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Patient Characteristics and Long-term Outcomes in Patients Undergoing Transcatheter Aortic Valve Implantation in a Failed Surgical Prosthesis versus in a Native Valve: A Danish nationwide study

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Tweet: TAVI in a failed surgical aortic prosthesis as compared to TAVI in a native valve, was not associated with significantly different short- and long-term mortality.

ABSTRACT

Background: Valve-in-valve-transcatheter aortic valve implantation (TAVI) is a feasible and increasingly used treatment option for failed surgical aortic prosthesis, but data from clinical practice are limited.

Objectives: We aimed to examine patient characteristics and outcomes of patients undergoing TAVI in a surgical valve (valve-in-valve TAVI) compared with patients undergoing TAVI in a native valve.

Methods: Using nationwide registries, we identified all Danish citizens, who underwent TAVI from January 1, 2008, to December 31, 2020.

Results: A total of 6070 patients undergoing TAVI were identified; 247 (4%) patients had a history of SAVR (The valve-in-valve cohort). The median age of the study population was 81 (25^{th}-75^{th} percentile 77-85) and 55% were men. Patients with valve-in-valve-TAVI were younger but had a greater burden of cardiovascular comorbidities compared with patients with native-valve-TAVI. Within 30 days post-procedure, 11 (0.2%) and 748 (13.8%) patients who underwent valve-in-valve-TAVI and native-valve-TAVI, respectively, had a pacemaker implantation. The cumulative 30-day risk of death among patients with valve-in-valve-TAVI was 2.4% (95% CI: 1.0% to 5.0%) and 2.7% (95% CI: 2.3% to 3.1%) in patients with native-valve-TAVI, respectively. Correspondingly, the cumulative 5-year risk of death was 42.5% (95% CI: 34.2% to 50.6%) and 44.8% (95% CI: 43.2% to 46.4%), respectively. In multivariable Cox proportional hazard analysis, valve-in-valve-TAVI was not associated with a significantly different risk of death at 30 days (Hazard ratio (HR)= 0.95, 95% CI 0.41-2.19) and 5 years (HR=0.79, 95% CI 0.62-1.00) post-TAVI compared with native-valve-TAVI.

Conclusions: TAVI in a failed surgical aortic prosthesis as compared to TAVI in a native valve, was not associated with significantly different short- and long-term mortality, suggesting that valve-in-valve-TAVI is a safe procedure.

Key words: Transcatheter Aortic Valve Implantation, failed surgical aortic prosthesis, valve-in-valve TAVI.

Abbreviations List

TAVI: Transcatheter aortic valve implantation

SAVR: Surgical aortic valve replacement

NOMESCO: Nordic Medico-Statistical Committee

ICD-8: International Classification of Diseases, 8th revision.

ICD-10: International Classification of Diseases, 10th revision.

HR: Hazard ratio

CI: Confidence interval

CABG: Coronary artery bypass graft surgery

INTRODUCTION

The number of patients with a failed surgical aortic valve prosthesis is increasing.[1] Treatment of these patients is a clinical challenge, and reintervention with either redo surgical aortic valve replacement or valve-in-valve transcatheter aortic valve implantation (TAVI), depending on the patient's surgical risk, is often required. In recent years, TAVI has surpassed surgical aortic valve replacement (SAVR) for the treatment of intermediate and high-risk surgical patients with symptomatic severe aortic stenosis in a native valve,[2,3] and it is considered to be non-inferior to SAVR in those with low surgical risk.[4–6] Along with the rapidly expanding volume of TAVI for native aortic valve stenosis, the number of TAVI in a failed surgical aortic prothesis is also increasing.[7] Recent studies comparing early and late outcomes among patients with a failed surgical aortic prothesis, treated with either valve-in-valve TAVI or redo-SAVR, concluded overall lower rates of early mortality and morbidity, adverse events, shorter length of hospital stay and improved survival in patients treated with valve-in-valve TAVI.[8–10] More recently, it has also been suggested that valve-in-valve TAVI, as compared with TAVI in a native valve, is associated with a similar – or even a lower – risk of heart failure hospitalization and short term-mortality.[11,12] However, data on clinical outcomes in patients with a failed surgical aortic prosthesis and long-term follow-up in population-based cohorts are scarce.[10,13]

There is a need for a long-term evaluation of the valve-in-valve procedure, and for benchmarking it is natural to compare with TAVI in a native valve. Consequently, we performed a nationwide cohort study to examine patient characteristics and clinical outcomes, including hospitalizations and all-cause mortality, in patients undergoing TAVI according to whether the procedure was performed as a valve-in-valve TAVI or in a native valve.

