Postoperative delirium and quality of life after transcatheter and surgical aortic valve replacement: A prospective observational study

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ABSTRACT

Objective: In older patients, postoperative delirium is a frequently occurring complication after surgical aortic valve replacement, leading to an excess in postoperative morbidity and mortality. It remains controversial whether transcatheter aortic valve implantation and minimally invasive surgical aortic valve replacement can reduce the risk of postoperative delirium. This study aimed to compare the incidence of postoperative delirium after transcatheter aortic valve implantation and surgical aortic valve replacement and the impact on long-term outcomes.

Methods: Between September 2018 and January 2020, we conducted an observational, prospective cohort study in patients aged 70 years or more undergoing transcatheter aortic valve implantation or surgical aortic valve replacement. The primary end point was the incidence of in-hospital postoperative delirium during 5 postoperative days assessed with the Confusion Assessment Method. Secondary end points included perioperative inflammation, postoperative complications, health status (EuroQol 5-dimensional questionnaire 5 levels), and mortality up to 6 months. Transcatheter aortic valve implantation and surgical aortic valve replacement were compared using propensity weighting to account for important baseline differences (European System for Cardiac Operative Risk Evaluation II, age, and frailty).

Results: We included 250 patients with a mean (standard deviation) age of 80 (±5.8) years and a European System for Cardiac Operative Risk Evaluation score of 5 (±4.7). In the propensity-weighted analysis, those undergoing surgical aortic valve replacement (N = 166) had a higher incidence of postoperative delirium compared with transcatheter aortic valve implantation (N = 84) (51% vs 15%: $P < .0001$). Furthermore, patients undergoing surgical aortic valve replacement experienced more inflammation, a greater depth of anesthesia, and more intraoperative hypotension. After surgical aortic valve replacement, 41% of patients experienced an improved health status compared with 12% after transcatheter aortic valve implantation ($P < .0001$). No outcome differences were noted within the surgical aortic valve replacement groups.

Conclusions: Transcatheter aortic valve implantation is associated with a lower risk for postoperative delirium. Nevertheless, patients undergoing surgical aortic valve replacement experience the greatest improvement in quality of life. Heart teams should consider these outcomes in shared decision-making in the choice of transcatheter aortic valve implantation or surgical aortic valve replacement. (J Thorac Cardiovasc Surg 2023;166:156-66)

Difference in QoL 6 months after TAVI and SAVR.

CENTRAL MESSAGE

Compared with SAVR, TAVI significantly reduces the incidence of POD at the expense of a reduced improvement in QoL.

PERSPECTIVE

POD was assessed in 250 patients after TAVI and SAVR (mean euroSCORE II 7 vs 4, respectively). Incidence of POD was higher in the SAVR group even after propensity weighting for known predisposing risk factors. Nevertheless, QoL 6 months after the procedure was considerably improved in the SAVR group compared with the TAVI group.

See Commentaries on pages 167 and 169.

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Informed consent statement: After providing oral and written information concerning the study, written informed consent was obtained, and the patient was enrolled.

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Abbreviations and Acronyms

BIS = bispectral index
CI = confidence interval
CPB = cardiopulmonary bypass
CRP = C-reactive protein
EEG = electroencephalography
EFT = Essential Frailty Toolset
EQ-VAS = EuroQol Visual Analogue Scale
EQ-5D-5L = EuroQol 5-dimensional questionnaire 5 levels
euroSCORE = European System for Cardiac Operative Risk Evaluation
GA = general anesthesia
IADL = Instrumental Activities of Daily Living
ICU = intensive care unit
LOS = length of stay
MAC = monitored anesthesia care
POD = postoperative delirium
QoL = quality of life
RR = relative risk
SAVR = surgical aortic valve replacement
TAVI = transcatheter aortic valve implantation
TF = transfemoral
TFI = Tilburg Frailty Indicator

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Postoperative delirium (POD) may affect up to 50% to 70% of patients aged more than 60 years undergoing cardiac surgery.[1,2] Several prospective studies confirmed that POD is associated with important short-term consequences such as prolonged length of stay (LOS) in the intensive care unit (ICU) and the hospital, and increased postoperative morbidity and mortality.[3] Moreover, POD has a long-lasting impact with functional and cognitive decline, leading to an increase in the use of healthcare resources and costs.[4]

Numerous risk factors are associated with the development of POD. These factors can be classified into predisposing factors (eg, including advanced age, impairment in cognition and activities of daily living, comorbidities, and frailty) and precipitating factors (eg, invasiveness and duration of surgery, drugs used perioperatively [including anesthetics], use of cardiopulmonary bypass [CPB], perioperative inflammation, admission to an ICU, and blood product transfusion).[2] Only precipitating factors are eligible for modification in clinical practice.

In the treatment of aortic valve stenosis, transcatheter aortic valve implantation (TAVI) in comparison with surgical aortic valve replacement (SAVR) allows to abrogate the use of CPB, is associated with less inflammation, and can be performed solely under sedation and monitored anesthesia care (MAC).[5,6] However, it is largely unknown whether these advantages translate into a lower risk for POD. Moreover, a comparison of SAVR and TAVI populations concerning neurocognitive outcome is notoriously difficult because of inherent differences in the spectrum of predisposing risk factors for POD.[5,7] In many countries, the use of TAVI is mainly restricted to older and sicker patients with a high intrinsic risk for the development of POD.[8] Last, the technique of SAVR has advanced in recent years, with many patients now being operated using a minimally invasive approach through mini-sternotomy or thoracotomy.[9] These techniques are also associated with less perioperative inflammation and potential benefits regarding enhanced recovery possibly affecting neurocognitive outcomes.[10] However, whether minimally invasive cardiac surgery reduces the incidence of POD is largely unknown.[11]

Therefore, the current study aimed to determine the incidence of POD in patients aged more than 70 years undergoing TAVI full sternotomy or mini-sternotomy SAVR. We hypothesized that in older patients, the incidence of POD is lower in patients undergoing TAVI than in patients undergoing SAVR with mini-sternotomy, with patients undergoing SAVR with full sternotomy having the highest incidence.

MATERIALS AND METHODS

Study Design

This observational, prospective cohort study was approved by the local Ethics Committee of the University Hospitals Leuven, Belgium (S61710, August 27, 2018) and conducted according to the ethical principles of the Declaration of Helsinki and Good Clinical Practices. The trial was registered at www.clinicaltrials.gov on May 19, 2019 (registration number: NCT03950440). This article adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[12]

Setting

This study was performed in the University Hospitals Leuven from September 24, 2018 (first patient in), to July 13, 2020 (last patient out). Patients were evaluated by a multidisciplinary heart team for TAVI, SAVR, or medical treatment following international guidelines while considering the restrictive reimbursement policy for TAVI in Belgium.[13] All consecutive patients scheduled for TAVI or SAVR were evaluated for eligibility. Baseline data were collected during visit 0, and the last follow-up occurred 6 months postoperatively (visit 8) (Figure 1). Data concerning adverse events during hospitalization and composite end points at 1 month and 6 months postoperatively were extracted from hospital records. Missing outcome data were obtained from the treating cardiologist or general practitioner.

