unit (kg/m^2) during short-term or long-term follow-up after TAVI [15–17]. However, a recent study among patients (n = 4571) undergoing TAVI demonstrated that an increase in BMI was associated with higher risk of mortality in patients with elevated BMI (>32 kg/m^2) [20]. Moreover, a 'U' shape association between BMI a continuous variable and mortality was found among patients with diabetes, acute heart failure and in patients undergoing cardiac surgery [29, 31, 32].

While performing TAVI in overweight or obese individuals may be challenging due to vascular access site and fluoroscopic visualisation [33], there were no differences in vascular and bleeding complications observed between the BMI groups in our cohort. These findings are in line with a recent meta-analysis evaluating the effect of BMI on outcome after TAVI [21]. This could be explained by improved TAVI technique and sustained efficacy of TAVI. However, previous studies using early-generation transcatheter aortic valves and techniques reported higher postoperative complication rates among overweight/obese and

underweight individuals after TAVI. For instance, in a multi-centre study (n = 940), higher rates of postoperative minor stroke, minor vascular complications and acute kidney injury stage 1 were observed among obese individuals following TAVI [15]. Consistent with these findings, another study (n = 409) reported higher incidence of major postoperative vascular complications and a trend toward more major and life-threatening bleeding events among obese patients after TAVI [17]. Furthermore, a higher rate of major vascular complications was observed in patients with underweight. However, according to another study, BMI < 20 compared with BMI > 20 was not associated with adverse events following TAVI [34]. Inconsistencies in reported results could be explained by different definitions of BMI, i. e., BMI either as a categorical or continuous variable, which could lead to uncertainty in defining the cut-off points and interpretation of results. Therefore, studies should report their results according to the standardised BMI classification, i. e., WHO classification.

The mechanism behind the obesity paradox remains unclarified [35]. However, there are several possible factors that could explain the paradoxical effect of BMI on clinical outcomes. For instance, excess body weight may increase metabolic reserve and counteract the negative effects of acute injuries. Furthermore, patients with ischaemic heart failure appear to have a higher level of TNF-a concentrations compared with those with a non-ischaemic aetiology [36]. Moreover, adipose tissue has been shown to produce TNF-a receptors [37], therefore, overweight and obese patients may have a protective buffer from the negative effect of increasing TNF-a by producing higher levels of these receptors. Furthermore, several other investigators argue that the obese group, consisting of younger individuals, seeks medical care earlier, is treated medically more aggressively, and therefore benefits more from medical and interventional treatments [38]. However, these differences did not affect the outcome after adjustments in the multivariate model, even though obese individuals in our cohort were younger and used more baseline medications, i. e., diuretics, angiotensin II receptor antagonists, lipid-lowering agents, or insulin, compared with the normal weight group.

BMI either as a continuous or categorical variable has been frequently used to define body weight. However, BMI does not discriminate between the component of body fat, the type and location of fat in the body, or the degree of metabolic diseases that it can cause. In the clinical setting, high muscle mass/low fat has been associated with improved survival in patients with cardiovascular disease [39]. Accordingly, loss of muscle mass has been associated with increased mortality in patients undergoing TAVI [40]. That is why future studies are necessary to determine the most favourable body weight to improve outcome after TAVI.

This study has several important limitations. First, this retrospective, single-centre analysis is subjected to the limitations common to this type of analysis. An observational analysis, including the current study, cannot prove or disprove the existence of a paradoxical relationship between BMI and mortality. Second, we used BMI as a surrogate of body weight. However, combining BMI and measures of central obesity, such as waist circumference and waist to hip ratio, may be more valuable in the assessment of mortality risk after TAVI, since central obesity predicts mortality more reliably than BMI alone in patients with coronary heart disease [41]. Third, in contrast to other findings, only overweight was associated with decreased mortality in patients in our cohort. However, it is possible that patients with a more severe profile of comorbidities and a high surgical risk for TAVI were refused to

undergo TAVI, which could have affected current results. Fourth, we may not have included all possible (unknown) confounding factors that may have influenced the results. For instance, to address the likely bias attributed to patients with cachexia, we excluded patients with BMI < 18.5. However, as most elderly suffer from lower muscle mass, this will introduce bias attributable to unassured confounders [40]. Fifth, we could not address the effect of BMI changes over time, which may have influenced our results. Finally, although late mortality after TAVI may be attributed to the non-cardiac causes [42], we could not address the cause of death in patients included in this study. Future studies are needed to evaluate cause of death to provide a better understanding of the mechanism of the observed association between BMI and mortality.

Conclusions

Being overweight is associated with improved survival after TAVI. Furthermore, TAVI is safe in different BMI groups with respect to the postoperative complications rate.

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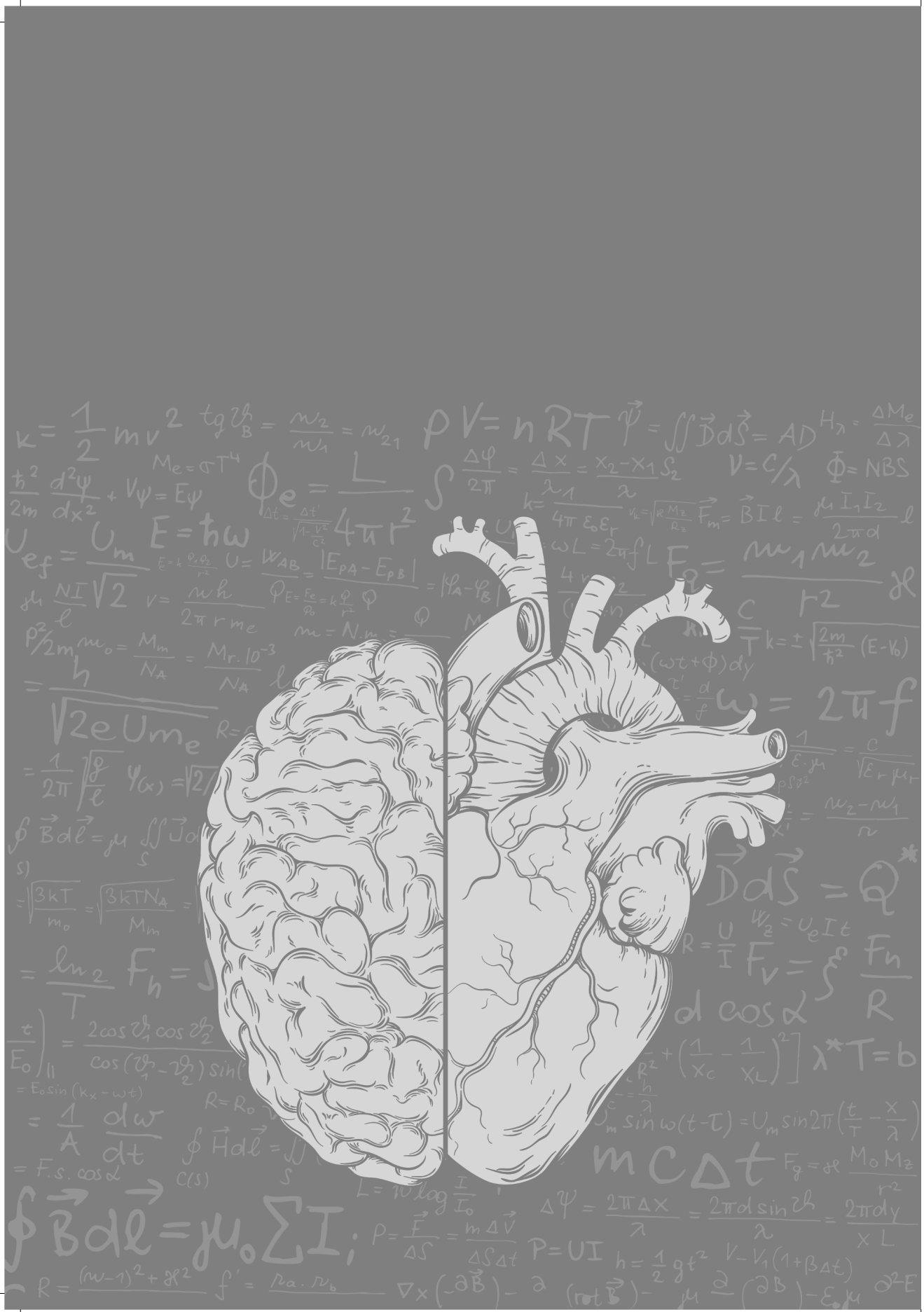

Chapter 7

Impact of baseline cigarette smoking status on clinical outcome after transcatheter aortic valve replacement

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ABSTRACT

Objectives: To explore the prevalence of smoking, and its association with clinical and mortality outcome among patients undergoing transcatheter aortic valve replacement (TAVR).

Background: Less data exist regarding the effect of baseline smoking status on clinical and mortality outcome among patients undergoing TAVR.

Methods: Consecutive patients who underwent TAVR at two high volume Dutch centers were included. Smoking status was prospectively questioned by a structured interview at admission. Primary endpoint was 1-year all-cause mortality after TAVR.

Results: A total of 913 consecutive patients (80.1 ± 7.6 years; logistic EuroSCORE: 16.5 ± 9.9%) who underwent TAVR for severe aortic valve stenosis were included. There were 47% (*n* = 432) males, and 57% (*n* = 522) never-smokers, and 35% (*n* = 317) prior-smokers, and 8% (*n* = 74) current smokers. Smokers (i.e., prior-smokers or current-smokers) were younger compared to never-smokers (78.9 ± 7.9 and 76.4 ± 8.0 vs. 81.3 ± 7.1, *P* ≤0.001, respectively). Median follow-up time was 365 (interquartile range [IQR]: 280–365) days. Overall, prior-smoking was not associated with all-cause mortality at 1-year following TAVR (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.55–1.23). After stratification according to sex, male prior-smokers showed better 1-year survival after TAVR than male never-smokers (12% vs. 20%; *P* = 0.018, respectively, HR 0.52, 95% CI 0.29–0.89), while this reversed effect was not observed among female prior-smokers versus female never-smokers after TAVR (HR 1.70, 95% CI 0.95–3.05).

Conclusions: In general, baseline prior-smokers had similar 1-year mortality outcome after TAVR compared with baseline never-smokers. However, there was a reversed association between baseline prior-smoking status and 1-year mortality after TAVR among males, which could partially be explained due to the favorable baseline characteristics.