METHODS

Data sources

All Danish citizens are assigned a unique and permanent civil registration number, which allows linkage of nationwide registries at an individual level. For this study, data were obtained from the following three nationwide administrative registries: The Danish Civil Registration System, which contains data on sex, birth date, and vital status (i.e., whether a person is alive, dead, resident in Denmark, disappeared, or emigrated, along with the date of these events);[14] the Danish National Patient Registry, which holds information on hospital admissions and outpatient visits according to the International Classification of Diseases (ICD) and surgical procedures according to the Nordic Medico-Statistical Committee (NOMESCO) classification;[15] and the Danish National Prescription Registry, which contains information on all claimed drug prescriptions in Denmark including the quantity, strength and dispending date of the drug.[16]

Study population

In this study, all Danish citizens undergoing first-time TAVI between 1 January 2008 and 31 December 2020 were included.

Covariates

Information on medical treatment was obtained by identifying all claimed prescriptions from the Danish National Prescription Registry. Comorbidity was defined as in-hospital and outpatient diagnoses (ICD-8 and -10 diagnosis codes) at any time before the date of the TAVI procedure, except for diabetes and hypertension, which were identified using claimed drug prescriptions.[17,18] Additionally, frailty status was assessed using the cumulative frailty risk score, which is also described elsewhere.[19] Briefly, a cumulative frailty risk score was calculated for each patient using

the past 10 years in-hospital ICD-codes. Patients were divided into the following frailty risk groups according to the corresponding cumulative frailty risk score: 1) low, 2) intermediate, and 3) high.

Outcomes

In the present study, we examined the risk of death from any cause at 30 days, 1 year, and 5 years post-procedure. We also examined the risk of rehospitalization from any cause, and from cardiovascular causes, at 30 days, 1 year, and 5 years post-procedure. Patients were followed from the date of the TAVI procedure until the outcome of interest, death, emigration, or end of study (31 December 2021), whichever came first.

Statistics

Baseline characteristics were reported as frequencies with percentages or medians with 25-75th percentiles, and differences between valve-in-valve TAVI and native valve TAVI were tested by the Chi-square test for categorial variables and the Mann-Whitney test for continuous variables. The cumulative incidence of all-cause mortality was estimated using the Kaplan-Meier estimator and all-cause rehospitalization using the Aalen-Johansen estimator (taking into account the competing risk of death), and differences between valve-in-valve-TAVI and native valve TAVI were assessed using log-rank test (all-cause mortality) and Gray's test (all-cause hospital admission). Cox proportional hazards regression models were used to compare the rate of outcomes between groups, and hazard ratios (HR) with 95% confidence intervals (CIs), adjusted for age (included as a categorical variable: <76 years, 76-80 years, 81-85 years and ≥86 years), sex, year of procedure (included as a categorical variable: 2008-2010, 2011-2013, 2014-2016 and 2017-2020), ischemic heart disease, heart failure, atrial fibrillation, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, CABG, frailty (included as a categorical variable: low, intermediate and high),

and liver disease were reported. Patients with native valve TAVI served as the reference group in all models. All statistical analyses were performed with SAS (version 9.4, SAS Institute, NC, USA). A two-sided p value <0.05 was considered statistically significant.

To account for potential differences in baseline characteristics and residual confounding, we matched patients undergoing valve-in-valve TAVI with individuals undergoing a native valve TAVI in a 1:2 ratio on age (up to 2-years difference), sex, year of procedure (up to 2-years difference), a history of ischemic heart disease, heart failure, atrial fibrillation, diabetes, and chronic kidney disease. Cox proportional hazards regression models conditional on the matching (comparing cases with their matched controls) were used to compare the rate of outcomes between groups.

Ethics

This study was approved by the Danish Data Protection Agency [approval number: P-2019-191]. In Denmark, retrospective registry-based studies, in which individuals cannot be identified, do not require ethical approval.