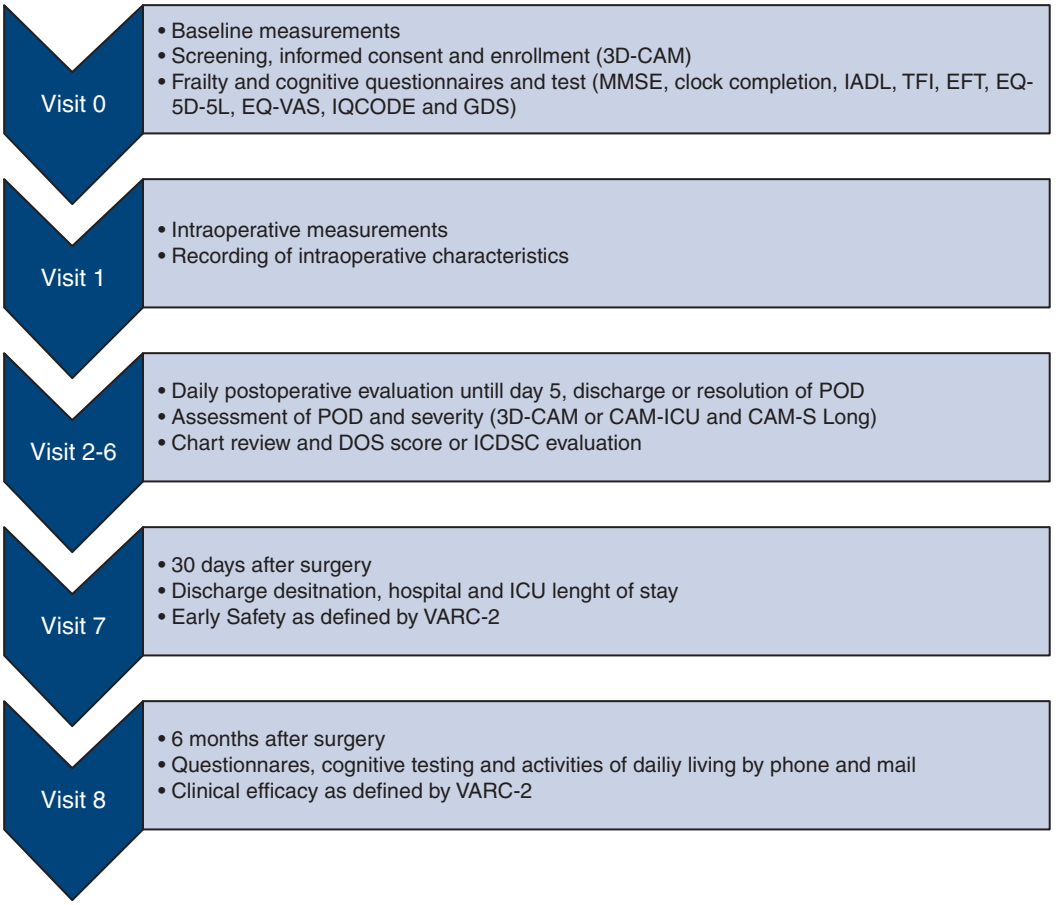


FIGURE 1. Schematic illustration of the study visits. *3D-CAM*, 3-Minute Diagnostic Confusion Assessment Method; *MMSE*, Mini Mental State Examination; *IADL*, instrumental activities of daily living; *TFL*, Tilburg frailty indicator; *EFT*, Essential frailty toolset; *EQ-5D-5L*, EuroQol 5 dimensional questionnaire 5 levels; *EQ-VAS*, EuroQol Visual Analogue Scale; *IQCODE*, Informant Questionnaire on Cognitive Decline in the Elderly; *GDS*, Geriatric Depression Scale; *POD*, postoperative delirium; *CAM-ICU*, Confusion Assessment Method for the Intensive Care Unit; *CAM-S Long*, delirium severity measure based on CAM Long version; *DOS*, delirium observation scale; *ICDSC*, intensive care delirium screening checklist; *VARC-2*, Valve Academic Research Consortium-2.

Participants

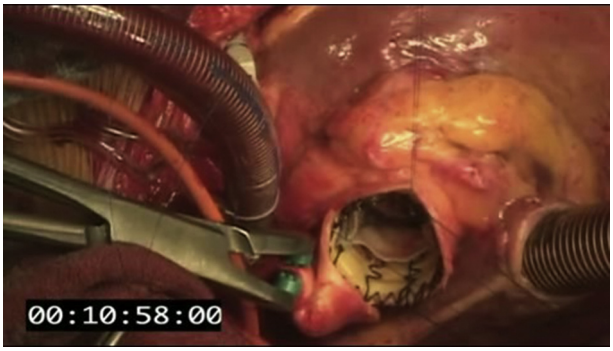
Inclusion. One day before surgery, all patients scheduled for SAVR or TAVI were screened for eligibility. We included patients aged 70 years or more and scheduled for aortic valve replacement surgery by TAVI or SAVR with or without concomitant revascularization or surgical ablation for atrial fibrillation. Exclusion criteria were the presence of delirium at baseline (assessed with the 3-minute Diagnostic Confusion Assessment Method,[14] insufficient Dutch proficiency, or refusal to give written informed consent). After providing oral and written information concerning the study, written informed consent was obtained, and the patient was enrolled.

Baseline assessment. After enrollment, frailty, quality of life (QoL), cognitive and neuropsychiatric functioning were assessed by qualified research personnel using the following tools: Mini-Mental State Examination, clock completion test, self-administered Instrumental Activities of Daily Living (IADL), Tilburg Frailty Indicator (TFI), Essential Frailty Toolset (EFT), self-administered EuroQol 5-dimensional questionnaire 5 levels (EQ-5D-5L) validated Dutch version, and EuroQol Visual Analogue Scale (EQ-VAS). In addition, medical records were used to extract baseline data and calculate European System for Cardiac Operative Risk Evaluation (euroSCORE) II. Appendix E1 ("Baseline Assessment" shows further details.

Anesthesia and surgical approach. All patients received anesthetic, surgical, and interventional care according to our institutional standards. TAVI was primarily performed using the transfemoral (TF) access, and only infrequently via a transapical, trans-subclavian, or transcarotid approach. Depending on the concomitant need for coronary revascularization, SAVR was performed with full sternotomy (Video 1) or upper J or T inverted mini-sternotomy.

Anesthetic management was tailored to the type of procedure. For SAVR, general anesthesia (GA) was maintained using a balanced anesthesia technique with dexmedetomidine, remifentanil, and sevoflurane (targeting a bispectral index [BIS] of 40-60). All patients received standard American Society of Anesthesiologists monitoring, transesophageal echocardiography, central venous pressure, and BIS. At the discretion of the attending anesthesiologist, some patients received a pulmonary artery catheter or cerebral oximetry. After surgery, patients were transported, while still intubated and mechanically ventilated, to a high-dependency unit.

The majority of those receiving TF TAVI received MAC under analgosedation with remifentanil, propofol, and local anesthetic infiltration of the groin without intubation.[6] TAVI approaches other than TF were performed under GA using remifentanil and either sevoflurane or propofol, targeting a BIS of 40 to 60. All patients undergoing TAVI received monitoring comparable to that used in SAVR, with the distinction that no transesophageal



VIDEO 1. Stepwise SAVR performed with a full sternotomy using the Perceval S Aortic bioprosthesis (Sorin Group). Video available at: https://www.jtcvs.org/article/S0022-5223(21)01626-3/fulltext.

echocardiography was used during MAC. After skin closure, sedatives were stopped and patients undergoing TAVI with GA were extubated in the interventional suit. All patients were then transferred to a high dependency unit.

Procedural and postoperative results were extracted according to the definitions of to the Valve Academic Research Consortium 2. Appendix E1 ("Anesthesia and Surgical Approach") shows further details.

Study End Points

Primary end point. The primary outcome was the incidence of in-hospital POD during the first 5 postoperative days. Starting the first postoperative day, daily assessment of POD was performed by trained research nurses. A patient was classified as having POD when she/he had a positive result in the 3-minute Diagnostic Confusion Assessment Method for non-ventilated patients or Confusion Assessment Method for the ICU for intubated patients.[14,15] In addition, subjects' records were checked daily for the results of the Delirium Observations Scale performed by the nurses on the ward, for signs and symptoms being suggestive for POD and for administration of antipsychotic therapy over the previous 24 hours. Before initiating the study, all research personnel had received specific training based on the 3-minute Diagnostic Confusion Assessment Method training manual for clinical use.

Inter-rater reliability for POD assessments by our trained study nurses had been confirmed in our previous studies. Patients who developed POD were further evaluated daily until resolution of delirium or hospital discharge. The nursing staff was encouraged by institutional standards to evaluate and report delirium symptoms every shift based on the Delirium Observation Scale on the ward.

Secondary end points. Secondary end points included severity of POD (evaluated with the delirium severity measure based on the Confusion Assessment Method Severity Long Version), duration of POD, ICU and hospital LOS, and discharge destination. After discharge, composite end points for early safety (at 30 days) and clinical efficacy (at 6 months) of TAVI and SAVR were recorded as defined by Valve Academic Research Consortium 2.[16] Six months after the procedure, patients were contacted by telephone to evaluate EQ-5D-5L and IADL and by mail for the cognitive failure questionnaire and the EQ-VAS. All study visits are summarized in Figure 1.

Sample Size Calculation and Statistical Analysis

Sample size estimation. Yearly, approximately 250 patients undergo aortic valve replacement (assuming 70 TAVIs and 180 SAVRs) at our institution. Our group has recently reported an overall incidence of 41% of POD in older patients undergoing a broad mix of on-pump cardiac surgery in our hospital.[17] The sample size of the current study was based on a conservative estimate of a 20% POD rate in SAVR. The minimal recruitment period was initially expected to equal 1 year, with the option to extend it if the number of patients was not reached.