BACKGROUND

Nearly 21% (i.e., 1.1 billion) of the world population age≥15 years are tobacco users.[1] Tobacco use remain the cause of ~6 million preventable deaths per year worldwide, which account for 12% of all male and 6% of all female deaths in the world per year.[2,3] Tobacco smoking decreases at least 10 years of life expectancy, and kills up to half of its users.[1,4–6] Furthermore, tobacco smoking increases the risk of coronary artery disease (CAD), peripheral artery disease (PAD), respiratory diseases (e.g., asthma, chronic obstructive pulmonary disease [COPD]), and cancer.[2,3,7,8] In addition, smoking cessation would prevent ≥80% of incident CAD and 40% of all cancers.[9]

In contrast to the overwhelming data showing harmful health consequences of cigarette smoking, surprisingly, some studies have shown better survival outcome among smokers (e.g., prior-smokers or current-smokers) compared with never-smokers, a phenomenon called "smoking paradox." The smoking paradox is mainly observed among certain groups of patients, including patients with acute myocardial infarction (AMI),[10–21] heart failure,[22] CAD or acute cerebral stroke,[23–25] and among patients who underwent cardiopulmonary resuscitation for inhospital cardiac arrest.[26] Moreover, tobacco smoking showed to be an independent protective predictor of adverse left ventricle-remodeling among patients with AMI.[27] Currently, transcatheter aortic valve replacement (TAVR) has become the treatment of choice among older high-risk patients or inoperable patients with severe symptomatic aortic valve stenosis (AS).[28,29] A study by Agarwal et al observed lower in-hospital mortality among smokers (i.e., prior-smokers or current-smokers) compared with never-smokers undergoing TAVR, suggesting the existence of "smokers paradox" among patients undergoing TAVR.[30] The exact mechanism of this paradox need to be clarified, specifically among older and frail patients who are suitable for TAVR.

Given the fact that majority of the smokers who undergo TAVR consist of males, therefore we hypothesized that gender may be a major confounding factor causing such a "smokers paradox." Several studies comparing outcomes of TAVR in females versus males yield varying results, with some suggesting improved outcome among females.[31–33] However, these analyses did not sufficiently address the possible role of smoking status on outcome after TAVR. By means of this descriptive study, we aimed to explore sex differences in the prevalence of smoking at baseline, and its association with clinical and mortality among patients undergoing TAVR.

METHODS

Study design

Consecutive patients admitted to the University Medical Center Utrecht, the Netherlands, and Erasmus Medical Center, Rotterdam, the Netherlands from August 26, 2008 to February 23, 2017, with a diagnosis of severe AS were included. In both centers, data regarding patient characteristics, procedural, and in-hospital events were prospectively collected in an electronic institutional database and retrospectively analyzed. Due to the retrospective nature of this study the requirement of ethical committee approval was waived. The main outcome of interest was 1-year all-cause mortality, which was defined as patients who expired during 1 year after the procedure. We had mortality data for all 913 patients who were

included in the study. Smoking status was self-reported and was prospectively questioned by a structured interview at admission. Frailty was subjectively measured prior to allocating TAVR by an interventional cardiologist and/or cardiothoracic surgeon based on the informal "eyeballing" (including cognition function, physical weakness and walking speed). Body mass index was defined as the weight in kilograms divided by the square of the height in meters. Hypercholesterolemia was defined as a previous diagnosis of hyperlipidemia or the use of lipid-lowering medications before admission. PAD was defined as claudication, history of peripheral surgery/or angioplasty, or stenosis of ≥50% of the iliofemoral axis which was assessed prior to TAVR by multislice computed tomography. Atrial fibrillation (AF) at baseline was defined as a history of AF (i.e., permanent, persistent, or paroxysmal) before TAVR or as the presence of AF on hospital admission.

Diagnosis of COPD was based on the medical history. Depending on the degree of calcification, size of the iliofemoral arteries, and severity of disease in the iliofemoral arteries valve replacement was performed either via the transfemoral (TF), or non-TF TAVR such as transapical, transaortic, or trans-subclavian approach. All TF procedures involved a fully percutaneous technique. General anesthesia was used according to current local practice.

All periprocedural complications were evaluated according to Valve Academic Research Consortium-2.[34] Vascular complications were documented for all procedural "access sites," defined as any location traversed by a guidewire, a catheter, or a sheath during the procedure, including arteries, veins, left ventricular apex, and the aorta. All patients were monitored for at least 72 hr and discharged on a regimen of life-long low-dose aspirin (80–100 mg per day) or oral anticoagulant (in case of clinical indication), and 3 months clopidogrel (75 mg per day). Post-discharge survival data were collected by contacting the Municipal Civil Registries.

Statistical analysis

Patients were categorized as never-smokers, prior-smokers, and current-smokers. For the entire analyses within the groups never-smoking was used as the reference group. Categorical variables were expressed as frequencies and percentages and compared with the one-way ANOVA, chi-square, or Fisher's exact test when appropriate. Continuous variables were expressed as mean and standard deviation if normally distributed or as median (interquartile range [IQR]) if skewed and compared with the Student's *t*-test or the Mann–Whitney *U* test, respectively. Survival during the follow-up was evaluated according to the Kaplan– Meier methods and compared between males versus females and stratified according to the sex and smoking status using the log-rank test. Univariate Cox regression was used to assess the impact of prior-smoking on baseline factors. A multivariable Cox proportional hazards analysis were performed to analyze the association between baseline prior-smoking status and 1-year all-cause mortality after TAVR.

Variables with univariate *P*-value ≤0.10 and/or variables considered to be relevant according to clinical judgment (purposeful selection of variables) were included in the multivariate model. All tests were two-tailed and a *P*-value ≤0.05 was considered statistically significant. All data were processed using IBM Statistical Package for Social Science for Windows, version 24.0 (IBM Corporation, Armonk, NY).

RESULTS

Patient and procedural characteristics

A total of 913 consecutive patients (80.1 ± 7.6 years; logistic EuroSCORE: 16.5 ± 9.9%; 47% males) who underwent TAVR for AS were included. There were 57% (*n* = 522) never-smokers, 35% (*n* = 317) prior-smokers, and 8% (*n* = 74) current-smokers. Due to low sample-size current-smoking was excluded in the multivariate cox regression models. All baseline variables are shown in Tables 1–3. Univariate and multivariate analysis are shown in Tables

Table 1. Baseline and procedural characteristics according to smoking status.

	All patients	Smoking status			p
	n= 913	Never (n= 522)	Prior (n= 317)	Current (n= 74)	
Age, years	80.1±7.6	81.3±7.1	78.9±7.9	76.4±8.0	<0.001
Sex, male	432 (47)	178 (34)	209 (66)	45 (61)	<0.001
Frailty	362 (40)	204 (39)	129 (41)	29 (39)	0.879
BMI, Kg/m^2	26.6±4.7	26.7±4.7	27.0±4.6	24.7±4.4	0.001
Logistic EuroSCORE, %	16.5±9.9	16.8±9.9	16.6±10.6	14.2±7.5	0.099
e-GFR	56.0±23.1	55.4±22.7	56.3±24.2	59.8±21.2	0.336
Hypercholesterolemia	421 (46)	211 (41)	175 (56)	35 (47)	<0.001
PAD	204 (22)	108 (21)	67 (21)	29 (39)	0.001
AF, any	298 (33)	183 (35)	98 (31)	17 (23)	0.084
COPD, any class	200 (22)	83 (16)	89 (28)	28 (38)	<0.001
Prior PCI	319 (35)	179 (34)	109 (35)	31 (42)	0.428
Prior CABG	149 (16)	68 (13)	68 (22)	13 (18)	0.006
Medication use					
Aspirin	446 (49)	261 (50)	138 (44)	47(64)	0.009
Thienopyridine/P2Y12-i[a]	233 (26)	136 (26)	74 (24)	23 (32)	0.415
Coumarins	288 (32)	180 (35)	90 (29)	18 (25)	0.096
Beta-blocker	524 (58)	306 (59)	178 (56)	40 (54)	0.683
CCBs	209 (23)	127 (24)	68 (22)	14 (19)	0.455
ACE-i	305 (34)	160 (31)	118 (38)	27 (37)	0.108
Procedural					
General anesthesia	372 (41)	182 (35)	151 (48)	39 (53)	<0.001
Non-transfemoral approach[b]	138 (15)	59 (11)	57 (18)	22 (30)	<0.001
Balloon-expandable valve	558 (61)	322 (62)	188 (60)	48 (65)	0.670

Abbreviations: ACE-i, angiotensin converting enzyme inhibitors; AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

[a]At least one of the following: clopidogrel, ticagrelor, prasugrel, or other.

[b]At least one of the following: transapical, transaortic, or trans-subclavian approach.

Table 2. Baseline and procedural characteristics according to sex.

	All patients (n= 913)	Female (n= 481)	Male (n= 432)	p
Age, years	80.1±7.6	81.3±6.8	78.6±8.2	<0.001
Prior smoking	317 (38)	108 (24)	209 (54)	<0.001
Current smoking	74 (12)	29 (8)	45 (20)	<0.001
Frailty	362 (40)	212 (44)	150 (35)	0.004
BMI, Kg/m^2	26.6±4.7	27.1±5.3	26.1±3.9	<0.001
Logistic EuroSCORE, %	16.5±9.9	16.7±9.3	16.3±10.8	0.113
e-GFR	56.0±23.1	53.6±22.0	58.8±23.9	0.004
Hypercholesterolemia	421 (46)	215 (45)	206 (48)	0.328
PAD	204 (22)	95 (20)	109 (25)	0.047
AF, any	298 (33)	159 (33)	139 (32)	0.777
COPD, any class	200 (22)	87 (18)	113 (26)	0.003
Prior PCI	319 (35)	128 (27)	191 (44)	<0.001
Prior CABG	149 (16)	35 (7)	114 (27)	<0.001
Medication use				
Aspirin	446 (49)	220 (46)	226 (53)	0.036
Thienopyridine/P2Y12-i[a]	233 (26)	105 (22)	128 (30)	0.008
Coumarins	288 (32)	148 (31)	140 (33)	0.612
Beta-blocker	524 (58)	281 (59)	243 (56)	0.464
CCBs	209 (23)	113 (24)	96 (22)	0.625
ACE-i	305 (34)	149 (31)	156 (36)	0.109
Procedural				
General anesthesia	372 (41)	190 (40)	182 (42)	0.401
Non-transfemoral approach[b]	138 (15)	67 (14)	71 (16)	0.291
Balloon-expandable valve	558 (61)	310 (65)	248 (58)	0.026

[a]At least one of the following: clopidogrel, ticagrelor, prasugrel, or other.

[b]At least one of the following: transapical, transaortic, or trans-subclavian approach.

4 and 5. Total and stratified data are shown in Figures 1–3. Kaplan–Meier estimates for cumulative survival are shown in Figures 4 and 5.