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RESULTS

A total of 6,070 patients underwent first-time TAVI between 1 January 2008 and 31 December 2020 and comprised the study population. Of these, 247 (4.1%) patients had a prior SAVR (Figure 1) and were defined as the valve-in-valve cohort. The median age was 81 (25^{th}-75^{th} percentile 77-85), and 55% were men. Baseline characteristics according to groups are shown in Table 1. Overall, patients with valve-in-valve TAVI were younger but had a greater burden of cardiovascular comorbidities (i.e., heart failure, ischemic heart disease, and atrial fibrillation) and were frailer compared with patients with TAVI in a native valve. In patients with valve-in-valve TAVI, the median time from SAVR to TAVI procedure was 3175 days. The distribution of sex was similar between groups. In total, 25 (10.1%) patients with valve-in-valve TAVI and 549 (9.4%) patients with native valve TAVI had a pacemaker implantation prior TAVI procedure. Within 30 days post-procedure, 11 (0.2%) and 748 (13.8%) patients who underwent valve-in-valve TAVI and native valve TAVI, respectively, had a pacemaker implantation. The number of patients, who had a prior coronary artery bypass graft surgery (CABG) was 93 (37.7%) of patients with valve-in-valve TAVI and 593 (10.2%) of patients with native valve TAVI.

Mortality

Within 30 days post-procedure, 6 (2.4%) and 157 (2.7%) patients who underwent valve-in-valve TAVI and native valve TAVI, respectively, had died (Table 2). The cumulative 30-day risk of death was 2.4% (95% CI: 1.0% to 5.0%) in patients undergoing valve-in-valve TAVI and 2.7% (95% CI: 2.3% to 3.1%) in patients undergoing native valve TAVI (Figure 2A). At 1-year post-procedure, 24 (9.7%) patients with valve-in-valve TAVI and 598 (10.3%) patients with native valve TAVI, respectively, died. The corresponding numbers at 5 years post-procedure were 71 (28.7%) and 1968 (33.8%) patients, respectively. The cumulative 5-year risk of death was 42.5% (95% CI: 34.2% to

50.6%) in patients with valve-in-valve-TAVI and 44.8% (95%% CI: 43.2% to 46.4%) in patients with TAVI in a native valve (Figure 2A). In multivariable Cox proportional hazard analysis, patients undergoing valve-in-valve-TAVI did not have a significantly different rate of death from any cause than those undergoing native valve TAVI at 30 days (HR 0.95 [95% CI 0.41-2.19]), 1 year (HR 0.96 [95% CI 0.63-1.45]) and 5 years (HR 0.79 [95% CI 0.62-1.00]).

Rehospitalizations

Overall, the number of rehospitalizations from any cause, and from cardiovascular causes, was not significantly lower in the group of patients with valve-in-valve TAVI compared with native-valve TAVI at 30 days, 1 year, and 5 years post-procedure (Table 2). Figure 2B depicts Kaplan-Meier curves for rehospitalizations for patients with valve-in-valve TAVI and native valve TAVI. Within 30 days post-procedure, a total of 40 (16.6%) patients with valve-in-valve-TAVI and 1,131 (19.9%) patients with native valve TAVI were hospitalized from any cause. 5 years after the procedure, 182 (75.5%) patients with valve-in-valve TAVI and 4,433 patients (78.1%) with native valve TAVI had a hospitalization. In multivariable Cox proportional hazard analysis, patients with valve-in-valve TAVI did not have a significantly different risk of rehospitalization from any cause than those undergoing native valve TAVI at 30 days (HR 0.80 [95% CI 0.58-1.10]), at 1 year (HR 0.80 [95% CI 0.66-0.97]) and at 5 years (HR 0.85 [95% CI 0.73-0.99]). Patients with valve-in-valve TAVI did not have a significantly different risk of rehospitalization from cardiovascular causes than those undergoing native valve TAVI at 30 days (HR 0.89 [95% CI 0.54-1.46]), 1 year (HR 0.86 [95% CI 0.64-1.14]), and 5 years (HR 0.87 [95% CI 0.76-1.01]).