Based on this assumption, a 1-year recruitment yields 89% power to detect an absolute risk reduction of 15% in the incidence of POD (5% in the TAVI group and 20% in SAVR group) using a 2-sided chi-square test with alpha equal to 0.05. Note that this calculation is an approximation because the primary analysis is not based on a classic chi-square test but the calculation of a relative risk (RR), considering a potential difference in the number of evaluable days and differences in the patient mix.

Statistical analysis. Results were reported for the comparison of SAVR with TAVI and for the comparison of mini- with full-sternotomy SAVR. For the incidence of in-hospital POD within the first 5 postoperative days (primary outcome), the RR (and 95% confidence intervals [CIs]) was reported. Patients without any POD event and discharged before postoperative day 5 were assumed to remain without POD. The estimate was obtained with a Poisson regression model.

Other dichotomous outcomes were also evaluated with the RR model. Depending on the distribution of the other outcomes, median (interquartile range) and mean (standard deviation) were reported and groups were compared using Mann–Whitney *U* tests and independent *t* tests. Hospital LOS was compared between groups using a log-rank test censoring patients who were transferred to another hospital. A log-rank test was also used to compare the duration of POD within the group of patients with POD, censoring patients with POD at the time of discharge.

Potential differences in baseline characteristics between groups, related to the observational character of the study, can induce bias when comparing primary and secondary outcomes. To reduce the risk of bias, each subject was weighted by its inverse probability of being in its specific group, conditional on the following variables suspected a priori to be related to POD (and potentially to other outcomes): age, euroSCORE II, TFI, and EFT. Propensity scores were obtained with a multivariable logistic regression model. For all outcomes, results were reported from the unweighted and weighted analyses, and verified in an extension of the weighted models, the so-called double robust approach.

In additional exploratory analyses, preoperative, intraoperative, and postoperative characteristics were compared between patients using Mann–Whitney *U* and chi-square tests. All analyses were performed using SAS software version 9.4 of the SAS System for Windows (SAS Institute Inc). The alpha-level has been set at 0.05. For the secondary outcomes, a Bonferroni-Holm correction for multiple testing was applied for both comparisons (TAVI vs SAVR and mini-sternotomy vs full sternotomy), separately. For further details, see Appendix E1 ("Statistical Analysis").

RESULTS

Participants

Between September 2018 and January 2020, we screened 334 patients of whom 250 patients were included: 84 patients in the TAVI group and 166 patients in the SAVR group (Figure 2). Eleven patients died within the follow-up window. The remaining 239 patients were contacted at 6 months by telephone and mail obtaining response rates of 92% and 82%, respectively. Response rates did not differ between the TAVI and SAVR groups.

Baseline Characteristics and Procedural Data

Patients who underwent TAVI had a higher burden of predisposing risk factors for POD than patients who underwent SAVR: greater age, higher mean euroSCORE II, and more

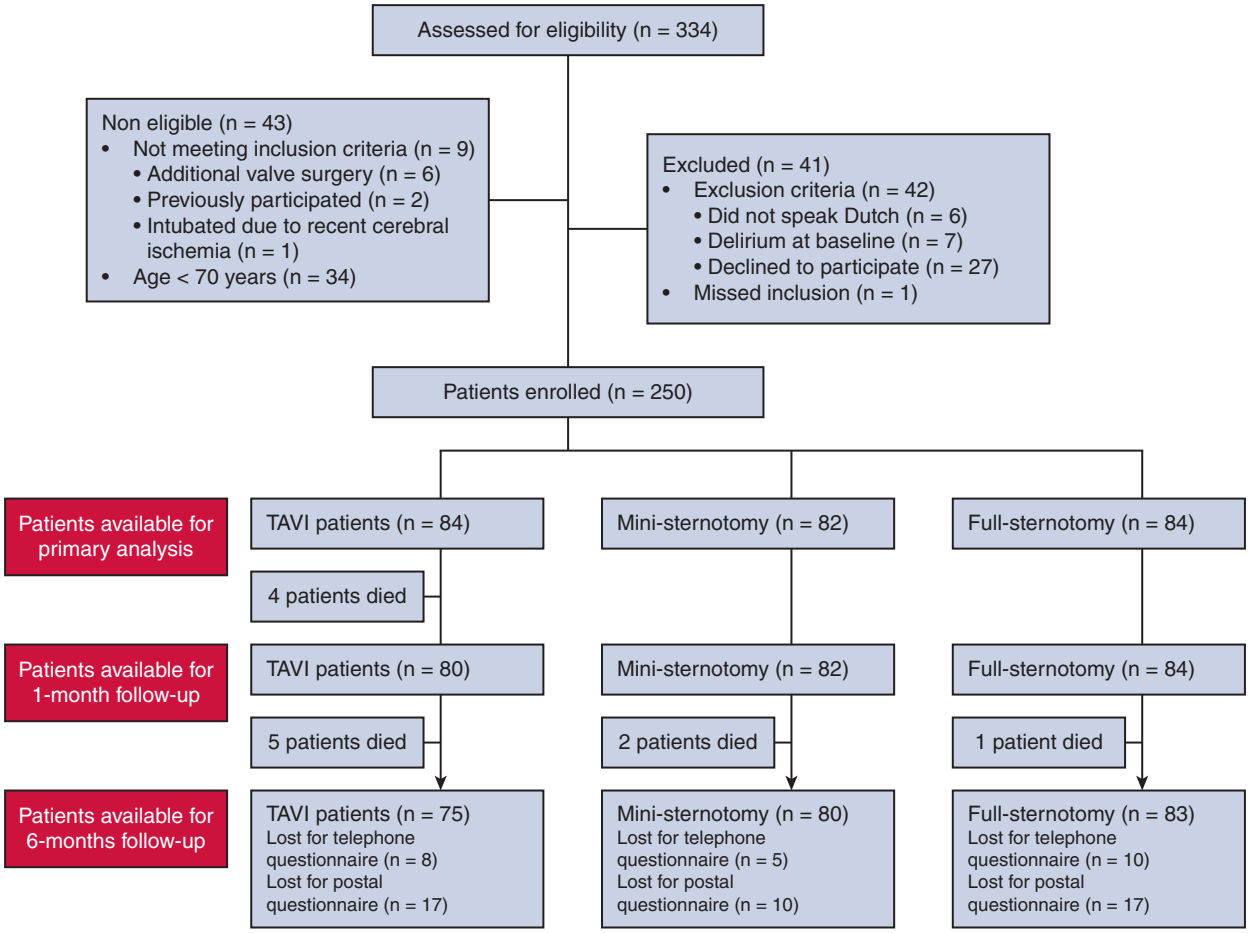


FIGURE 2. Flow diagram based on the STROBE recommendations. *TAVI*, Transcatheter aortic valve implantation.

frailty according to EFT, TFI, and IADL. Baseline EQ-VAS was lower in the TAVI group than the SAVR group. Between mini- and full-sternotomy SAVR, only euroSCORE II was different (Table 1). After propensity weighting, the TAVI group was comparable to the SAVR group regarding baseline characteristics, except for the male/female ratio and EQ-VAS. Despite the propensity weighting in the SAVR group, the euroSCORE II remained different (Table 2).

Within the TAVI group, 88% of the procedures were performed through TF access and 81% of these patients received MAC. Anesthesia and procedural times were significantly shorter in patients undergoing TAVI versus mini-sternotomy versus full sternotomy. Mean intraoperative BIS was significantly higher during TAVI procedures than in SAVR procedures, as was the case for mean intraoperative arterial blood pressure (Table E1).

The discriminative ability (area under the curve) of the model used to create the weights equaled 0.791 for TAVI versus SAVR and 0.819 for the within SAVR comparison of mini- with full sternotomy.

Primary Outcome

Overall, POD during the first 5 postoperative days occurred in 93 patients, being 37% of all cases (Table E2). After propensity weighting, the POD incidence was significantly lower in the TAVI group (15%) compared with the SAVR group (51%) (RR, 0.29; 95% CI, 0.16-0.51; $P < .0001$), also after double robust adjustment (RR, 0.26; 95% CI, 0.16-0.44; $P < .0001$) (Table 3). In a post hoc analysis, the incidence of POD was significantly lower in the TF-TAVI group (all receiving MAC) than in the SAVR group (12% vs 49%, RR, 0.24; 95% CI, 0.10-0.55; $P = .0008$). POD incidences did not differ significantly between mini- or full-sternotomy SAVR (50% vs 53%, RR, 0.93; 95% CI, 0.65-1.33; $P = .70$) (Table 3). Additional sensitivity analyses are provided in Appendix E1 ("Primary Outcome").