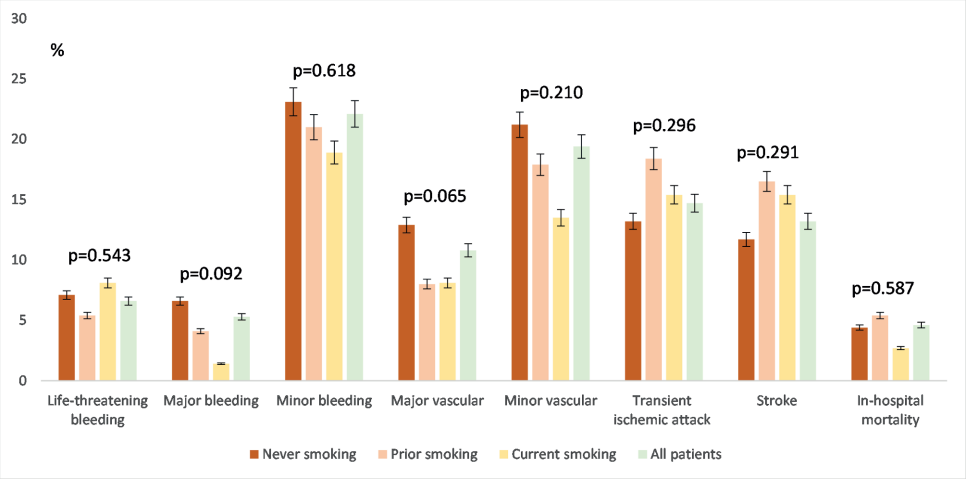

Figure 1. Total peri-procedural clinical outcome after TAVR.

Stratified by smoking status

Prior-smokers were younger compared with never-smokers (78.9 ± 7.9 vs. 81.3 ± 7.1, *P* ≤0.001, respectively); were more frequently males (66% vs. 34%, *P* ≤0.001, respectively). Moreover, prior-smokers suffered more from hypercholesterolemia (56% vs. 41%, *P* ≤0.001, respectively), COPD (28% vs. 16%, *P* ≤0.001, respectively), and had often history of coronary artery bypass surgery (CABG) (22% vs. 13%, *P* = 0.004, respectively). During the procedure prior-smokers compared with never-smokers underwent frequently non-TF TAVR (18% vs. 11%, *P* ≤0.001, respectively).

There were no differences in clinical hospital outcome between the prior-smokers or current-smokers compared with never-smokers after TAVR. After a median follow-up of 365 (280–365) days—there were 13.4% (*n* = 70) deaths among never-smokers, 13.9% (*n* = 44) deaths among prior-smokers, and 20.3% (*n* = 15) among current-smokers (*P* = 0.281). After adjustment for age, sex, logistic EuroSCORE, e-GFR, PAD, COPD, and non-TF TAVR, prior-smoking was not associated with 1-year mortality after TAVR (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.55–1.23). There was a significant interaction between sex and smoking status with respect to 1-year all-cause mortality outcome (*P* =0.001). For this reason we divided the groups (never-smokers, prior-smokers, and current-smokers) according to sex.

Stratified by sex

In contrast to other studies in the cardiovascular field where females have been historically underrepresented, the proportion of females in TAVR is nearly 50%,[32] which could contribute to a more satisfactory gender-based analysis. Males compared with females were younger (78.6 ± 8.2 vs. 81.3 ± 6.8, *P* ≤0.001), were often prior-smokers or current-smokers (54% vs. 24%, *P* ≤0.001, and 20% vs. 8%, *P* ≤0.001, respectively), had more often PAD (25% vs. 20%, *P* = 0.047), suffered often from COPD (26% vs. 18%, *P* = 0.003), and had often prior history of PCI and CABG (44% vs. 27%, *P* ≤0.001, and 27% vs. 7%, P≤0.001, respectively). However, males compared with females were less frail (35% vs. 44%, *P* = 0.004), and had

Table 3. Baseline and procedural characteristics according to sex and smoking status.

	Female				Male			
	Never (n=344)	Prior (n=108)	Current (n=29)	P	Never (n=178)	Prior (n=209)	Current (n=45)	P
Age, years	82.2±6.1	79.3±7.8	78.4±7.4	<0.001	79.4±8.5	78.8±7.9	75.1±8.2	0.010
Frailty	146 (42)	51 (48)	15 (52)	0.445	58 (33)	78 (37)	14 (31)	0.538
BMI, Kg/m^2	27.1±5.1	27.4±5.9	25.3±5.2	0.152	25.8±3.8	26.7±3.8	24.3±3.9	<0.001
Logistic EuroSCORE	16.8±9.5	16.8±8.9	15.9±7.9	0.872	16.9±10.7	16.5±11.4	13.1±7.0	0.092
e-GFR	53.3±21.1	52.8±25.3	59.9±19.1	0.282	59.4±24.9	58.0±23.5	59.7±22.6	0.824
Hypercholesterolemia	143 (42)	58 (54)	14 (48)	0.089	68 (38)	117 (57)	21 (47)	0.002
PAD	64 (19)	23 (21)	8 (28)	0.456	44 (25)	44 (21)	21 (47)	0.002
AF, any	120 (35)	33 (31)	6 (21)	0.243	63 (35)	65 (31)	11 (24)	0.335
COPD, any class	44 (13)	35 (32)	8 (29)	<0.001	39 (22)	54 (26)	20 (44)	0.009
Prior PCI	91 (27)	27 (25)	10 (35)	0.586	88 (49)	82 (39)	21 (47)	0.135
Prior CABG	25 (7)	7 (7)	3 (10)	0.784	43 (24)	61 (29)	10 (22)	0.440
Medication use								
Aspirin	165 (48)	40 (37)	15 (52)	0.128	96 (54)	98 (48)	32 (71)	0.015
Thienopyridine/P2Y12-i[a]	72 (21)	23 (22)	10 (36)	0.209	64 (36)	51 (25)	13 (29)	0.064
Coumarins	115 (34)	26 (25)	7 (25)	0.179	65 (37)	64 (32)	11 (24)	0.247
Beta-blocker	207 (60)	58 (55)	16 (55)	0.541	99 (56)	120 (58)	24 (53)	0.836
CCBs	86 (25)	20 (19)	7 (24)	0.421	41 (23)	48 (23)	7 (16)	0.519
ACE-i	104 (30)	37 (35)	8 (28)	0.613	56 (32)	81 (39)	19 (42)	0.211

	Female				Male			
	Never (n=344)	Prior (n=108)	Current (n=29)	P	Never (n=178)	Prior (n=209)	Current (n=45)	P
Procedural								
General anesthesia	114 (33)	60 (56)	16 (55)	<0.001	68 (38)	91 (44)	23 (51)	0.236
Access				<0.001				0.005
Transfemoral	311 (90)	81 (75)	22 (76)	-	152 (85)	179 (86)	30 (67)	-
Non-transfemoral approach[b]	33 (10)	27 (25)	7 (24)	-	26 (15)	30 (14)	15 (33)	-
Balloon-expandable valve	219 (64)	70 (65)	21 (72)	0.641	103 (58)	118 (57)	27 (60)	0.916

[a]At least one of the following: clopidogrel, ticagrelor, prasugrel, or other.

[b]At least one of the following: transapical, transaortic, or trans-subclavian approach.

Table-4. Association of Cigarette Smoking with Mortality in Individuals after Transcatheter Aortic Valve Replacement.

	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age, years	1.01 (0.98-1.03)	0.528	1.00 (0.98-1.03)	0.722
Sex, male	0.69 (0.49-0.98)	0.037	0.68 (0.46-1.01)	0.057
Prior smoking[a]	1.05 (0.72-1.53)	0.807	0.83 (0.55-1.23)	0.349
Frailty	1.18 (0.83-1.67)	0.362	-	
BMI, Kg/m^2	0.98 (0.95-1.02)	0.332	-	
Logistic EuroSCORE	1.02 (1.00-1.04)	0.009	1.01 (0.99-1.03)	0.269
e-GFR	0.99 (0.98-0.99)	0.001	0.99 (0.98-0.99)	0.014
Hypercholesterolemia	0.93 (0.65-1.32)	0.671	-	
PAD	1.71 (1.18-2.45)	0.004	1.06 (0.67-1.66)	0.809
AF, any	1.17 (0.82-1.67)	0.398	-	
COPD, any class	1.43 (0.97-2.10)	0.068	1.10 (0.71-1.71)	0.683
Prior PCI	1.03 (0.72-1.47)	0.885	-	
Prior CABG	0.65 (0.38-1.12)	0.122	-	
Medication use				
Aspirin	0.93 (0.66-1.31)	0.674	-	
Thienopyridine/P2Y12-i[b]	1.01 (0.68-1.49)	0.980	-	
Coumarins	1.14 (0.79-1.64)	0.489	-	
Beta-blocker	0.85 (0.60-1.21)	0.371	-	
CCBs	1.03 (0.68-1.54)	0.907	-	
ACE-i	0.86 (0.60-1.30)	0.434	-	
Procedural				
Non-transfemoral approach[c]	2.77 (1.91-4.02)	<0.001	2.99 (1.91-4.71)	<0.001
Balloon-expandable valve	0.84 (0.59-1.19)	0.316	-	

[a]The hazard ratio was calculated using the never-smoker group as reference.

[b]At least one of the following: clopidogrel, ticagrelor, prasugrel, or other.

[c]At least one of the following: transapical, transaortic, or trans-subclavian approach.

Table-5. Sex-Specific Association of Cigarette Smoking with Mortality in Individuals after Transcatheter Aortic Valve Replacement.