Sensitivity analysis

A number of sensitivity analyses were performed to test the robustness of our findings: (i) To account for potential collinearity, we did an adjusted multivariable Cox proportional hazard analysis and found no significantly different rate of death and rehospitalization from any cause or rehospitalization from cardiovascular causes at 30 days, 1 year and 5 years. (ii) To account for potential differences in baseline characteristics and residual confounding, we matched patients undergoing valve-in-valve TAVI with individuals undergoing a native valve TAVI. In total, 225 patients with valve-in-valve TAVI were matched with 450 patients with native valve TAVI. The median age of the study population was 80 (25^{th}-75^{th} percentile 77-84), and 57% were men. Baseline characteristics of the matched population are displayed in Supplementary Table 1. Mortality and readmissions at 30 days, 1 year, and 5 years are shown in Supplementary Table 2. The cumulative 30-day risk of death was 1.8% (95% CI: 0.6 to 4.2%) in patients with valve-in-valve TAVI in a failed surgical aortic prosthesis and 2.2% (95% CI: 1.1 to 3.9%) in patients with native valve TAVI (Supplementary Figure 1A). Correspondingly, the 5-year risk of death was 41.8% (95% CI: 33.1% to 50.3%) in patients with valve-in-valve TAVI and 44.4% (95% CI: 38.4% to 50.2%) in patients with native valve TAVI. Supplementary figure 1B depicts Kaplan-Meier curves for rehospitalizations for patients with valve-in-valve TAVI and native valve TAVI. In line with the main analysis, patients undergoing valve-in-valve TAVI did not have a significantly different rate of death from any cause and rehospitalizations from any cause, and from cardiovascular causes, compared with patients undergoing native valve TAVI (Supplementary Table 2).

DISCUSSION

In this Danish nationwide real-world cohort study, we compared clinical outcomes post-TAVI procedure between patients with a failed surgical aortic prosthesis and patients with a native valve. The principal findings of this study were: (1) Patients undergoing valve-in-valve TAVI were younger but had a greater burden of cardiovascular comorbidities (higher prevalence of heart failure, ischemic heart disease and atrial fibrillation) and were more frail compared with those undergoing native valve TAVI; (2) valve-in-valve TAVI was not associated with a significantly different rate of death and rehospitalizations from any cause, and from cardiovascular causes, compared with native valve TAVI, although the rates, numerically, were lower in those undergoing valve-in-valve TAVI and patients were frailer compared with those undergoing native valve TAVI.

Patient characteristics

With ongoing research focused on valve-in-valve-procedures, the number of procedures is growing, which makes it even more important to examine outcomes and patient characteristics in an all-comer cohort. In our study, we found that patients with valve-in-valve TAVI were younger, had more cardiovascular comorbidities and a greater degree of frailty. Furthermore, the number of patients, who had a prior CABG was 93 (37.7%) of patients with valve-in-valve TAVI and 593 (10.2%) of patients with native valve TAVI.

Current clinical guidelines present valve-in-valve TAVI as an established treatment option for a failed surgical aortic prosthesis, although it is not always appropriate or feasible due to complications like incompatible surgical valve design, which can cause coronary occlusion, which makes redo-SAVR a more beneficial option.[3] Therefore, patients with a very high priori risk for coronary occlusion in case of valve-in-valve TAVI may be not offered TAVI. On the other hand, patients with prior CABG are protected from this risk. This could mean that patients selected for

valve-in-valve TAVI may be going through a more thorough patient selection. However, patients undergoing valve-in-valve TAVI still had higher baseline comorbidities, which are independently associated with higher morbidity and mortality.

Mortality and rehospitalizations

Observational studies have shown that redo-SAVR is a high-risk procedure to patients with a failed surgical aortic prosthesis, and observational studies comparing valve-in-valve TAVI to redo SAVR have shown that valve-in-valve TAVI is associated with better short-term outcomes i.e. all-cause mortality, in-hospital composite adverse outcomes such as myocardial infarction, stroke and major bleeding, and reduced length of hospital stay.[7–10,13] Though, there is a lack of randomized controlled trials examining valve-in-valve TAVI, and this could be due to the difficult setup and that such a setup could be considered unethical. However, current data could indicate that valve-in-valve TAVI is a safe procedure in patients with no contraindications, but an important comparison would be to evaluate valve-in-valve TAVI compared with native valve TAVI.