Secondary Outcomes

The onset of POD was not significantly different between the groups. Duration of POD was comparable between

TABLE 1. Observed (unweighted) baseline characteristics and demographic data

Variable	TAVI (n = 84)	SAVR All (n = 166)	P*	SAVR Intragroup comparison Mini-sternotomy (n = 82)	SAVR Intragroup comparison Full sternotomy (n = 84)	P†
Patient characteristics						
Age, y	83 [5.92]	78 [4.99]	**<.001**	78 [5.26]	78 [5.26]	.80
BMI, kg/m^2	26.7 [4.96]	28.0 [4.19]	**.03**	28.2 [3.82]	27.8 [4.54]	.61
Weight, kg	74 [14.5]	78 [14.1]	**.01**	78 [13.2]	77 [15.0]	.87
Female	32 (38)	70 (42)	.54	37 (45)	33 (39)	.45
Preoperative status						
euroSCORE II	7.28 [5.98]	3.77 [3.33]	**<.001**	2.47 [1.47]	5.03 [4.09]	**<.001**
Ejection fraction			.06			**.01**
>50%	62 (74)	143 (86)		76 (93)	67 (80)	
31%-50%	15 (18)	16 (10)		6 (7)	10 (12)	
<30%	7 (8)	7 (44)		0	7 (8)	
Urgency			.19			**.05**
Elective	81 (96)	153 (92)		79 (96)	74 (88)	
Urgent	3 (4)	13 (8)		3 (4)	10 (12)	
Extracardiac arteriopathy	31 (37)	42 (25)	.06	14 (17)	28 (33)	**.02**
Atrial fibrillation	37 (44)	37 (22.3)	**.0004**	15 (18)	22 (26)	.22
Tilburg Frailty Indicator	4.38 [2.4]	3.7 [2.25]	**.02**	3.73 [2.28]	3.66 [2.22]	.81
Essential Frailty Toolset	1.29 [0.95]	0.77 [0.87]	**<.001**	0.76 [0.83]	0.79 [0.92]	.99
IADL	9.9 [3.25]	11.99 [2.57]	**<.001**	12.02 [2.78]	11.95 [2.36]	.56
MMSE	26.43 [2.55]	26.63 [3.19]	.12	26.49 [3.90]	26.77 [2.33]	.86
Clock completion	2.71 [2.51]	3.19 [2.41]	.14	3.23 [2.41]	3.15 [2.43]	.84
IQCODE	3.32 [0.36] n = 60	3.23 [0.35] n = 135	.21	3.25 [0.33] n = 64	3.22 [0.37] n = 71	.35
EQ-VAS	62 [17.3]	70 [18.0]	**<.001**	71 [17.8]	69 [18.3]	.41
Geriatric depression scale	1.60 [1.70]	1.30 [1.47]	.26	1.21 [1.25]	1.39 [1.66]	.70

Comparison between groups without propensity weighting. Data are presented as mean and standard deviation [SD] or as an absolute number/total number (n/N) with the percentage (%) of the whole. All reported *P* values are 2 sided. Bold indicates statistical significance at $P < .05$. *TAVI*, Transcatheter aortic valve implantation; *SAVR*, surgical aortic valve replacement; *BMI*, body mass index; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *IADL*, Instrumental Activities of Daily Living; *MMSE*, Mini-Mental State Examination; *IQCODE*, Informant Questionnaire on Cognitive Decline in the Elderly; *EQ-VAS*, EuroQol Visual Analogue Scale. *TAVI versus all SAVR. †Mini-sternotomy versus full sternotomy.

TAVI and SAVR. After SAVR, hospital LOS was significantly longer (Table 3).

The overall composite end points for early safety at 30 days and clinical efficacy at 6 months did not differ between the groups. However, the incidence of major vascular complications and valve dysfunction was significantly higher in the TAVI group (Table 3). Six months after the procedure, the QoL (EQ-5D-5L) was significantly higher in the SAVR group than in the TAVI group (Figure 3, Table 3).

Postoperative inflammation as reflected by the serum levels of C-reactive protein (CRP) was significantly higher after SAVR than after TAVI, without any significant difference between the mini- and full-sternotomy groups (Table 3). The observed results in relation with POD are provided in Table E3 and Appendix E1 ("Secondary Outcomes").

DISCUSSION

In the present study, we found a significant lower incidence of POD after TAVI than after SAVR during the first 5 postoperative days. The observed (unweighted) incidence of POD in our study after TAVI was 24%, which is comparable to previously reported incidences ranging from 13% to 44%.[3,18-20] In many countries, patients receiving TAVI usually have a higher surgical risk than patients allocated to SAVR as reflected by an increased age, higher euroSCORE II, and frailty scores.[19] Of note, these factors are also well-known predisposing risk factors for the development of POD[2] and were significantly more present in our TAVI population. In an attempt to correct for these baseline differences, we used propensity weighting with a double robust approach to match our TAVI population with the SAVR population. Even after this adjustment, the TAVI group experienced significantly less POD than the SAVR group. The reasons why TAVI was associated with a lower POD incidence remain speculative. Although the impact of underlying patient-related risk factors was weakened by the applied statistical methodology, TAVI differs from SAVR with respect to a variety of precipitating factors for POD.[20] In fact, our study showed significantly lower postoperative CRP levels in those undergoing TAVI, most

TABLE 2. Propensity-weighted baseline characteristics and demographic data

Variable	TAVI (n = 84)	SAVR All (n = 166)	P*	SAVR Intragroup comparison Mini-sternotomy (n = 82)	SAVR Intragroup comparison Full sternotomy (n = 84)	P†
Patient characteristics						
Age, y	79 [6.41]	80 [5.24]	.56	80 [5.45]	79 [5.06]	.92
BMI, kg/m^2	27.9 [4.88]	27.9 [4.09]	.98	27.9 [3.84]	27.9 [4.35]	.98
Weight, kg	80 [16.5]	77 [14.3]	.38	76 [13.8]	78 [14.8]	.59
Female	24.7 (29.5)	79 (47.6)	**.02**	47.4 (58)	31.7 (38)	**.02**
Preoperative status						
euroSCORE II	4.83 [4.77]	4.08 [2.84]	.23	3.55 [1.85]	4.60 [3.48]	.03
Ejection fraction			.34			.10
>50%	64.8 (77)	142 (86)		72 (88)	69.8 (83)	
31%-50%	14.2 (17)	19.2 (12)		10 (12)	9.5 (11)	
<30%	5.1 (6)	4.8 (3)		0 NA	4.8 (6)	
Urgency			**.01**			.14
Elective	82.3 (98)	151 (91)		77.7 (95)	72.8 (87)	
Urgent	1.7 (2)	16 (9)		4.3 (5)	11.2 (13)	
Extracardiac arteriopathy	22 (26)	46 (28)	.74	23 (28)	23 (28)	.98
Atrial fibrillation	26.2 (31)	49.7 (30)	.88	23.2 (28)	26.5 (32)	.73
Tilburg Frailty Indicator	4.03 [2.26]	3.89 [2.21]	.70	3.92 [2.20]	3.86 [2.23]	.87
Essential Frailty Toolset	1.00 [0.84]	0.85 [0.89]	.33	0.75 [0.82]	0.95 [0.95]	.22
IADL	10.88 [2.91]	11.56 [2.87]	.16	11.65 [2.90]	11.46 [2.85]	.74
MMSE	26.8 [2.51]	26.4 [2.95]	.41	26.3 [3.38]	26.5 [2.46]	.68
Clock completion	3.42 [2.35]	2.98 [2.46]	.26	2.89 [2.48]	3.06 [2.45]	.72
IQCODE	3.30 [0.36]	3.26 [0.36]	.63	3.30 [0.32]	3.23 [0.39]	.35
EQ-VAS	59 [18.3]	72 [18.2]	**<.001**	74 [18.2]	70 [18.1]	.26
Geriatric depression scale	1.41 [1.74]	1.34 [1.44]	.83	1.25 [1.20]	1.44 [1.64]	.43

Comparison between groups with propensity weighting. Data are presented as mean and SD or as an absolute number (n) with the percentage (%) of the whole. All reported *P* values are 2 sided. Bold indicates statistical significance at $P < .05$. *TAVI*, Transcatheter aortic valve implantation; *SAVR*, surgical aortic valve replacement; *BMI*, body mass index; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *IADL*, Instrumental Activities of Daily Living; *MMSE*, Mini-Mental State Examination; *IQCODE*, Informant Questionnaire on Cognitive Decline in the Elderly; *EQ-VAS*, EuroQol Visual Analogue Scale. *TAVI versus all SAVR. †Mini-sternotomy versus full sternotomy.