	Female				Male			
	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age, years	0.99 (0.96-1.03)	0.713	0.99 (0.96-1.04)	0.812	1.02 (0.99-1.06)	0.131	1.02 (0.98-1.06)	0.371
Prior smoking[a]	1.98 (1.14-3.43)	0.016	1.70 (0.95-3.05)	0.074	0.55 (0.33-0.92)	0.023	0.52 (0.29-0.89)	0.018
Frailty	1.23 (0.73-2.10)	0.431	-		1.21 (0.75-1.95)	0.437	-	
BMI, Kg/m^2	1.02 (0.97-1.07)	0.474	-		0.94 (0.88-0.99)	0.040	1.00 (0.93-1.08)	0.941
Logistic EuroSCORE	1.00 (0.98-1.03)	0.792	-		1.03 (1.01-1.05)	0.001	1.04 (1.01-1.06)	0.006
e-GFR	0.99 (0.98-1.00)	0.148	-		0.98 (0.97-0.99)	0.000	0.99 (0.98-1.00)	0.117
Hypercholesterolemia	1.41 (0.84-2.37)	0.195	-		0.64 (0.39-1.04)	0.069	0.84 (0.48-1.46)	0.531
PAD	1.70 (0.96-2.99)	0.067	1.22 (0.63-2.38)	0.557	1.65 (1.02-2.69)	0.042	1.00 (0.55-1.84)	0.989
AF, any	0.99 (0.58-1.73)	0.997	-		1.34 (0.83-2.15)	0.234	-	
COPD, any class	1.40 (0.75-2.60)	0.289	-		1.36 (0.83-2.24)	0.222	-	
Prior PCI	0.70 (0.37-1.32)	0.272	-		1.15 (0.73-1.83)	0.543	-	
Prior CABG	0.43 (0.11-1.77)	0.244	-		0.60 (0.33-1.09)	0.092	0.55 (0.26-1.13)	0.104
Medication use								
Aspirin	0.84 (0.48-1.42)	0.520	-		0.96 (0.60-1.52)	0.851	-	
Thienopyridine/P2Y12-I[b]	0.81 (0.42-1.56)	0.527	-		1.10 (0.66-1.82)	0.719	-	
Coumarins	1.18 (0.69-2.04)	0.548	-		1.09 (0.67-1.79)	0.724	-	
Beta-blocker	0.72 (0.43-1.22)	0.222	-		0.99 (0.62-1.58)	0.970	-	
CCBs	1.40 (0.80-2.47)	0.242	-		0.77 (0.42-1.40)	0.383	-	
ACE-i	1.01 (0.58-1.77)	0.972	-		0.73 (0.44-1.22)	0.231	-	

	Female				Male			
	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Procedural								
Non-transfemoral approach[c]	2.53 (1.42-4.51)	0.002	2.39 (1.21-4.72)	0.013	2.90 (1.77-4.72)	0.000	3.47 (1.91-6.32)	<0.001
Balloon-expandable valve	0.90 (0.52-1.55)	0.705	-		0.83 (0.52-1.32)	0.424	-	

[a]The hazard ratio was calculated using the never-smoker group as reference.

[b]At least one of the following: clopidogrel, ticagrelor, prasugrel, or other.

[c]At least one of the following: transapical, transaortic, or trans-subclavian approach.

better glomerular filtration rate (58.8 ± 23.9 vs. 53.6 ± 22.0, *P*=0.004). For the subgroup analysis according to sex, differences in characteristics between females (never-smokers, prior-smokers, and current-smokers) and males (never-smokers, prior-smokers, and current-smokers) were compared.

STRATIFIED BY GENDER

Female: prior-smokers vs. never-smokers

Female patients consisted of 72% (*n* = 344) never-smokers, 22% (*n* = 108) prior-smokers, and 6% (*n* = 29) current smokers. Compared with female never-smokers, female prior-smokers, and current-smokers were younger (82.2 ± 6.1 vs. 79.3 ± 7.8 and 78.4 ± 7.4, *P* ≤0.001,respectively), but suffered more from COPD (13% vs. 32% and 29%, *P* ≤0.001, respectively), and underwent often non-TF TAVR (10% vs. 25% and 24%, *P* ≤0.001, respectively) with the use of general anesthesia (33% vs. 56% and 55%, *P* ≤0.001, respectively). After adjustments baseline prior-smoking was not associated with 1-year mortality outcome following TAVR among females (HR 1.70, 95% CI 0.95–3.05).

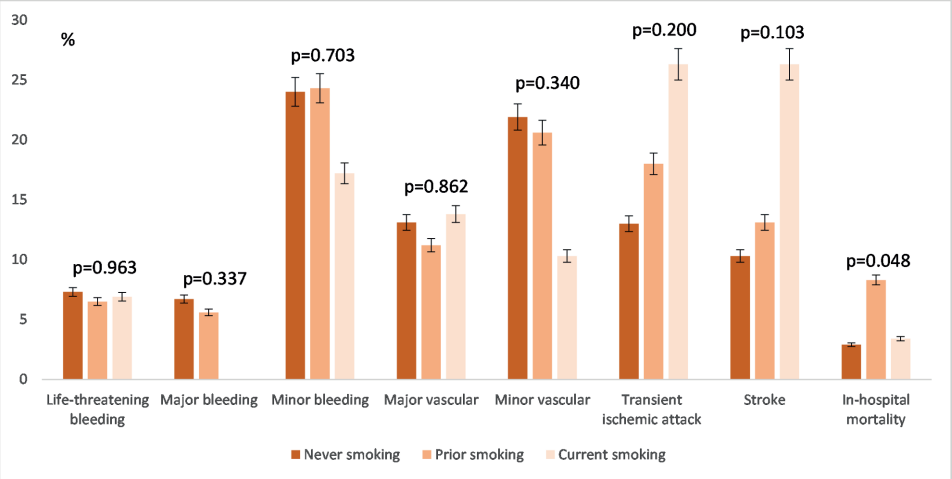

Figure 2. Peri-procedural clinical outcome among females after TAVR.

Male: prior-smokers vs. never-smokers

Male patients comprised 41% (*n* = 178) never-smokers, 49% (*n* = 209) prior-smokers, and 10% (*n* = 45) current-smokers. Compared with male never-smokers, male prior-smokers and current-smokers had favorable baseline characteristics including younger age (79.4 ± 8.5 vs. 78.8 ± 7.9 and 75.1 ± 8.2, *P* ≤0.000, respectively) and nearly similar comorbidity profile. After adjustments baseline prior-smoking status was inversely associated with 1-year mortality after TAVR among males (HR 0.52, 95% CI 0.29–0.89) (Table 5).

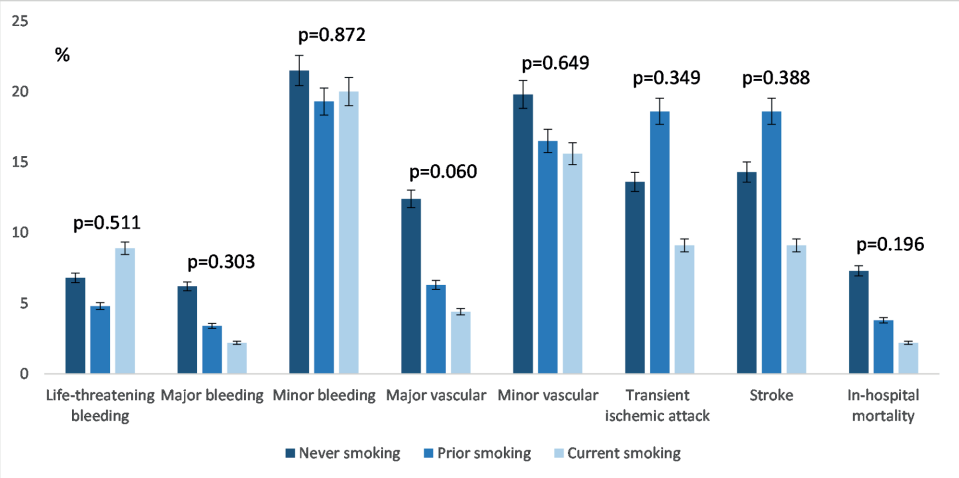

Figure 3. Peri-procedural clinical outcome among males after TAVR.

DISCUSSION

We explored sex differences in the prevalence of smoking and investigated the association between baseline prior-smoking status and 1-year mortality after TAVR. Nearly half of patients admitted for TAVR were prior-smokers or current-smokers (43%). Stratified by sex, prevalence of never-smokers were higher among female than male at the time of TAVR (72% vs. 41%). Smokers (i.e., prior-smokers or current-smokers) consisted of younger individuals than never-smokers. After adjustment for possible confounding factors, we observed better 1-year survival among male prior-smokers compared with male ever-smokers, whereas among females prior-smoking did not affect 1-year survival post-TAVR.

The paradoxical association between smoking and clinical outcome among patients with primary AMI was first introduced >40 years ago.[35] Nearly 35-years ago another study among 2,955 patients with AMI showed that patients who were smoking at the time of AMI had better survival up to 1-year during the follow-up than never-smokers.[36] Similarly, several other randomized controlled trials such as "International Tissue Plasminogen Activator/Streptokinase Mortality Trial,"[17] and "Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries" (GUSTO-1) trial[16] revealed lower mortality rate among prior-smokers or current-smokers compared with never-smokers receiving thrombolytic therapy after AMI. According to a recent meta-analysis, better survival among smokers compared with never-smokers could be explained due to younger age, male gender, lower incidence of diabetes, and extent of CAD.[37]

A recent study among patients (n = 8,345) undergoing TAVR reported lower in-hospital mortality among who were smokers at baseline (i.e., prior-smokers or current-smokers) compared with never-smokers.[30] Moreover, smokers seem to have less postprocedural bleeding complications after TAVR than never-smokers.[30] However, we did not observe any association between prior-smoking and clinical outcome following TAVR, which could be explained due to the lack of adequate power, and exclusion of current-smokers from the

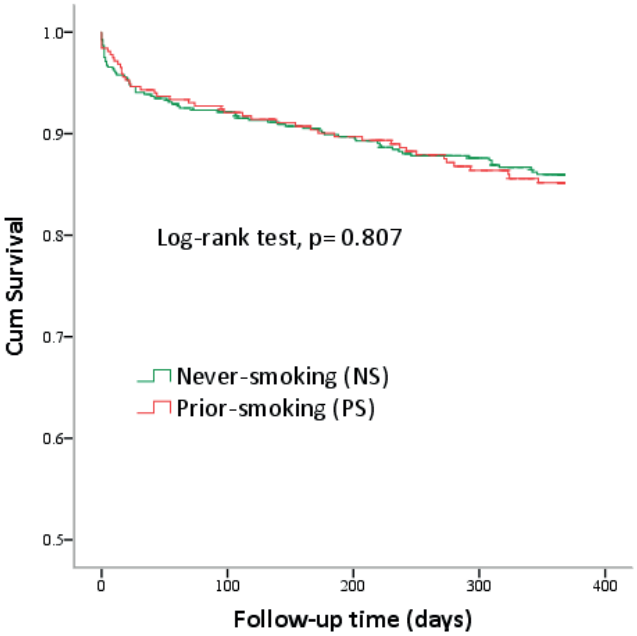

Figure 4. One-year Kaplan-Meier estimates of death from any cause according to smoking status.