Previous studies have shown valve-in-valve TAVI to have similar short-term mortality rates as native valve TAVI, which is also consistent with our results.[12,20] In our study, we evaluated the short-term and long-term mortality and found no significantly different rates of readmission and mortality for valve-in-valve TAVI at short-term and long-term follow-up. Although the procedure and the techniques are similar in the two procedures, valve-in-valve TAVI is a treatment of patients at a different stage of the disease. To overcome this limitation of potential more thorough patient selection of patients undergoing valve-in-valve TAVI, we performed a sensitivity analysis in which we carefully matched the two groups. Our data did not show a significantly different risk of death and readmissions at long-term in valve-in-valve TAVI compared with native valve TAVI. The cumulative 30-day risk of death was lower in patients with valve-in-valve TAVI, although in Cox

regression analysis, 30-day mortality risk of death was not significant different in the group with valve-in-valve TAVI compared to native valve TAVI, which could be due to higher risk of complication during valve-in-valve TAVI procedure. However, in the sensitivity analysis with matched population, the cumulative 30-day incidence of death was similar. The 30-days risk of readmissions were lower in the group with valve-in-valve TAVI compared with native valve TAVI. In general, our findings underline that mortality and readmission rates are not significantly different for valve-in-valve TAVI compared with native valve TAVI, indicating that valve-in-valve TAVI is a safe procedure, although there is a need for more data.

Strengths and limitations

The main strength of this study is the large nationwide cohort of patients undergoing valve-in-valve TAVI and native valve TAVI in a real-world setting with long-term follow-up. In Denmark, the health care system is funded by taxes and provides equal access to health care for all residents regardless of insurance. However, data on characteristics and complications in relation to procedures were not available in this study, including hemodynamic performance and salvage SAVR. Since the number of patients available for the analysis of rehospitalizations was low at 5 years after the procedure in the ViV arm, the 5-year cumulative incidence estimate of this outcome may be less reliable. There is the lack of granularity and the missing information on the type and mechanism of failed surgical bioprostheses failure that precludes any inference on the interplay between the specific anatomical scenario and the clinical outcomes. Furthermore, the study has limitations inherent to all non-randomized observational studies, including the possibility of residual confounding and confounding by indication. Although we did try to minimize the former by carefully matching the groups, the possibility of residual confounding cannot be precluded. In addition to its retrospective nature, the relatively long study period may have introduced time

selection and learning curve biases. However, our results are in line with those reported in previous studies.[12,20]

CONCLUSIONS

TAVI in a failed surgical aortic prosthesis as compared to TAVI in a native valve, was not associated with significantly different short- and long-term mortality, suggesting that valve-in-valve-TAVI is a safe procedure.

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Figure legends

Figure 1: Flow chart of the study population selection process

Abbreviations: TAVI transcatheter aortic valve implantation; *SAVR* surgical aortic valve replacement.

Figure 2: Mortality and readmissions after TAVI in a native valve or in a failed surgical aortic prosthesis

A) Mortality in patients with TAVI in a failed surgical aortic prosthesis or in a native valve

B) Readmissions in patients with TAVI in a failed surgical aortic prosthesis or in a native valve.

Abbreviations: TAVI transcatheter aortic valve implantation; *SAVR* surgical aortic valve replacement.

TABLES AND FIGURES

Table 1: Baseline characteristics of study population

	Patients with TAVI in a failed surgical aortic prosthesis n = 247	**Patients with TAVI in a native valve n = 5823**
Demographics, N (%)		
Age, years, median (25th-75th percentile)	80 (76-84)	82 (77-85)
Male, N (%)	138 (55.9)	3206 (55.1)
Comorbidities/medical history, N (%)		
Heart failure	115 (46.6)	1770 (30.4)
Ischemic heart disease	161 (65.2)	2932 (50.4)
Stroke	31 (12.6)	791 (13.6)
Atrial fibrillation	111 (44.9)	2000 (34.4)
Peripheral artery disease	24 (9.7)	467 (8.0)
Hypertension	188 (76.1)	4183 (71.8)
Diabetes	48 (19.4)	1189 (20.4)
Malignancy	49 (19.8)	1234 (21.2)
Chronic kidney disease	26 (10.5)	611 (10.5)
Chronic obstructive pulmonary disease	40 (16.2)	918 (15.8)
Liver disease	8 (3.2)	169 (2.9)
Prior coronary artery bypass graft surgery	93 (37.7)	593 (10.2)
Prior pacemaker implantation	25 (10.1)	549 (9.4)
Frailty risk group, N (%)		
High	10 (4.1)	226 (3.9)
Intermediate	102 (41.3)	1659 (28.5)
Low	135 (54.7)	3938 (67.6)
Concomitant pharmacotherapy, N (%)		

