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Brief title: ViV TAVR versus redo SAVR.

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Conflict of Interest Disclosures
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Abstract
Background Valve in Valve (VIV) Transcatheter aortic valve replacement (TAVR) and redo surgical aortic valve replacement (SAVR) represent the two treatments for aortic bioprosthesis failure. Clinical comparison of both therapies remains limited by the number of patients analyzed.
Objective The objective of this study was to analyze the outcomes of VIV TAVR versus redo SAVR at a nationwide level in France.
Methods Based on the French administrative hospital-discharge database, the study collected information for patients treated for aortic bioprosthesis failure with isolated VIV TAVR or redo SAVR between 2010 and 2019. Propensity score matching was used for the analysis of outcomes.
Results A total of 4327 patients were found in the database. After matching on baseline characteristics, 717 patients were analyzed in each arm. At 30 days VIV TAVR was associated with lower rates of the composite of all-cause mortality, all-cause stroke, myocardial infarction and major or life-threatening bleeding (OR 0.62, 95% CI 0.44-0.88, p=0.03). During follow-up (median 516 days), the combined endpoint of cardiovascular death, all-cause stroke, myocardial infarction or rehospitalization for heart failure was not different between the two groups (OR 1.18, 95% CI 0.99–1.41, p=0.26). Rehospitalization for heart failure and pacemaker implantation were more frequently reported in the VIV TAVR group. A time-dependent interaction between all-cause and cardiovascular mortality following VIV TAVR was reported (p-interaction <0.05).
Conclusion We observed that VIV TAVR was associated with better short-term outcomes than redo SAVR. Major cardiovascular outcomes were not different between the two treatments during long term follow up.

Condensed abstract: We analyzed the outcomes of VIV TAVR versus redo SAVR in a propensity-matched analysis at a nationwide level in France. At 30 days, VIV TAVR was associated with a lower rate of major clinical events (composite of all-cause mortality, all-cause stroke, myocardial infarction, major or life-threatening bleeding) (OR 0.62, 95% CI 0.44-0.88, p=0.03). During follow-up, the combined endpoint of cardiovascular death, all-cause stroke, myocardial infarction or rehospitalization for heart failure was not different between VIV TAVR and redo SAVR group (OR 1.18, 95% CI 0.99–1.41, p=0.26). Overall, outcomes of VIV TAVR were significantly improved since 2015.

Key words: Valve in valve, TAVR, aortic bioprosthesis.

Abbreviations
Commission Nationale de l'Informatique et des Libertés (CNIL)
Confidence intervals (CIs)
Incidence Rate Ratios (IRR)
International Classification of Diseases, Tenth Revision (ICD-10)
Odd ratios (OR)
Programme de Médicalisation des Systèmes d'Information (PMSI)
Surgical aortic valve replacement (SAVR)
Standard deviation (SD)
Transcatheter aortic valve replacement (TAVR)
Valve in Valve (VIV)

Introduction

Worldwide bioprosthetic aortic surgical valve are increasingly favored over mechanical prosthesis. However, bioprosthesis durability is limited over time, with a risk of structural valve degeneration, represented by restenosis or regurgitation or both within 10 to 20 years (1-3). In those patients, according to ESC guidelines the treatment of choice is a redo surgical aortic valve replacement (SAVR) (4). However, compared to primary AVR, this procedure is associated with higher morbidity and mortality, mostly due to technical aspects of redo surgery, advanced age, and associated co-morbidities (5, 6).

Transcatheter aortic valve replacement (TAVR) has emerged as the recommended treatment for severe native aortic stenosis in high surgical risk patients (4, 7). Recent data have also shown that TAVR is non-inferior to surgery in low- and intermediate-risk patients (8, 9). Improvement of this technique has offered an alternative to treat degenerated surgical aortic bioprosthetic valves. Valve in valve (VIV) TAVR proved to be a technically feasible option in most of the cases and is associated with reasonable outcomes in those patients. Therefore, VIV TAVR procedures have increased over the last years and are expected to continue growing.

The French Programme de Médicalisation des Systèmes d'Information (PMSI), a mandatory administrative database, offers a unique opportunity to assess exhaustive and comprehensive data on all consecutive TAVR and SAVR performed in France. Therefore, based on this large, nationwide, administrative French database, we aimed to compare long term outcomes of VIV TAVR versus redo SAVR.

Methods

Study design

This longitudinal cohort study was based on the national hospitalization database

covering hospital care from the entire French population. The data for all patients admitted with aortic stenosis in France from January 2010 to June 2019 were collected from the national administrative PMSI database, which was inspired by the US Medicare system. Through this program, which was implemented in 2004, medical activity is recorded in a database, computed, and rendered anonymous. It includes more than 98% of the French population (67 million people) from birth (or immigration) to death (or emigration), even if a person changes occupation or retires. This process allows the determination of each hospital's budget, in the 1546 French healthcare facilities for both public and private hospitals. Each hospitalization is encoded in a standardized dataset, which includes information about the patient (age and sex), hospital, stay (date of admission, date of discharge, and mode of discharge), pathologies, and procedures. Routinely collected medical information includes the principal diagnosis and secondary diagnoses. In the PMSI system, identified diagnoses are coded according to the International Classification of Diseases, Tenth Revision (ICD-10). All medical procedures are recorded according to the national nomenclature, Classification Commune des Actes Medicaux (CCAM). The PMSI contains individual pseudoanymised information on each hospitalization that are linked to create a longitudinal record of hospital stays and diagnoses for each patient. The reliability of PMSI data has already been assessed and this database has previously been used to study patients with cardiovascular conditions, including those with aortic stenosis treated with TAVR (10-12).