probably indicating a higher degree of postoperative inflammation in those undergoing SAVR because of the use of CPB and the larger magnitude of surgical trauma/stress. Propagation of systemic inflammation within the brain has been brought forward as one possible mechanism of POD.[21] This hypothesis is also supported by other studies in both cardiac and noncardiac surgical patients in whom increased postoperative CRP levels were found to be an independent risk factor for POD.[22,23]

Another important difference between TAVI and SAVR in our study was the predominant use of MAC for the TAVI procedure. MAC allows for the avoidance or at least significant dose-reduction of administered anesthetics, the majority of which being GABA-ergic agonists and implicated in the pathophysiological model of an impaired cerebral neurotransmitter balance resulting in POD.[24] In fact, we found that patients receiving TF-TAVI with POD had received GA more frequently than MAC. This finding is in accordance with a recent report in which GA was found to be independently associated with POD in patients undergoing TAVI.[3] In line with the potentially protective effects of reduced anesthetic doses, in our study, patients undergoing SAVR and patients with POD were found to have more frequently experienced a greater depth of anesthesia as indicated by the proportion of patients spending time below BIS values of 40. Notably, there is controversy whether the avoidance of an inadequately profound depth of anesthesia is able to prevent POD. Although earlier studies reported a reduction of POD incidences when anesthesia was titrated according to processed electroencephalography (EEG), more recent trials did no longer report a beneficial effect of EEG-guided anesthesia with respect to the occurrence of POD.[25] As a consequence, recent expert recommendations no longer recommend the use of processed EEG for the prevention of delirium.[26]

Intraoperative hypotension is a well-known contributor to postoperative organ injury.[27] In our study, patients undergoing TAVI had significantly higher intraprocedural blood pressures. However, it is questionable whether this contributed to the lower POD incidence. Several systematic reviews could not find an association between intraoperative hypotension and cognitive outcome.[27] A recent randomized controlled trial in cardiac surgery could not find a beneficial effect on the incidence of POD for high-target blood

TABLE 3. Propensity-weighted comparison of postoperative outcomes

	TAVI	SAVR				
				Intragroup comparison		
Outcomes	(n = 84)	All (n = 166)	P*	Mini-sternotomy (n = 82)	Full sternotomy (n = 84)	P†
Incidence of POD	13 (15)	85 (51)	**<.0001**	41 (50)	45 (53)	.70
Severity of POD‡	7 [5-8]	5 [3-7]	.03	5 [3-7]	5 [3-7]	.70
Onset of POD,‡ d	4 [3-5]	4 [3-5]	.46	3 [1:5]	4 [3-5]	.08
Duration of POD,‡ d	6 [4-6]	4 [3-6]	.54	3 [3-5]	4 [3-7]	.03
Postoperative CRP, mg/dL	33 [23-68]	187 [140-238]	**<.0001**	187 [140-228]	179 [13-259]	.90
LOS ICU, h	29 [23-49]	49 [27-90]	**.0002**	49 [27-99]	46 [27-76]	.76
LOS hospital, d	3 [3-7]	10 [7-14]	**<.0001**	9 [7-14]	11 [8-15]	.44
Discharged home	75 (91)	88 (53)	**<.0001**	41 (50)	47 (56)	.58
Early safety (30 d)	31 (37)	42 (25)	.17	22 (26)	20 (24)	.79
All-cause mortality			NA	0	0	NA
All stroke	5.3 (6)	5.4 (3)	.40	4.2 (5)	1.2 (1)	.30
Life-threatening bleeding	11.3 (14)	10.8 (7)	.24	4.2 (5)	6.6 (8)	.51
AKI 2 or 3	6.8 (8)	23.4 (14)	.19	9.2 (11)	14 (17)	.46
Major vascular complication	20.7 (25)	1.1 (1)	**.0007**	1 (1)	0	NA
Clinical efficacy (6 mo)	31.5 (38)	38.5 (23)	.08	21 (25)	18 (21)	.62
All-cause mortality	5.8 (7)	2.3 (1)	.02	1.4 (2)	0.9 (1)	.68
All stroke	6.9 (8)	7.0 (4)	.30	4.2 (5)	2.8 (3)	.65
Rehospitalization	4.6 (5)	17.0 (10)	.17	6 (7)	11 (13)	.28
NYHA 3 or 4	6.6 (8)	19.8 (12)	.39	9.2 (11)	11 (13)	.82
Valve dysfunction	17.9 (21)	4.5 (3)	**.0006**	3.2 (4)	1.3 (2)	.30
QoL and functionality						
EQ-5D-5L						
6 mo vs baseline						
Worse	26 (40)	35 (24)		18 (24)	18 (25)	
Mixed	21 (33)	33 (23)		17 (23)	16 (23)	
Equal	10 (16)	18 (12)		9 (12)	9 (13)	
Better	8 (12)	59 (41)	**<.0001**§	31 (42)	28 (40)	.78§
EQ-VAS (6 mo)	68 (12)	73 (17)	.04	71 (17)	75 (17)	.27
IADL (6 mo)	9.6 (3.5)	10.5 (3.4)	.23	10.3 (3.3)	10.6 (3.5)	.72
Cognitive failure questionnaire	30 (13)	27 (14)	.16	26 (14)	27 (14)	.71

Comparison of postoperative outcome between groups with propensity weighting. Data are presented as median [interquartile range], mean (SD) or as an absolute number (%). These statistics and the *P* values refer to the result after weighting (inverse probability of treatment weighting). Note that due to weighting, the number of patients can have a decimal value. *P* values obtained with the double-robust approach were comparable (data not shown). Given the low number of events, this approach was not applied for the separate items of early safety. *P* values in bold are significant. For the secondary outcomes, a Bonferroni-Holm correction for multiple testing was applied for both comparisons separately. *TAVI*, Transcatheter aortic valve implantation; *SAVR*, surgical aortic valve replacement; *POD*, postoperative delirium; *CRP*, C-reactive protein; *LOS*, length of stay; *ICU*, intensive care unit; *NA*, not applicable; *AKI*, acute kidney injury; *NYHA*, New York Heart Association; *QoL*, quality of life; *EQ-5D-5L*, EuroQol 5 dimensional questionnaire 5 levels; *EQ-VAS*, EuroQol Visual Analogue Scale; *IADL*, Instrumental Activities of Daily Living. *TAVI versus all SAVR. †Mini-sternotomy versus full sternotomy. ‡Evaluated within the patients with POD. §*P* value for comparison of better versus the other categories.

pressure management.[28] Another study even described an increased incidence of POD in patients in whom blood pressures exceeded the upper limit of autoregulation.[29]

Prolonged surgery is another known precipitating factor for POD.[26] In the present study, procedural times were shorter in the TAVI group and in the overall population of nondelirious patients. Shorter procedural times reflect a lower magnitude of surgical stress and allow for a shorter exposure to anesthetics, both of which may have a protective effect against POD.

Our observed POD rate of 44.0% after SAVR is comparable with previously published results of our group and other reported incidences ranging from 41.0% to 66.0%.[17,19,20] Between mini- and full-sternotomy SAVR, we found no differences in postoperative outcomes, neither before nor after propensity weighting.

In comparison with SAVR, we found that patients after TAVI reported lower QoL (ie, EQ-5D-5L) after 6 months compared with baseline. These findings are in contrast to the results of a retrospective study showing an improved

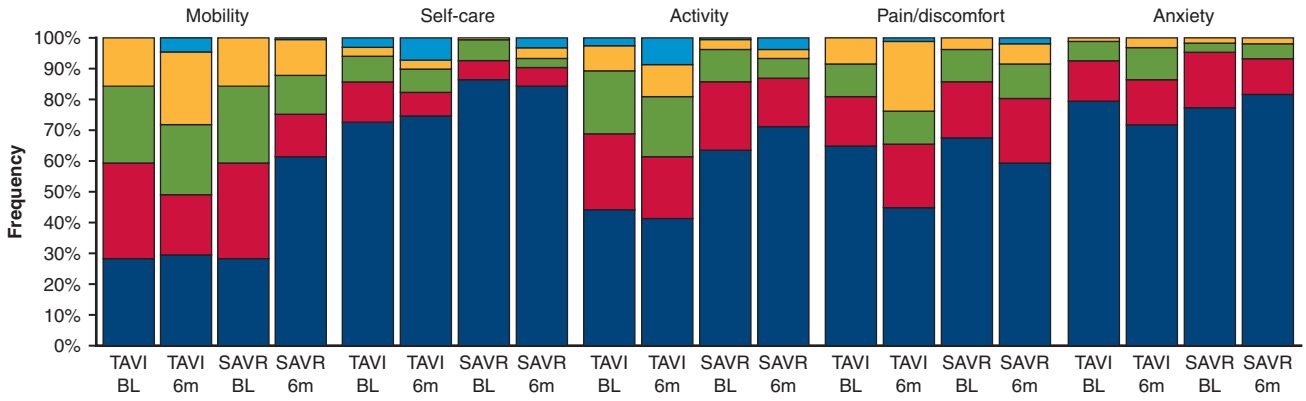


FIGURE 3. QoL comparison (unweighted) between TAVI and SAVR for the 5 dimensions of the EQ5D5L questionnaire at baseline and 6 months postoperatively. *Blue*, no constraints; *Red*, slight constraints; *Green*, moderate constraints; *Yellow*, severe constraints; *Cyan*, extreme constraints or unable to do. *TAVI*, Transcatheter aortic valve implantation; *BL*, baseline; *6m*, 6 months; *SAVR*, surgical aortic valve replacement.