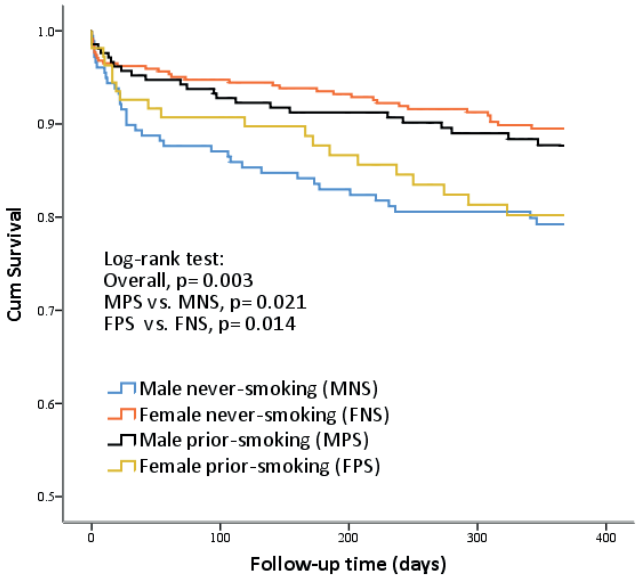

Figure 5. One-year Kaplan-Meier estimates for death from any cause stratified by sex and smoking status.

final analysis. Furthermore, less postprocedural bleeding complications which has been previously observed among smokers undergoing TAVR could be explained due to biological-related factors and procedural-related factors.[30] For instance, smoking has been shown to reduce blood flow and tissue perfusion/oxygenation to the lower-extremity musculature.[38,39] Moreover, smokers undergo more often non-TF TAVR that is associated with less vascular complications compared with TF TAVR[40]; therefore, a possible selection-bias could not be excluded.

According to the literature gender-differences exist regarding mortality in smokers with greater mortality among females compared with males at 6-months.[37,41] In line with findings among patients with CAD, we observed better 1-year survival among male prior-smokers compared with male never-smokers. Not the smoking status, but younger age, less frailty profile, and fewer baseline comorbidities among male prior-smokers may explain this observation.[37] In addition, no safe level of smoking exists for developing vascular diseases.[42] Even one cigarette per day may increase the risk for CAD and stroke, which is much more pronounced among individuals who smoke ≥20 cigarettes per day.[42] Also exposure to environment/secondhand cigarette smoke may increase the risk for incident CAD and deaths from CAD,[43–45] supporting the notion that smoking has a harmful effect on general health and survival outcome.

The exact mechanism of smoking paradox is unknown. However, there is some hypothesis. For instance, smokers consist of younger individuals with favorable baseline characteristics who seek medical care earlier, and are treated more aggressively. These patients therefore benefit more from medical and interventional treatments, compared with never-smoking counterparts who are already aged at the time of medical or interventional treatments.[46] Furthermore, multiple preclinical and clinical studies confirmed the paradoxical effect of smoking on outcome after AMI and among patients undergoing elective PCI, and attributed the beneficial effects to cardiac gap junction remodeling and ischemic preconditioning.[47–49] Moreover, smokers compared with never-smokers may have faster epicardial flow as measured by angiography,[50] less target lesions revascularization,[51] and lower cardiac troponin level which is an indicators for cardiac damage.[52] In addition, it has been suggested that smoker's paradox exist duo to the fact that smokers have a greater thrombus burden leading to greater efficacy of thrombolytic therapy and antiplatelet therapy.[53,54] However, we did not assess the effect of antiplatelet therapy among smokers versus never-smokers on clinical outcome after TAVR, therefore, future studies are needed to investigate whether smoking affects antiplatelet therapy following TAVR. Furthermore, it is also plausible that smokers may have additional lifestyle factors that could contribute to the better survival. For instance, consumption of coffee has been associated with improved survival in the general population,[55,56] and smokers tend to consume more coffee than never-smokers.[57] However, smokers also seem to consume more alcohol than never-smokers that may negate the possible beneficial effect of coffee.

In light of increasing number of TAVR procedures among patients at high-risk for surgical aortic valve replacement, and expanding TAVR to lower-risk patients, it is important to investigate the potential role of traditional cardiovascular risk factors such as smoking on clinical outcome following TAVR. Our findings warrant additional evaluation and suggest the need for further study in larger cohorts of patients undergoing TAVR. Regarding the clinical implication of our findings, our aim was more explorative in nature, therefore our results

should not be taken as an endorsement for smoking or rational for continuation of smoking before or either after TAVR. Efforts to encourage smoking cessation by clinicians should continue in order to improve public health.

Study Limitations

There are several important limitation of this study. First, this is a retrospective analysis and is subjected to the limitations common to such analysis. Second, smoking status was self-reported and was not validated by biochemical tests. However, self-reported smoking habits have been found to be accurate in studies of different populations.[58] Therefore, the influence of misclassification of smoking status on the interpretation of our results was possibly limited. Third, there was a lack of detailed information regarding age at smoking initiation, type of smoking, number of cigarettes per day, duration of smoking, smoking status changes overtime, years since cessation, and or exposure to passive smoking, which may have influenced our results. For instance, a recent study among patients (n = 1,793) with complex CAD undergoing PCI or CABG showed that "smoking paradox" does not hold true when smokers change their smoking habit after the index.[59] Fourth, there may have been also other time-dependent factors interrelated with smoking behavior that we did not recorded such as social and education status and alcohol drinking status. Finally, we only measured all-cause mortality, and did not address the cause-specific death during the follow-up. Therefore, future studies are needed to evaluate the specific cause of death after TAVR among both genders according to their smoking status in order to target therapeutic strategies and prevent adverse events.

Conclusions

Smokers undergo earlier TAVR than never-smokers. Younger age and fewer comorbidities possibly account for most observed survival benefit among male prior-smokers undergoing TAVR. Smoking may not offer protection in the context of TAVR, but rather that smokers develop severe AS at younger age than never-smokers. In order to reduce the burden of cardiovascular disease smoking cessation should be encouraged.

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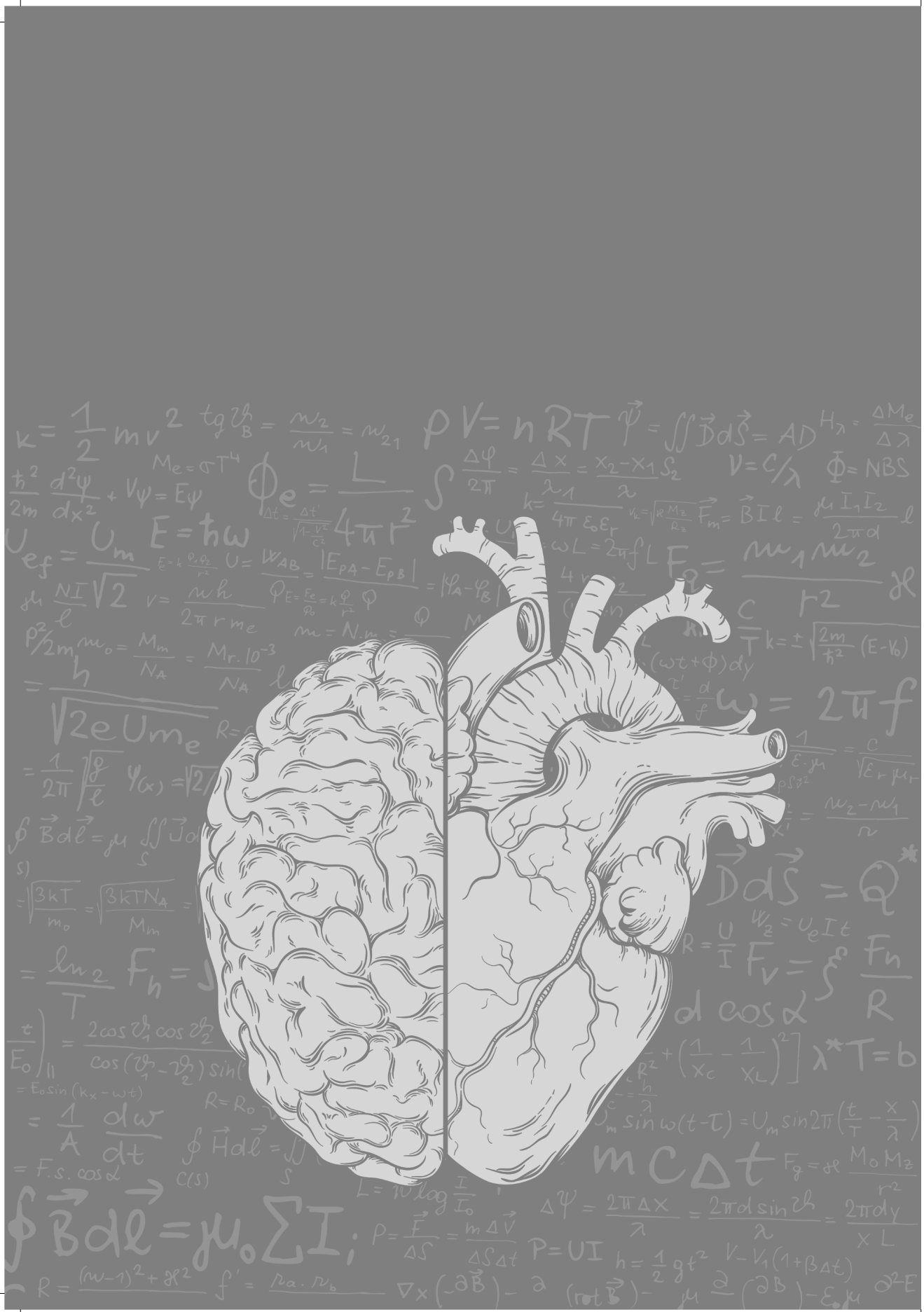

Chapter 8

Summary and General Discussion

In the last decade transcatheter aortic valve replacement (TAVR) improved substantially through advances in technology, including new devices with reduced profiles for easier transfemoral access, increased valve sizes in order to cover the majority of the anatomies to be treated, improved valve positioning with in some valves the possibility of recapturing the valve to proceed to a new deployment, and in general simplification of the procedure itself (1). Due to evidence-based clinical research, refinement of patient selection, and improved procedural outcomes, TAVR has become the treatment of choice among patients with severe aortic valve stenosis (AS) who are considered inoperable -or at higher surgical risk; this indication is recently expanded to the patients with AS who have intermediate -or even low surgical risk (1-6). However, despite improvement in technique and reduced procedural complications rate, some patients are at increased risk for neurocognitive complications following TAVR, such as postoperative delirium (POD), and periprocedural cerebral ischemic lesions detected with diffusion weighted magnetic resonance imaging (cerebral DWI-lesions). As well, the effect of traditional cardiovascular risk factors such as cigarette smoking and overweight- or obesity on the outcome after TAVR remain unknown. The aims of this thesis was to evaluate the clinical effect of these factors, and provide insights into the prevalence, pathophysiology, and prognostic effect of these potential prognostic factors following TAVR.

Although TAVR involves minimal invasive strategies to treat severe AS, delirium seems to occur frequently, and its etiology following TAVR remains unknown. In **Chapter 2** we investigated the incidence, predictors, and prognostic effect of delirium on outcome after TAVR. Interestingly, we observed that delirium occurs among 13.4% of patients undergoing TAVR, and more commonly among individuals after nontransfemoral TAVR. Moreover, delirium following TAVR was associated with longer hospital stay irrespective of periprocedural complication, and postoperative mortality after transfemoral TAVR access when adjusted for possible confounding factors.