The study was conducted retrospectively and, as patients were not involved in its conduct, there was no impact on their care. Ethical approval was not required, as all data were anonymized. The French Data Protection Authority granted access to the PMSI data. Procedures for data collection and management were approved by the Commission Nationale de

l'Informatique et des Libertés (CNIL), the independent National Ethical Committee protecting human rights in France, which ensures that all information is kept confidential and anonymous, in compliance with the Declaration of Helsinki (authorization number 1897139).

Study population

From 1 January 2010 to 30 June 2019, 520,662 adults (age ≥18 years) were hospitalized with a diagnosis of aortic stenosis (I350, I352, I060, and I062 using ICD-10 codes) as the principal diagnosis (i.e., the health problem that justified admission to hospital), the related diagnosis (i.e., potential chronic disease or health state during the hospital stay), or a significantly associated diagnosis (i.e., comorbidity or associated complication) and among them, 4327 patients were identified as having a history of surgically implanted aortic bioprothesis needing reintervention (for regurgitation or stenosis) with either SAVR or TAVR. For the analysis of TAVR procedures, we included all adults with a single percutaneous procedure (Classification Commune des Actes Medicaux code: DBLF001). We thus restricted the analysis to patients with previous bioprosthetic surgical aortic replacement who underwent either a TAVR or an isolated redo aortic surgery. Patient information (demographics, comorbidities, medical history, and events during hospitalization or follow-up) was described using data collected in the hospital records. For each hospital stay, combined diagnoses at discharge were obtained. Each variable was identified using ICD-10 codes. Based on this database, we were able to estimate a proxy of the EuroSCORE II (Supplemental File and Supplemental Figure 1). We also used the Charlson Comorbidity Index and the Claims-based Frailty Indicator to assess patient clinical status (13-15). Exclusion criteria were age <18 years.

Outcomes

Patients were followed until 30 June 2019 for the occurrence of outcomes. We aimed to

evaluate the incidence of all-cause death, cardiovascular death, all-cause stroke, rehospitalization for heart failure, myocardial infarction, major or life-threatening bleeding, new onset of atrial fibrillation and pacemaker implantation. Definitions of events respected the Valve Academic Research Consortium-2 consensus document (16). To increase validation of our analysis, we also evaluated incidence rates of non-cardiovascular death, cancer and urinary infection as negative control endpoints. The endpoints were evaluated with follow-up starting from date of either VIV TAVR or redo surgery until date of each specific outcome or date of last news in the absence of the outcome. Information on outcomes during follow-up was obtained by analysing the PMSI codes for each patient. All-cause death, heart failure, all-cause stroke, myocardial infarction, major or life-threatening bleeding, new onset of atrial fibrillation and permanent pacemaker implantations were identified using their respective ICD-10 or procedure codes. Mode of death (cardiovascular or non-cardiovascular) was identified based on the main diagnosis during hospitalization resulting in death. Rehospitalization was considered to be due to heart failure when heart failure was recorded as the first diagnosis. We also evaluated 30-day major clinical events in our analysis, which was a combination of all-cause mortality, all-cause stroke, myocardial infarction, major or life-threatening bleeding. A combined endpoint (cardiovascular death, all cause stroke, myocardial infarction and rehospitalization for heart failure) was evaluated for the long-term follow-up.

Statistical analysis

Qualitative variables are described as frequency and percentages and quantitative variable as means (standard deviations [SDs]). Comparisons were made using chi-square tests for categorical variables and the Student *t* test or non-parametric Kruskal–Wallis test, as appropriate, for continuous variables.

Owing to the non-randomized nature of the study, and considering for significant differences in baseline characteristics and year of implantation, propensity-score matching was used to control for potential confounders of the treatment outcome relationship. Propensity scores were calculated using logistic regression with treatment (i.e. VIV TAVR or redo surgery) as the dependent variable. The propensity score included all baseline characteristics listed in table 1. For each patient with VIV TAVR, a propensity score-matched patient with redo surgery was selected (1:1) using the one-to-one nearest neighbour method (with a calliper of 0.01 of the SD of the propensity score on the logit scale) and no replacement. We assessed the distributions of demographic data and comorbidities in the two cohorts with standardized mean differences, which were calculated as the difference in the means or proportions of a variable divided by a pooled estimate of the SD of that variable. A standardized mean difference of 5% or less indicated a negligible difference between the means of the two cohorts (Supplemental Figure 2 and 3).