QoL (ie, EQ-5D-3L) up to 1 year after TAVI compared with SAVR.[30] However, based on the euroSCORE II, patients in the latter study should be classified as low/intermediate risk rather than high risk (as in our study). Our results are in line with several other prospective studies in intermediate- and high-risk patients undergoing TAVI, also showing a functional decline or no benefit in QoL after TAVI.[31,32] Moreover, inter-group differences might be due to unknown differences in baseline characteristics for which our statistical analysis could not account.

In the weighted analysis of the present study, we found no differences for the Valve Academic Research Consortium 2 composite end points of early safety (at 30 days) and clinical efficacy (at 6 months) between TAVI and mini- or full-sternotomy SAVR. This is in line with several other reports in which TAVI was noninferior to SAVR regarding postoperative morbidity and mortality,[33-35] also in patients with a high predicted risk as in our study.[3] Notably, in both the TAVI and SAVR groups, the observed mortality was considerably lower than the predicted mortality. However, our study was not powered to observe differences in mortality.

Strengths and Limitations

Strengths of this study include the prospective design and the use of valid and reliable instruments for the assessment

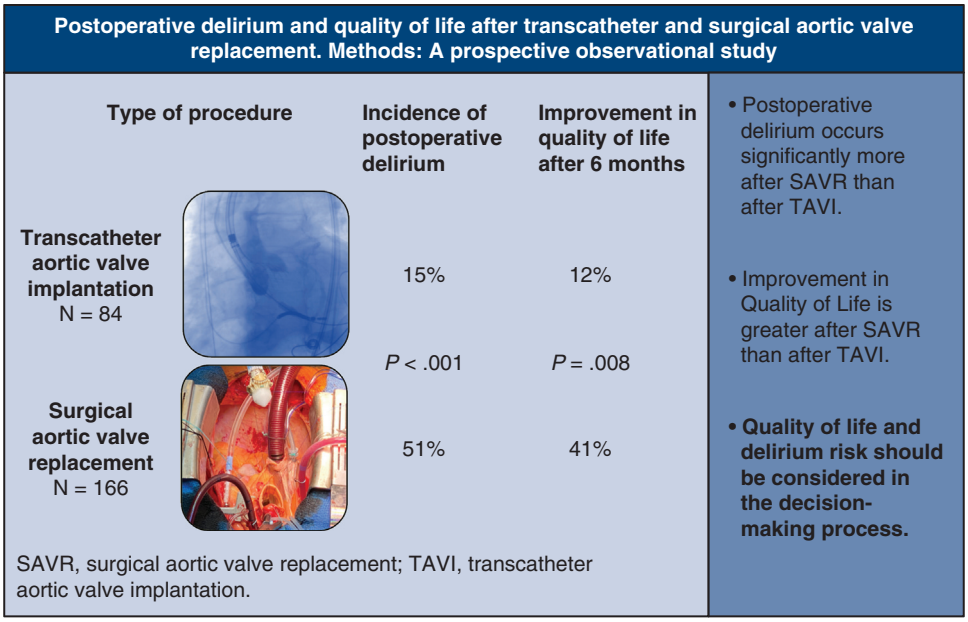


FIGURE 4. Comparing POD and QoL between TAVI and SAVR. In this prospective study, propensity weighting (for frailty and comorbidity) was used to compare the impact of the procedure on the incidence of POD. POD occurred more often after SAVR, these patients did report a better improvement in QoL at 6 months postoperatively. *SAVR*, Surgical aortic valve replacement; *TAVI*, transcatheter aortic valve implantation.

of a large variety of baseline and outcome data. The sample size is considerably higher than in many other studies on this topic.[19,20] During the study window, 334 patients were screened and only 9% refused to participate. Follow-up of the included patients was performed daily, and screening for POD was performed bedside by experienced and trained research personnel for a minimum of 5 consecutive days, including weekends and holidays. We achieved a response rate of 91% at 6 months, by which attrition bias was minimized.

We also acknowledge that our study suffers from several limitations. First, because of the nonrandomized design, there is a considerable risk for selection bias. We attempted to minimize the effect of known confounders using propensity weighting. However, we cannot exclude an impact of additional unknown confounders. Second, this is a single-center study so that the external validity of our findings has to be tested. Third, as a result of early discharge of our TAVI patients, we might have induced an attrition bias resulting in a potential overestimation of the effect size for differences in POD incidence. Fourth, the follow-up period was 6 months, which might be considered as too short for the detection of long-term consequences of POD. Finally, we are unable to differentiate between the impact of CPB and anesthetic regimen (MAC vs GA) on the incidence of POD.

CONCLUSIONS

In the present study, we showed that when compared with SAVR, TAVI reduces the incidence of POD considerably but at the expense of a reduced improvement of QoL. Our findings suggest that both delirium risk and QoL should be considered in decision-making for SAVR and TAVI (Figure 4).

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: aortic valve, cardiac surgery, delirium, frailty, postoperative outcome, quality of life, SAVR, TAVI

APPENDIX E1. MATERIALS AND METHODS

Baseline Assessment

After enrollment, frailty, QoL, and cognitive and neuropsychiatric functioning were assessed by qualified research personnel using the following tools: Mini-Mental State Examination,[E1] clock completion test,[E2] self-administered IADL,[E3] TFI,[E4] EFT,[E5] self-administered EQ-5D-5L validated Dutch version and EQ-VAS,[E6] 10-item geriatric depression scale,[E7] and an interview with a family member using the short form of the Informant Questionnaire on Cognitive Decline in the Elderly.[E8]

In addition, medical records were used to extract baseline data (demographic data, routine clinical examination, surgical and medical history, euroSCORE II,[E9] standard laboratory results, and concomitant medication).

Anesthesia and Surgical Approach

All patients received anesthetic, surgical, and interventional care according to our institutional standards. TAVI was primarily performed using the TF access and only infrequently via a transapical, trans-subclavian, or transcarotid approach. Depending on the concomitant need for coronary revascularization, SAVR was performed with full sternotomy, upper J, or T inverted mini-sternotomy.

Anesthetic management was tailored to the type of procedure. For SAVR, GA was maintained using a balanced anesthesia technique with dexmedetomidine, remifentanil, and sevoflurane (targeting a BIS of 40-60). All patients received standard American Society of Anesthesiologists monitoring, transesophageal echocardiography, central venous pressure, and BIS. At the discretion of the attending anesthesiologist, some patients received a pulmonary artery catheter or cerebral oximetry. After surgery, patients were transported, while still intubated and mechanically ventilated, to a high-dependency unit.

The majority of patients receiving TF TAVI received MAC under analgo-sedation with remifentanil, propofol, and local anesthetic infiltration of the groin without intubation.[E10] The balloon-expandable Sapien 3, Edwards Lifesciences or self-expandable Evolute R, Medtronic Inc valves were used in a 1:1 ratio. TAVI approaches other than TF were performed under GA using remifentanil and sevoflurane or propofol, targeting a BIS of 40 to 60. All patients receiving TAVI received monitoring comparable to that used in SAVR, with the distinction that no transesophageal echocardiography was used during MAC. After skin closure, sedatives were stopped and patients undergoing TAVI with GA were extubated in the interventional suit. All patients were then transferred to a high-dependency unit.