Delirium is an acute and fluctuating organic brain disorder that reflects patients vulnerability. Although the exact etiology of delirium remains unknown, several hypothesis has been proposed, including neuronal aging, neuroinflammation, oxidative stress, neurotransmitter deficiency, and disconnectivity (7, 8). Delirium is a multifactorial disorder that involves interactions of multiple patient-related or predisposing factors and exposure to multiple noxious insults or precipitating factors (9-12). Thus, the more an individual has predisposing factors, the less noxious insults are required to develop delirium. For instance, compared with younger individuals with lower vulnerability who may need multiple noxious insults to develop delirium, elderly with multiple comorbidities might develop delirium with a single noxious insult (e.g., urinary tract infection, pulmonary infection) (10).

Since patients undergoing TAVR are more prone to develop delirium duo to age, comorbid conditions, and some periprocedural noxious stimulus, determination of factors that influence the incidence of delirium after TAVR is of paramount importance in terms of implementation of preventive strategies to reduce the risk for POD. In our study, we identified several predictors of delirium after TAVR, including nontransfemoral access, older age, carotid artery disease, current smoking habit, and atrial fibrillation. These results may provide important insights for the implementation of preventive measures for POD after TAVR. Substantial impact of nontransfemoral access on the onset of delirium, as compared to the less invasive transfemoral access, suggest that several factors can explain this difference: a more advanced

cerebro-and cardiovascular pathology (i.e., atherosclerosis), the need for general anaesthesia during the nontransfemoral procedure, the intensive care unit stay, postoperative wound pain which goes together with increased use of opioids, and postoperative inflammation response (13). If reasonable, in order to reduce the burden of delirium after TAVR we recommend to avoid nontransfemoral access, and decrease the use of periprocedural general anaesthesia and opioids.

According to the literature intraoperative hypotension (IOH) is another potentially modifiable risk factor for POD (14-16). Patients undergoing TAVR experience IOH, and cerebral perfusion disturbances during valve deployment, especially when rapid ventricular pacing (RVP) is performed (17-19). To facilitate precise prosthesis positioning RVP is required during TAVR for temporary reduction in cardiac output, transvalvular flow, and cardiac motion (20). The possible effect of RVP on delirium occurrence remain unknown. Therefore future studies are needed to assess the possible effect of RVP on delirium after TAVR, in order to decrease the incidence of delirium following TAVR.

To date no medical treatment exist to prevent- or to treat delirium in hospital setting (21-23). Nonpharmacological preventive management seems to reduce the risk for delirium up to 30% to 40% (12, 21). Future larger studies are needed to investigate nonpharmacological preventive strategies among patients undergoing TAVR in order to improve outcome.

Prevalence of delirium in the community dwelling population is 1% to 2%, which rises up to 14% to 24% among elderly who are admitted to the hospital (9, 24). The incidence and prevalence of delirium following TAVR mainly depends on the clinical setting, patient characteristics, and sensitivity and specificity of detection method. Several studies have reported an incidence of delirium after TAVR between 0% and 44%, with the highest incidence rate among individuals undergoing nontransfemoral TAVR (24). In **Chapter 3** we gave a comprehensive review and meta-analysis of the literature on the incidence of POD after TAVR. The pooled incidence of delirium after TAVR was 8.1%, more frequently among nontransfemoral access compared with transfemoral access (i.e., 21.4% vs. 7.2%, respectively). Interestingly, using a specific measure for classifying delirium such as Confusion Assessment Method, an even higher incidence rate of POD after TAVR was identifiable (i.e., 13.5%) (25).

Patients with severe AS undergoing TAVR are at increased risk for clinical cerebrovascular events (CVEs) which is associated with morbidity, and early- and late mortality after TAVR (26, 27). The incidence of CVEs after TAVR ranges from 1% to 11%, from which half of these cases occur between 24 hour after the procedure (26, 28). This broad incidence range across the studies could be explained due to different diagnostic criteria used, study design, patient risk-profile, and systematic evaluation. Among the majority of studies evaluating CVEs after TAVR, clinical CVEs may be overlooked by a lack of adequate and systematic neurological evaluation in order to detect even minor stroke or transient ischemic attack (TIA). Hence, among patients undergoing aortic valve surgery it has been suggested that the incidence of CVEs may be even higher when the neurologic assessment is performed by skilled personnel (29). Several factors have been identified that may contribute to the occurrence of CVEs after TAVR, including female sex, chronic kidney disease, new-onset atrial fibrillation, prior

history of cerebrovascular disease, balloon post-dilatation of the valve prosthesis, and valve dislodgement-or embolization (26, 28, 30).

On the contrary, imaging studies using MRI have revealed cerebral ischemic lesions among >75% of the patients undergoing TAVR (31). The clinical effect of these lesions following TAVR remains unknown. Interestingly, in **Chapter 4** we observed an association between the number of cerebral DWI-lesions and POD after TAVR. Although cerebral DWI-lesions may affect the whole brain after TAVR, we observed more new DWI-lesions in the brain areas supplied by anterior cerebral artery among patients with delirium. Furthermore, delirium occurs commonly with other periprocedural complications after TAVR, therefore the true effect of cerebral DWI-lesions on delirium occurrence was unknown (32). In this chapter, after stratification of the data according to the presence of periprocedural complications (e.g., infection, cerebral ischemic stroke, paravalvular aortic regurgitation, cardiac conduction abnormalities, atrial fibrillation, vascular or bleeding complication), we observed more cerebral DWI-lesions in patients with POD after uncomplicated TAVR, suggesting a possible contribution of these lesions to the development of delirium after TAVR.

In order to reduce the burden of delirium after TAVR future studies are needed to investigate possible nonpharmacological strategies specifically in patients undergoing TAVR, such as avoiding nontransfemoral access, reduction of RVP rate during TAVR, and the use of cerebral embolic protection devices (EPD) during TAVR. The use of EPD during TAVR has been shown in several studies to be feasible, and it may protect the brain during the procedure, however, ~50% of the periprocedural CVEs occur >24 hour after TAVR, suggesting that some CVEs are not limited to procedural-related steps, such as catheter, wire, and valve manipulation (26, 28). Therefore, other factors than procedural features may also play a role in the development of CVEs after TAVR. Therefore, understanding the mechanism and the clinical impact of clinical -and subclinical cerebral ischemic lesions following TAVR are crucial in the understanding of delirium occurrence after TAVR.

According to the literature, some patients may experience early cognitive decline after TAVR, while some others may experience cognitive improvement at mid-term follow-up after TAVR (33). As TAVR extends to patients with lower-risk profile, assessment of cognitive status after TAVR may be crucial. In **Chapter 5** we explored the effect of TAVR on early and mid-term cognition outcome after TAVR using comprehensive neurocognitive batteries. Overall, we observed an improvement in immediate recall memory at 4 months follow-up after TAVR. Interestingly, this change was more often seen among patients who had lower preprocedural cognitive scores as compared with patients with average cognitive scores at baseline. Future studies are required to investigate predictive factors of cognitive decline, and ways to improve the management of patients who develop cognitive decline during the follow-up after TAVR.

Cardiovascular risk factors such as overweight or obesity, and smoking are known to be associated with all-cause and cardiac death in the general population. Current guidelines recommend to stop smoking and reduce weight in order to reduce the risk for all-cause and cardiac mortality. However, both overweight/obesity and smoking have been shown to have positive prognostic effect on outcome among patients with heart disease undergoing interventions. However, these possible prognostic variables are not included in the current risk models such as EuroSCORE. In **Chapter 6** and **7** we evaluated the prognostic effect of

preprocedural body mass index and smoking status on outcomes after TAVR. In both studies, we observed paradoxical associations between these variables and mortality outcome after TAVR among patients undergoing TAVR. Since TAVR indications are expanding towards lower risk patients, larger and well-designed studies are needed to assess the effect of these variables on outcomes after TAVR.

Conclusions

Delirium is a frequently overlooked complication after TAVR, which is associated with adverse outcome after TAVR. An easy-to-use and validated instrument such as the Delirium Observational Score -or Confusion Assessment Method are recommended to use in order to identify and diagnose delirium. Moreover, contributing factors should be recognized and minimized in order to reduce the incidence rate of delirium among patients undergoing TAVR. Furthermore, delirium should be managed multidisciplinary with nonpharmacological methods, in order to reduce its incidence, severity, and duration following TAVR. As TAVR indications are expanding, more research is needed to assess whether use of EPD during TAVR, and lesser RVP during valve implantation could contribute to the reduction of delirium rate after TAVR. Finally, some well-known cardiac risk factors may affect outcome after TAVR, therefore future studies are needed to assess the effect of these factors on outcome after TAVR adjusted for possible confounding factors.

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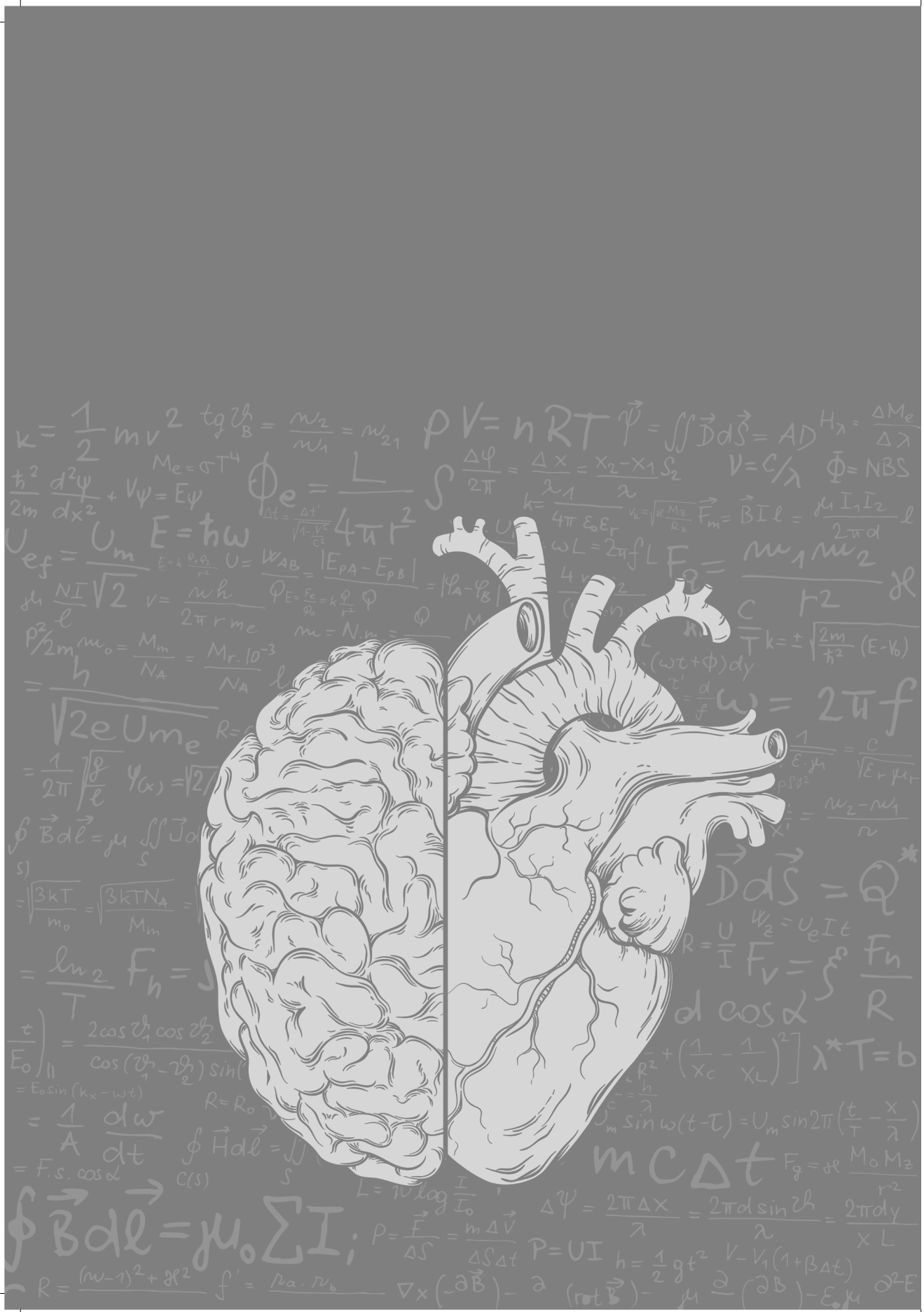