Loop diuretics	167 (67.6)	3005 (51.6)
Thiazides	34 (13.8)	1077 (18.5)
MRA	33 (13.4)	509 (8.7)
Aspirin	126 (51.0)	2710 (46.5)
ADP-receptor inhibitors	50 (20.2)	1447 (24.9)
Beta-blockers	136 (55.1)	2897 (49.8)
Calcium-blockers	83 (33.6)	1910 (32.8)
Oral anticoagulants	92 (37.3)	1913 (32.9)
RAS-inhibitors	132 (53.4)	3104 (53.3)
Statins	178 (72.1)	3691 (63.4)
Access, N (%)		
Transaortic	4 (1.6)	198 (3.4)
Transapical	27 (10.9)	704 (12.1)
Transfemoral	216 (87.5)	4921 (84.5)
Year of procedure, N (%)		
2008-2010	9 (3.6)	382 (6.6)
2011-2013	21 (8.5)	836 (14.4)
2014-2016	62 (25.1)	1439 (24.7)
2017-2020	155 (62.8)	3166 (54.4)

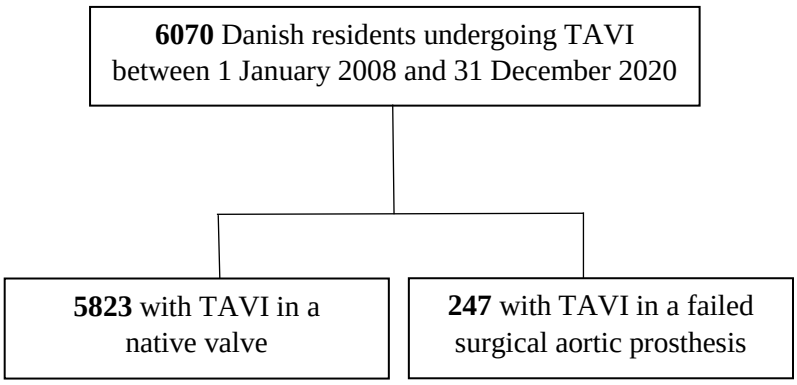
TAVI transcatheter aortic valve implantation, *ADP* adenosine diphosphate, *RAS* renin-angiotensin system

Table 2: Mortality and readmissions after TAVI in a native valve or in a failed surgical aortic prosthesis

	Patients with TAVI in a failed surgical aortic prosthesis n = 247	**Patients with TAVI in a native valve n = 5823**	**Hazard ratio (95% CI) ***
30-day mortality	6 (2.4%)	157 (2.7%)	0.95 (0.41-2.19)
1-year mortality	24 (9.7%)	598 (10.3%)	0.96 (0.63-1.45)
5-year mortality	71 (28.7%)	1968 (33.8%)	0.79 (0.62-1.00)
30-day hospital admissions	40 (16.6%)	1131 (19.9%)	0.80 (0.58-0.99)
1-year hospital admissions	113 (46.9%)	2977 (52.4%)	0.80 (0.66-0.97)
5-year hospital admissions	182 (75.5%)	4433 (78.1%)	0.85 (0.73-0.99)
30-day cardiovascular admissions	17 (7.1%)	452 (8.0%)	0.89 (0.54-1.46)
1-year cardiovascular admissions	51 (21.2%)	1288 (22.7%)	0.86 (0.64-1.14)
5-year cardiovascular admissions	94 (39.0%)	2260 (39.8%)	0.87 (0.76-1.01)

*Hazard ratios (HR) are adjusted for age (included as a categorical variable: <76 years, 76-80 years, 81-85 years and ≥86 years), sex, year of procedure (included as a categorical variable: 2008-2010, 2011-2013, 2014-2016 and 2017-2020), ischemic heart disease, heart failure, atrial fibrillation, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, CABG, frailty, and liver disease. TAVI in a native valve is used as reference. *TAVI* transcatheter aortic valve implantation.