Recorded intraoperative variables included anesthesia time, surgical time, duration of CPB, duration of aortic clamping, type of intervention, duration of mechanical ventilation, dosage of drugs used, blood loss, transfusion requirements, urine output, and hemodynamic and respiratory monitoring. Procedural and postoperative results were extracted according to the definitions of the Valve Academic Research Consortium 2.[E11]

Statistical Analysis

Results were reported for the comparison of SAVR with TAVI and for the comparison of mini- with full-sternotomy SAVR. For the incidence of in-hospital POD within the first 5 postoperative days (primary outcome), the RR and 95% CIs were reported. Patients with no POD event and discharged before postoperative day 5 were assumed to remain without POD. The estimate was obtained with a Poisson regression model.[E12]

Other dichotomous outcomes were also evaluated based on the RR model. Depending on the distribution of the other outcomes, median (interquartile range) and mean (SD) were reported, and groups were compared using Mann–Whitney *U* tests and independent *t* tests. Hospital LOS was compared between groups using a log-rank test censoring patients who were transferred to another hospital. A log-rank test was also used to compare the duration of POD within the group of patients with POD, censoring patients with POD at the time of discharge.

Potential differences in baseline characteristics between groups, related to the observational character of the study, can induce bias when comparing primary and secondary outcomes. To reduce the risk of bias, each subject was weighted by its inverse probability of being in its specific group, conditional on the following variables suspected a priori to be related to POD (and potentially to other outcomes): age, euroSCORE II, TFI, and EFT. The objective was to create a weighted sample in which the distribution of these variables was the same between groups. The probabilities of group membership are also known as propensity scores[E13] and were obtained with a multivariable logistic regression models contrasting each group (TAVI, full sternotomy, mini-sternotomy) with the other patients. The discriminative ability of the propensity model(s) was quantified using the area under the curve statistics (0.5 = full overlap, 1 = perfect discrimination). In the outcome analyses, each individual was weighted by the inverse of its probability to belong to its group. Thus, the more typical a subject is for the group it belongs to, the lower its weight. The weights were normalized to the sample size in each group, meaning the sum of weights in each group equals the sample size of that group. This approach is known as inverse probability of treatment weighting.[E14] It uses the propensity score to construct weights, contrary to the more classical approaches in which the score is used as a covariate in the analysis or is used to create a matched sample. For all outcomes, results were reported from the unweighted and weighted analyses, and also verified in an extension of the weighted models, the so-called double robust approach.[E15] In this approach, the confounders used to create the weights were added as covariates in the analysis models. Note that for the weighted version of the Mann–Whitney *U* test, a linear model on ranks was used.

Baseline characteristics of the patients were evaluated before and after weighting, to verify if the weighting resolved the imbalance in patient mix. In additional exploratory analyses, preoperative, intraoperative, and postoperative characteristics were compared between patients using Mann–Whitney *U* and chi-square tests. All analyses were performed using SAS software, version 9.4 of the SAS System for Windows (SAS Institute Inc). For the secondary outcomes, a Bonferroni-Holm correction for multiple testing was applied for both comparisons (TAVI vs SAVR and mini-sternotomy vs full sternotomy) separately.

RESULTS

Primary Outcome

A sensitivity analysis was performed by comparing the POD incidence in patients treated with TAVI and in patients receiving mini-sternotomy SAVR (isolated AVR, n = 82) (15% vs 50%, RR, 0.23; 95% CI, 0.13-0.44; $P < .001$). In addition, a second sensitivity analysis was performed by comparing those undergoing TAVI with those undergoing isolated SAVR via full or mini-sternotomy (n = 100) (15% vs 47%, RR, 0.26; 95% CI, 0.14-0.46; $P < .001$). Both sensitivity analyses were not different than the original comparison of TAVI versus SAVR (15% vs 52%, RR, 0.26; 95% CI, 0.16-0.44; $P < .001$).

Secondary Outcomes of Patients With POD: Baseline and Procedural Characteristics

Patients experiencing POD were frailer, had a higher euroSCORE II, and had a lower preoperative hemoglobin than patients without POD (Table E2). Procedural time was significantly longer in patients experiencing POD without any difference in CPB time or aortic clamping time. Moreover, patients with POD more frequently had a mean BIS less than 40, had a lower mean arterial blood

pressure, and required more often transfusions intraoperatively than those without POD. The postoperative anticholinergic loading scale from day 1 to day 4 was significantly higher in the POD group. Postoperative inflammation (serum levels of CRP) was significantly higher in patients with POD (Table E2).

Postoperative ventilation, ICU, and hospital LOS durations were significantly longer in patients with POD. POD was also associated with an increase in postoperative morbidity as indicated by a higher incidence of pneumonia, conduction abnormalities, postoperative atrial fibrillation, and acute kidney injury. After 6 months, there was no difference between the non-POD and POD groups with respect to the composite end points or EQ-VAS. In contrast, the number of patients with better QoL (EQ-5D-5L) at 6 months compared with baseline was significantly higher in the non-POD group compared with the POD group (Table E2).

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TABLE E1. Observed (unweighted) anesthesia and surgery-related data

Variable	TAVI (n = 84)	SAVR All (n = 166)	P*	SAVR Intragroup comparison: Mini-sternotomy (n = 82)	SAVR Intragroup comparison: Full sternotomy (n = 84)	P†
Anesthesia and surgical related data						
Anesthesia time, min	124 [48]	259 [71]	<.001	222 [42]	295 [75]	<.001
GA	24 (28.6)	166 (100)	NA	82 (100)	84 (100)	NA
TAVI						
TF TAVI	74 (88)	NA	NA	NA	NA	NA
BE TAVI – Sapien 3	41 (49)	NA	NA	NA	NA	NA
SE TAVI – Evolut R	43 (51)	NA	NA	NA	NA	NA
Procedural time, min	77 [43]	201 [65]	<.001	167 [34]	235 [70]	<.001
CPB time, min	NA	86 [37]	NA	72 [26]	99 [40]	<.001
Aortic crossclamp time, min	NA	60 [28]	NA	49 [21]	70 [30]	<.001
Mean intraoperative BIS	76 [18]	40 [5.3]	<.001	40 [5.8]	40 [4.8]	.95
<40	5/80 (6)	79 (48)	<.001	36 (44)	43 (51)	.35
40-60	14/80 (18)	87 (52)		46 (56)	41 (49)	
Mean intraoperative MAP, mm Hg	83 [11]	66 [4.9]	<.001	66 [5.3]	67 [4.5]	.07
Intraoperative treatment						
Crystalloids, mL	828 [1293]	1811 [1714]	<.001	1603 [679]	2014 [2304]	.19
Packed red blood cells, mL	43 [173]	96 [197]	.001	66 [168]	125 [218]	.025

Data are presented as mean and SD or as an absolute number/total number (n/N) with the percentage (%) of the whole. *TAVI*, Transcatheter aortic valve implantation; *SAVR*, surgical aortic valve replacement; *GA*, general anesthesia; *NA*, not applicable; *TF*, transfemoral; *BE*, balloon-expendable; *SE*, self-expendable; *CPB*, cardiopulmonary bypass; *BIS*, bispectral index; *MAP*, mean arterial pressure. *TAVI versus all SAVR. †Mini-sternotomy versus full sternotomy.