Chapter 9

Dutch Summary (Nederlandse samenvatting)

Hoofdstuk 1 is een algemene introductie en inleiding van de onderwerpen van dit proefschrift. In dit hoofdstuk worden de specifieke onderdelen van dit proefschrift inleidend beschreven en worden het doel en de onderzoeksvragen uiteengezet.

Sinds de eerste introductie in 2002 door professor Alain Cribier, heeft transcathetergebonden aortaklepimplantatie (TAVR) een revolutie teweeggebracht in de behandeling van patiënten met ernstige symptomatische aortaklepvernauwing (1). Vergeleken met de standaard behandeling van de aortaklepstenose, de chirurgische methode (SAVR), TAVR is een minimale invasieve techniek die wordt uitgevoerd op een kloppend hart zonder tussenkomst van cardiopulmonale bypass of sternotomie (1). Bovendien worden patiënten na TAVR meestal kort na de ingreep ontslagen zonder langdurige herstelperiode in vergelijking met SAVR. Door de grote hoeveelheid onderzoeken, verbeterde patiënten selectie, en de technologische vooruitgang zoals nieuwe apparaten, verschillende klepmaten, katheters met lagere profielen voor betere transfemorale toegang, en versimpeling van de techniek is veiligheid en toepasbaarheid van TAVR in de afgelopen decennia zeer vooruit gegaan (2). Door de recente gunstige resultaten voor TAVR ten opzichte van SAVR, is TAVR nu ook goedgekeurd voor lager-risico patiënten (3-5). Een recente meta-analyse heeft laten zien dat ongeacht het peroperatieve risicoprofiel, TAVR superior blijkt te zijn aan SAVR in termen van korte- termijn mortaliteit en invaliderende/voorbijgaande beroerte (6).

Ondanks al deze verbeteringen in de techniek en de gunstige klinische uitkomsten, is TAVR echter geassocieerd met een aantal belangrijke periprocedurele complicaties, onder andere een postoperatief delirium. De Valve Academic Research Consortium-2 classificatie, die vaak gebruikt wordt voor de eindpuntdefinities na TAVR, heeft ook enige beperkingen omdat deze geen neurocognitieve eindpunten omvat na TAVR (7). **Hoofdstuk 2** beschrijft de incidentie, voorspellende factoren en het effect van postoperatief delirium op de klinische uitkomsten en mortaliteit na TAVR. De primaire uitkomst van deze studie was postoperatief delirium na TAVR. In deze studie was de incidentie van delirium na TAVR 13,4%, welke hoger was bij patiënten die een invasieve TAVR (via transapicale of transaortale benadering) hadden ondergaan. Delirium werd vaak gediagnostiseerd op de tweede dag na TAVR en was geassocieerd met langere ziekenhuisopname ongeacht de complicaties. Een aantal voorspellende factoren werden gevonden die mogelijk een rol spelen bij het optreden van delirium na TAVR. Deze zijn hogere leeftijd, carotis stenose, roken, invasieve vorm van TAVR en preprocedurele boezemfibrilatie. De sterkste voorspeller van delirium bleek de invasieve vorm van TAVR te zijn. Om de kans op een delirium na TAVR te minimaliseren adviseren wij, uiteraard wanneer geoorloofd, om de invasieve vorm van TAVR achterwege te laten en over te gaan op transfemorale TAVR.

Hoofdstuk 3 beschrijft de resultaten van een systematische literatuurstudie en meta-analyse van de observationele studies met betrekking tot de incidentie van delirium na TAVR. Volgens de gepoolde meta-analyse was de incidentie van delirium na TAVR 8,1%. Delirium werd vaker gediagnosticeerd na een invasieve TAVR dan bij de transfemorale TAVR (21,4% versus 7,2%, respectievelijk). Het gebruik van een ondersteunende diagnostische methode, zoals Confusion Assessment Method, was geassocieerd met een hogere incidentie van delirium na TAVR dan wanneer geen diagnostische methoden werden gebruikt. Deze meta-analyse heeft verder laten zien dat er een grote variatie bestaat in de gerapporteerde incidentie van delirium na TAVR. Deze grote variatie in de incidentie kan waarschijnlijk te

maken hebben met verschillen in de studieopzet, aantal geïncludeerde patiënten, methode van diagnostiek van delirium en mogelijk andere niet-gerapporteerde verschillen. Grote gestandaardiseerde studies met duidelijke eindpuntdefinities zijn nodig om uit te zoeken wat de werkelijke incidentie van delirium na TAVR bedraagt, om op die manier gerichte preventieve maatregelen te kunnen ontwikkelen.

Incidentie van 30-dagen periprocedurele invaliderende/voorbijgaande beroerte na TAVR bedraagt ongeveer 3,1% (8). Dit is echter het topje van de ijsberg. Volgens de literatuur heeft meer dan 75% van de patiënten na TAVR waarneembare cerebrale schade op MRI (9). Hoewel het effect van deze stille cerebrale schade op klinische uitkomsten na TAVR onduidelijk is zijn volgens de literatuur deze cerebrale ischemische laesies gerelateerd aan cognitieve stoornissen en toename van de kans op toekomstige beroerte (10, 11). In **hoofdstuk 4** hebben wij een associatie gevonden tussen deze waarneembare cerebrale schade op MRI direct na TAVR en het postoperatief delirium. Vooral de frontale regio's van de hersenen welke belangrijk zijn voor de planning, sociale contacten en executieve functies waren meer aangetast bij delirante patiënten. Hoewel er in deze studie een associatie is gevonden tussen het aantal nieuwe cerebrale laesies en het postoperatief delirium na TAVR is een mogelijk causaal verband moeilijk aan te tonen. Dit komt omdat delirium een multifactorieel syndroom is en er meerdere, zowel patiënt gebonden als procedureel gebonden factoren een rol kunnen spelen. Lange-termijn effecten van deze stille cerebrale laesies zijn echter nog niet bekend. Mogelijke klinische effecten van deze stille cerebrale schade zullen straks meer zichtbaar worden bij patiënten die een laag-risico hebben en relatief jonger zijn dan de huidige populatie patiënten die een TAVR ondergaan (3-5).

Hoofdstuk 5 rapporteert het beloop van de cognitieve functie van patiënten tijdens de follow-up na TAVR. Deze studie illustreert dat cognitieve status tijdens de follow-up van 3 tot 4 maanden na TAVR vrijwel stabiel blijft zonder verslechtering ten opzichte van de baseline. Een verbetering van het "immediate recall memory" werd in alle patiënten tijdens de follow-up waargenomen. Toename in verbetering van "immediate recall memory" en van "mini mental state examination" werd geobserveerd bij patiënten die op de baseline lagere cognitieve scores hadden.

In de algemene populatie is overgewicht geassocieerd met cardiovasculaire ziekten. De richtlijnen adviseren om af te vallen om zo de kans op cardiovasculaire ziektes te reduceren. Volgens de literatuur hebben patiënten die een myocard infarct krijgen echter een betere prognose dan patiënten met een myocard infarct met een normaal gewicht, de zogenaamde "obesity paradox". De literatuur is niet eenduidig over de effecten van overgewicht op de prognose na TAVR. De huidige risicostratificatie modellen die vaak gebruikt worden om het risico op sterfte na TAVR te berekenen, houden onvoldoende rekening met preoperatieve factoren zoals body mass index (BMI) (12, 13). In **hoofdstuk 6** wordt het effect van BMI op de klinische uitkomsten en mortaliteit na TAVR beschreven. Er werden 549 consecutieve patiënten geïncludeerd (80,2±7,5 jaar oud, en EuroSCORE 17,3%±9,9%). Van deze patiënten had 43% een normaal gewicht (BMI (18.5 tot 24.9 kg/m2), 36% overgewicht (BMI 25.0 tot 29.9 kg/m2), en 20% obesitas (BMI ≥30 kg/m2). Onze studie laat zien dat er geen verschil bestaat in de peri-procedurele complicatie uitkomsten na een TAVR tussen patiënten met een normaal gewicht ten opzichte van patiënten met een overgewicht of obesitas. Met andere woorden, gewicht van de patiënt speelt geen belangrijke rol in het voorkomen van

de complicaties na TAVR. Volgens de analyses van deze studie bleek dat patiënten met een overgewicht betere prognose hadden dan patiënten met een normaal gewicht. Het exacte mechanisme van de obesity paradox is nog niet opgehelderd. De meest gangbare gedachte hierover is dat patiënten met een overgewicht meer lichaamsreserves hebben om na de operatie de operatiewond sneller te laten herstellen. In tegenstelling tot de patiënten met een normaal gewicht die na een operatie mogelijk in een katabole toestand terecht komen door tekort aan lichaamsreserves voor de herstel van de operatiewond. Toekomstige grotere studies zijn nodig om de associatie tussen het lichaamsgewicht en de klinische uitkomsten na een TAVR op een grotere schaal te onderzoeken.