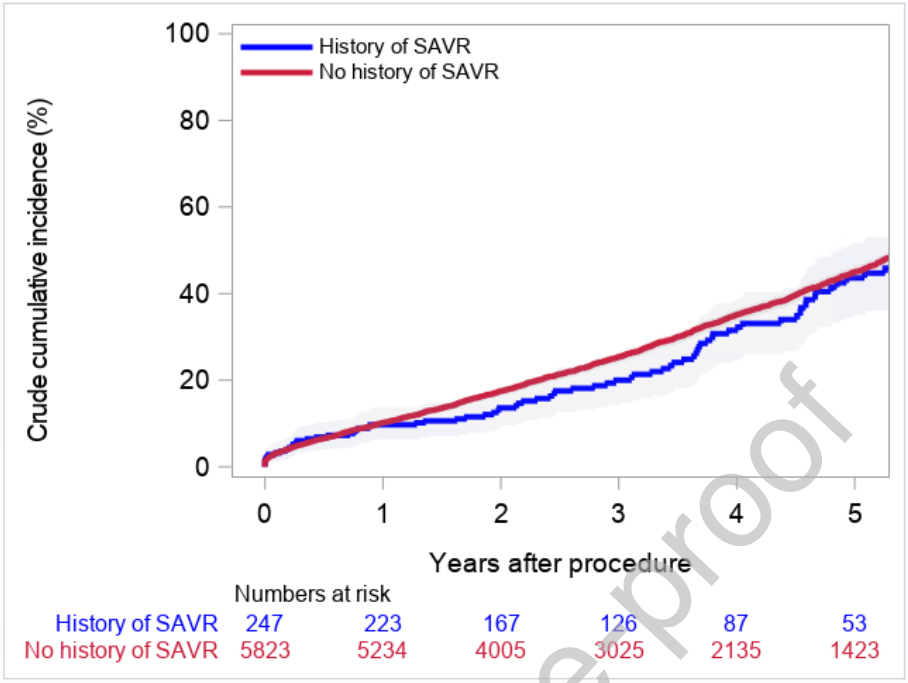
Figure 1: Flow chart of the study population selection process



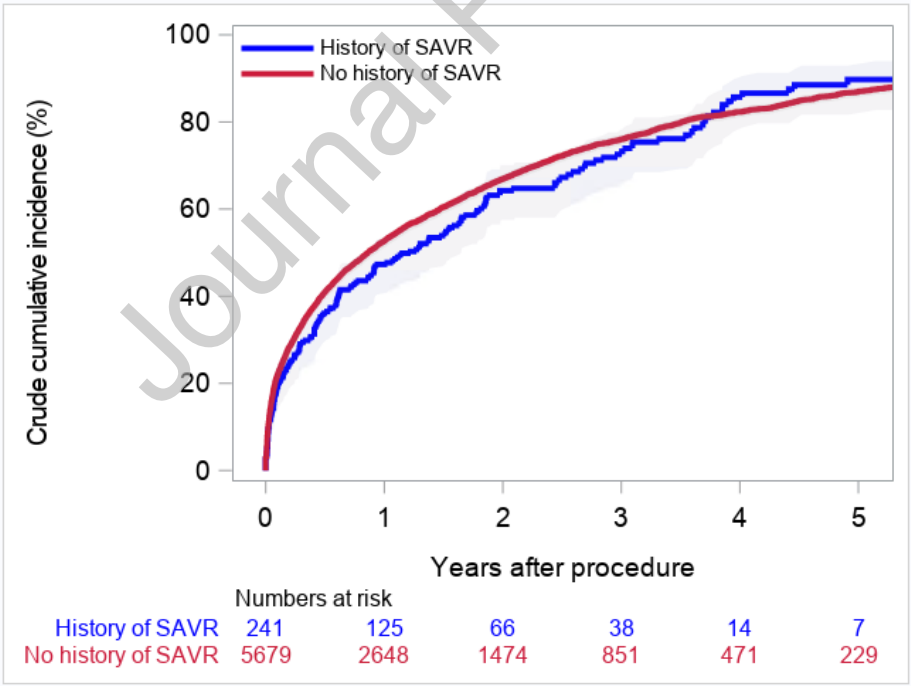
TAVI transcatheter aortic valve implantation; *SAVR* surgical aortic valve replacement.

Figure 2: Mortality and readmissions after TAVI in a native valve or in a failed surgical aortic prosthesis

A



B



A) Mortality in patients with TAVI in a failed surgical aortic prosthesis or in a native valve **B)** Readmissions in patients with TAVI in a failed surgical aortic prosthesis or in a native valve. TAVI transcatheter aortic valve implantation; *SAVR* surgical aortic valve replacement.