TABLE E2. Comparison of observed (unweighted) postoperative outcomes

Outcomes	TAVI (n = 84)	SAVR All (n = 166)	P*	SAVR Intragroup comparison: Mini-sternotomy (n = 82)	SAVR Intragroup comparison: Full sternotomy (n = 84)	P†
Incidence of POD	20 (24)	73 (44)	.004	32 (39)	41 (49)	.20
Severity of POD‡	6 [4-12]	5 [3-7]	.12	5 [3-7]	5 [3-7]	.95
Onset of POD,‡ d	4 [2.5-4.5]	4 [3-5]	.94	3 [2.5-5]	4 [3-5]	.23
Duration of POD,‡ d	4 [2.5-8]	4 [3-5]	.67	3 [2.5-5]	4 [3-6]	.03
Postoperative CRP, mg/dL	40 [24-87]	183 [141-245]	<.0001	186 [142-230]	176 [139-258]	.90
LOS ICU, h	29 [25-68]	47 [27-91]	.03	47 [26-102]	46 [27-76]	.93
LOS hospital, d	4 [3-10]	9 [7-13]	.001	8 [7-12]	10 [7.5-13]	.29
Discharged home	71 (88)	102 (61)	<.0001	47 (57)	55 (66)	.28
Permanent pacemaker	8 (10)	8 (5)	.15			
Following Sapien 3	2 (5)					
Following Evolut R	6 (14)					
Early safety (30 d)	28 (33)	36 (22)	.04	18 (22)	18 (21)	.93
All-cause mortality	4	0	.012§	0	0	NA
All stroke	7 (8)	4 (2)	.04	3 (4)	1 (1)	.33
Life-threatening bleeding	9 (11)	11 (7)	.26	5 (6)	6 (7)	.79
AKI 2 or 3	11 (13)	6.8 (8)	.81	7 (9)	13 (15)	.18
Major vascular complication	11 (13)	1 (1)	.003	1 (1)	0	.50§
Clinical efficacy (6 mo)	36 (43)	38 (23)	.001	21 (26)	17 (20)	.41
All-cause mortality	8 (10)	3 (2)	.012	2 (2)	1 (1)	.55
All stroke	9 (11)	6 (4)	.03	3 (4)	3 (4)	.98
Rehospitalization	9 (11)	17 (10)	.91	7 (9)	10 (12)	.48
NYHA 3 or 4	11 (13)	16 (10)	.41	8 (10)	8 (10)	.96
Valve dysfunction	13 (16)	6 (4)	.002	4 (5)	2 (2)	.40
QoL and functionality						
EQ-5D-5L						
6 mo vs baseline						
Worse	27 (40)	37 (25)		20 (26)	17 (23)	
Mixed	21 (31)	30 (20)		13 (17)	17 (23)	
Equal	8 (12)	26 (17)		14 (18)	12 (16)	
Better	11 (16)	57 (38)	.0004§	30 (39)	27 (37)	.80§
EQ-VAS (6 mo)	67 (15)	73 (16)	.007	71 (18)	75 (15)	.14
IADL (6 mo)	8.3 (3.5)	11.0 (3.2)	<.0001	10.8 (3.2)	11.1 (3.2)	.48
Cognitive failure questionnaire	30 (17)	27 (15)	.26	28 (16)	27 (13)	.60

Comparison of postoperative outcome between groups without propensity weighting. Data are presented as median [interquartile range], mean (SD) or as an absolute number (%). *TAVI*, Transcatheter aortic valve implantation; *SAVR*, surgical aortic valve replacement; *POD*, postoperative delirium; *CRP*, C-reactive protein; *LOS*, length of stay; *ICU*, intensive care unit; *NA*, not applicable; *AKI*, acute kidney injury; *NYHA*, New York Heart Association; *QoL*, quality of life; *EQ-5D-5L*, EuroQol 5 dimensional questionnaire 5 levels; *EQ-VAS*, EuroQol Visual Analogue Scale; *IADL*, Instrumental Activities of Daily Living. *TAVI versus all SAVR. †Mini-sternotomy versus full sternotomy. ‡Evaluated within the patients with POD. §*P* value for comparison of better versus the other categories. *P* value from Fisher exact test because there were zero events in 1 group.

TABLE E3. Observed results in relation with postoperative delirium

Variable	Non-POD (n = 157)	POD (n = 93)	*P*
Preoperative characteristics			
Age, y	80 [5.9]	80 [5.4]	.18
BMI, kg/m^2	27 [3.9]	28 [5.3]	.31
Female	59/157 (38)	43/93 (46)	.18
euroSCORE II	4.34 [3.9]	5.96 [5.2]	.002
Creatinine, μmol/L	1.1 [0.5]	1.24 [0.6]	.10
Previous cardiac surgery	23/157 (15)	11/93 (12)	.53
Chronic lung disease	23/157 (15)	10/93 (11)	.38
LV ejection faction <50%	7/157 (4.6)	7/93 (7.5)	.52
Urgent surgery	6/157 (3.8)	10/93 (11)	.03
≥2 procedures	32/157 (20)	34/93 (37)	.005
Tilburg Frailty Indicator	3.6 [2.3]	4.4 [2.4]	.013
Essential Frailty Toolset	0.78 [0.89]	1.23 [1.0]	<.001
IADL	11.8 [2.6]	10.4 [3.3]	<.001
MMSE	26.9 [3.1]	25.9 [2.7]	.001
Clock completion	3.4 [2.3]	2.4 [2.5]	.002
IQCODE	3.2 [0.31]	3.3 [0.39]	.039
EQ-VAS	67 [18]	68 [18]	.86
Albumin, g/L	43.4 [3.5]	42.5 3.6	.060
Hemoglobin, g/dL	13.2 [1.8]	12.6 [1.7]	.033
Preoperative atrial fibrillation	42/157 (27)	32/93 (34)	.20
Intraoperative characteristics			
TAVI	64/157 (41)	20/93 (22)	.003
Minimal access sternotomy	50/157 (32)	32/93 (34)	
Full sternotomy	43/157 (27)	41/93 (44)	
Sedation (only TAVI)	52/64 (80)	9/20 (45)	.003
Anesthesia time, min	198 [90]	240 [86]	<.001
Procedural time, min	145 [82]	184 [78]	<.001
CPB time, min	86 [34]	86 [40]	.50
N = 166			
Aortic crossclamp time, min	60 [24]	58 [32]	.15
N = 166			
Mean intraoperative BIS			<.001
<40	42/153 (27)	42/93 (45)	
40-60	61/153 (40)	40/93 (43)	
>60	50/153 (33)	11/93 (12)	
Mean intraoperative MAP, mm Hg	73 [13]	69 [7.8]	.05
8Transfusion			
Fresh-frozen plasma, mL	11 [78]	59 [237]	.028
Packed red blood cells, mL	52 [164]	124 [222]	.002
Blood platelets, mL	26 [109]	68 [192]	.06
Postoperative characteristics			
Ventilatory time, min	151 [89-298]*	370 [180-742]*	<.001
ICU stay, yes	105/157 (67)	76/93 (82)	.011
Duration of ICU stay, d	1 [1-2]*	3 [2-5]*	<.001
Pneumonia	10/157 (6)	14/93 (15)	.02
Conduction abnormalities	106/157 (68)	75/93 (81)	.03
Postoperative atrial fibrillation	69/157 (44)	56/93 (60)	.01
Length of hospital stay, d	6.5 [4-9]*	12 [8-16]*	<.001
SAVR, d	7 [6-10]*	12 [9-16]*	<.001
TAVI, d	4 [3-6]*	12 [7-22]*	<.001
Mean creatinine level, μmol/L	1.04 [0.4]	1.37 [0.99]	.002
Max CRP level, mg/dL	126 [88]	198 [92]	<.001

(Continued)

TABLE E3. Continued

Variable	Non-POD (n = 157)	POD (n = 93)	*P*
Early safety (30 d)			
All-cause mortality	2/157 (1)	2/93 (2)	.59
All stroke	2/157 (1)	9/93 (10)	.002
Life-threatening bleeding	7/157 (5)	13/93 (14)	.007
AKI 2 or 3	6/157 (4)	25/93 (27)	<.001
Major vascular complication	6/157 (4)	6/93 (6.)	.35
Valve-related dysfunction	2/157 (1)	1/93 (1.1)	.89
Clinical efficacy (6 mo)			
All-cause mortality	5/157 (3)	6/93 (6)	.22
All stroke	6/157 (4)	9/93 (10)	.06
Rehospitalization	14/17 (9)	12/93 (10)	.32
NYHA 3 or 4	13/157 (8)	14/93 (15)	.10
Valve dysfunction	13/157 (8)	6/93 (6)	.60
EQ-5D-5L			
Equal/Better	72/139 (52)	30/78 (38)	<.001
EQ-VAS (6 mo)	72 [15]	69 [18]	.31
N = 185			
IADL (6 mo)	10.8 [3.2]	9.0 [3.9]	<.001
N = 218			
Cognitive failure questionnaire (6 mo)	28 [15]	29 [16]	.83
N = 185			

Data are presented as mean and SD [95% CI], *median and interquartile range, or absolute number/total number (n) with the percentage (%) of the whole. *POD*, Postoperative delirium; *BMI*, body mass index; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *LV*, left ventricle; *IADL*, Instrumental Activities of Daily Living; *MMSE*, Mini-Mental State Examination; *IQCODE*, Informant Questionnaire on Cognitive Decline in the Elderly; *EQ-VAS*, EuroQol Visual Analogue Scale; *TAVI*, transcatheter aortic valve implantation; *CPB*, cardiopulmonary bypass; *BIS*, bispectral index; *MAP*, mean arterial pressure; *ICU*, intensive care unit; *SAVR*, surgical aortic valve replacement; *CRP*, C-reactive protein; *AKI*, acute kidney injury; *NYHA*, New York Heart Association; *EQ-5D-5L*, EuroQol 5 dimensional questionnaire 5 levels.