Hoofdstuk 7 evalueert de klinische en prognostische effecten van roken op de uitkomsten na TAVR. Data uit 2 grote Nederlandse TAVR centra (Erasmus MC en UMC Utrecht) werden gepoold en geanalyseerd. In totaal werden 913 patiënten geïncludeerd (80,1±7,6 jaar, en EuroSCORE 16,5%±9,9%). De man-vrouw verhouding was nagenoeg hetzelfde (47% vs. 53%). De prevalenties van niet-rokers, ex-rokers en de actuele rokers waren respectievelijk 57%, 35%, en 8%. In deze studie waren (ex)rokers jonger dan niet-rokers. Over het algemeen werd geen verschil gevonden in de klinische uitkomsten en mortaliteit tussen de groepen. Na de stratificatie volgens het geslacht, werd echter een paradoxaal verband gevonden tussen de 1-jaars overleving bij mannelijke ex-rokers. De bevindingen in deze studie suggereren geen causale verband, maar een associatie. Het exacte mechanisme hierachter is nog niet bekend. Degeneratieve aortaklepstenose en het atherosclerose proces delen samen gemeenschappelijke paden en risicofactoren (14, 15). Hypothetisch gezien hebben rokers een hogere kans op verergering van het atherosclerose proces en zullen daardoor wellicht eerder in hun leven in aanmerking komen voor een TAVR. De combinatie van een TAVR in relatief jongere leeftijd met de leefstijl adviezen kunnen hypothetisch er voor zorgen dat ex-rokers relatief betere prognose hebben na een TAVR dan patiënten die nooit eerder gerookt hebben. Uit de resultaten van deze studie kunnen we dus verder afleiden dat roken het atherosclerose en het degeneratieve proces versnelt, waardoor men op een relatief jongere leeftijd voor TAVR in aanmerking komt. Roken is zeer schadelijk voor de gezondheid. Daarom adviseren wij ten alle tijden stoppen met roken, en een gezonde leefstijl.

Hoofdstuk 8 geeft een algemene discussie. De bevindingen die zijn beschreven in dit proefschrift worden bediscussieerd en de onderzoeksvragen worden beantwoord.

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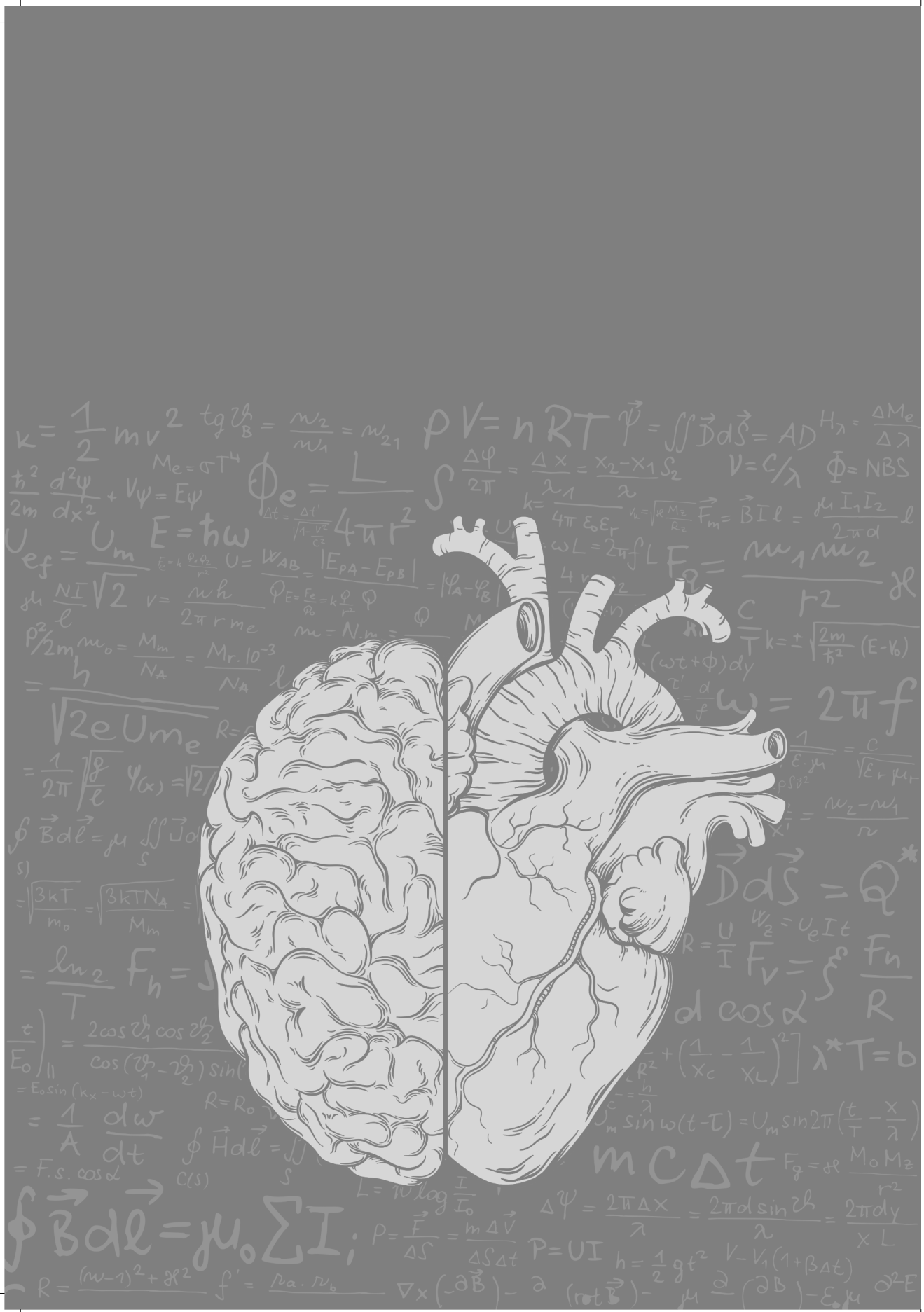

Curriculum vitae auctoris

Masieh Abawi was born in Kabul, Afghanistan on November 17th, 1984. At the age of 14, he moved together with his mother and sister to the Netherlands as political refugees. After graduating from Dutch language school, he attended secondary school (Zaanlands Lyceum) in Zaandam and finished his pre-medical school in 2005.

In 2007 he started medical school at the Erasmus Medical Center in Rotterdam. Parallel to his medical school Masieh joined Philosophy at the Erasmus School of Philosophy in Rotterdam until 2012.

During his preclinical years of medical school he initiated to write a book about cardiology together with other medical students under the supervision of prof. dr. Jaap Deckers.

In 2013 he graduated from preclinical years of medical school and initiated his master of science research at the department of cardiology in Erasmus MC Rotterdam, under the supervisions of prof. dr. Peter P.T. de Jaegere & dr. R.T. van Domburg.

In 2014 he started his PhD program entitled “transcatheter aortic valve replacement”, at the department of cardiology in University Medical Center Utrecht, under the supervisions of prof. dr. P.A.F.M Doevendans, dr. P.R. Stella, and dr. P. Agostoni. In 2019 he completed both his doctorate of Medicine & of Philosophiae.

Masieh published his works in several international peer reviewed journals, and attended multiple national and international congresses to present his works. As a clinical researcher, he has been involved with numerous multicenter investigational studies in cardiovascular medicine. Moreover, Masieh has been awarded with national and international prizes for the best abstracts, and has been frequently interviewed by several medical journal for his cutting-edge work regarding delirium after transcatheter aortic valve replacement

Masieh is currently working as a visiting lecturer in Cardiology at the Healthcare Academy Erasmus MC, Rotterdam, and residence in Cardiology at the Langeland hospital, in Zoetermeer, The Netherlands.

PHD Portfolio

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THESIS

Bachelor thesis (2013):
Title: The Effectiveness of Percutaneous Coronary Intervention plus Optimal Medical Therapy versus Optimal Medical Therapy alone in Stable Coronary Artery Disease. *Systematic Review*
Tutor: Prof. Dr. Jaap W. Deckers, Dept. Cardiology, Erasmus MC, Rotterdam

Master thesis (2014):
Title: The Impact of Obesity on the Mortality Outcome after Percutaneous Coronary Intervention among patients with Diabetes.
Tutors: Prof. Dr. Peter P.T. de Jaegere, and Dr. Ron van Domburg, Dept. Cardiology, Erasmus MC, Rotterdam

PhD thesis (2020):
Title: Role of novel predictive factors on clinical outcome after transcatheter aortic valve replacement.
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Co-promotors: Dr. Pieter R. Stella, and Dr. Pierfrancesco Agostoni

PHD TRAININGS

2015 NIH Stroke Scale – (Test Group A)
2015 Academic Writing in English
2015 Writing a Scientific Paper in English
2015 Research planning & Time management
2015 Giving Effective Oral Presentations in English
2016 A004 - Rankin Scale mRS – (English)
2016 Basic Course for Clinical Investigators **(BROK®-course)**

HONORS & AWARDS

2006 Top-10 National Chemistry Olympiade Award, *The Netherlands*
2015 First Price Poster (Professor Snellen Poster Prize) Dutch Society of Cardiology (NVVC) Spring Congress, *Noordwijkerhout, The Netherlands*
2015 Top-50 Poster Award, TCT Congress 2015, *San Francisco, CA, USA*

REVIEWER

Catheterization and Cardiovascular Interventions
Circulation: *Cardiovascular Intervention*
Circulation
European Heart Journal
Journal of the American Geriatrics Society
Structural Heart: The Journal of the Heart Team
Trials

SYMPOSIA & CONFERENCES

Oral presentations

2015 Dutch Society of Cardiology (NVVC) Spring Congress *Noordwijkerhout, The Netherlands*
2015 EuroPCR2015*, Paris, France*
2015 *Euro*PCR's got talent- 2015*, Paris, France*
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2016 PCR-London Valves, London, *UK*
2016 *Euro*PCR's got talent-2016, *Paris, France*
2016 Dutch Society of Cardiology (NVVC) Spring Congress, *Noordwijkerhout, The Netherlands*
2016 Innovation for Health 2016 conference, *Rotterdam, The Netherlands*

Poster presentations

2015 Dutch Society of Cardiology (NVVC) Spring Congress, *Noordwijkerhout, The Netherlands*
2015 20th Years of Innovation ICI-meeting*, Tel Aviv, Israel*
2015 PCR-London Valves*, Berlin, Germany*
2015 European Society of Cardiology (ESC) Congress, *London, UK*
2015 TCT-2015, *San Francisco, CA, USA*
2015 Acute Cardiovascular Care, *Vienna, Austria*
2015 EuroPCR2015, *Paris, France*
2016 TCT-2016, Washington DC, *USA*
2016 PCR-London Valves, London, *UK*
2016 European Society of Cardiology (ESC) Congress, Rome, *Italy*
2016 EuroPCR2016, *Paris, France*
2016 AsiaPCR, *Singapore*

LIST OF PUBLICATIONS

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