For the analysis in the matched cohort, we report outcomes at 30 days and during whole follow up. A logistic regression model was used for all outcomes at 30 days and odds ratio (OR) were reported. The incidence rates (%/year) for each outcome of interest during follow-up was estimated in both groups and compared using incidence rate ratios. The corresponding asymptotic two-sided 95% confidence interval (CI) of the incidence rate ratio (IRR) was reported. P values are reported without and with correction for multiple comparisons using Bonferroni correction. A propensity score adjusted multivariable analysis for clinical outcomes during the whole follow-up in the unmatched cohort of patients was also performed using a Cox model and reporting hazard ratio. All comparisons with $p<0.05$ were considered statistically significant. All analyzes were performed using Enterprise Guide 7.1, (SAS Institute Inc., SAS

Campus Drive, Cary, North Carolina), USA and STATA version 12.0 (Stata Corp, College Station, TX).

Results

Baseline characteristics

Between 1 January 2010 and 30 of June 2019, 4327 patients were identified in the database, including 1773 patients (40.9 %) with redo surgical aortic valve replacement and 2554 patients with VIV TAVR (**Table 1**). In the unmatched population, patients treated with VIV TAVR were less frequently men, were older, and had higher Charlson comorbidity, frailty and EuroSCORE II indexes (**Table 1**). Aortic regurgitation and previous endocarditis were more often reported in redo SAVR group. Patients treated with VIV TAVR also had higher rates of previous pacemaker or defibrillator, chronic kidney and lung diseases (Table 1). Of note patients with redo surgery were more often included in the early years of the analysis, while VIV TAVR were more often included later.

After propensity score matching, there were 717 patients in each group. Baseline characteristics in these populations were well matched (**Table 2**, Supplemental Figure 1 and 2).

Clinical outcomes at 30 days.

In the unmatched population, all-cause death was reported in 122 (6.9%) patients with redo SAVR and 83 (3.3%) in VIV TAVR. In the matched population, all-cause death was reported in 52 (7.3%) patients with redo SAVR and 26 (3.6%) in VIV TAVR (OR 0.48, 95% CI 0.30-0.78; **Table 3**). Cardiovascular death (6.6% vs. 2.9%, OR 0.43, 95% CI 0.25-0.73), new onset of atrial fibrillation (4.0% vs. 0.6%, OR 0.13, 95% CI 0.05-0.38) were more often reported in redo SAVR group. Permanent pacemaker implantation (4.6% vs. 16.7%, OR 4.20, 95% CI 2.91-6.07) were less often reported after redo SAVR. Rates of all cause stroke (0.4% vs. 1.0%,

OR 2.35, 95% CI 0.60-9.11), myocardial infarction (0.4% vs. 0.1%, OR 0.33, 95% CI 0.03-3.20) and major or life-threatening bleeding (4.7% vs. 4.0%, OR 0.85, 95% CI 0.51-1.41) were not different between the two groups. The composite of major clinical events was observed in 12.6% of redo SAVR and 8.2% of VIV TAVR (OR 0.62, 95% CI 0.44-0.88).

Long term outcomes

Mean (SD) follow-up was 760 (795) days, (median [interquartile range] 516 [56-1208 days]) in the whole unmatched cohort. In the matched population, follow-up was 794 [675] days in redo SAVR group and 786 [819] days in VIV TAVR group (p=0.84). In the matched population, all-cause death was recorded in 317 patients (9.5% in redo SAVR versus 10.9% in VIV TAVR group; **Table 4, Figure 1A**). The incidence of cardiovascular death (IRR 1.04, 95% CI 0.75–1.44; **Table 4, Figure 1B**), all cause stroke (IRR 1.34, 95% CI 0.84–2.15, **Table 3**) myocardial infarction (IRR 1.41, 95% CI 0.72–2.79, **Table 3**) and new onset of atrial fibrillation (IRR 0.85 95% CI 0.59–1.21, **Figure 2A**) were not statistically different between the two groups (**Table 4**); while rehospitalization for heart failure (IRR 1.37, 95% CI 1.10–1.71; Table 4 and **Figure 2B**) and permanent pacemaker implantation (IRR 2.66, 95% CI 2.05–3.47; **Figure 2C**) were more frequently reported in the VIV TAVR group. The combined endpoint (cardiovascular death, all-cause stroke, myocardial infarction or rehospitalization for heart failure) was not significantly different between group (18.6% vs. 21.9% OR 1.18, 95% CI 0.99–1.41, **Table 4, Central Illustration**).

For the negative control analysis, there was no statistical difference between patients with VIV TAVR or redo surgery for the incidence of cancer, urinary infection or non-cardiovascular death (**Table 4**).

We performed an analysis of the outcomes according to the time period (before or after

1st January 2015) presented in Supplemental Tables 1 and 2. A significant interaction between period of treatment and all cause death (p interaction 0.04), cardiovascular death (p interaction 0.007) and the combined endpoint (p interaction 0.04) was observed. While those outcomes were more frequently observed after VIV TAVR than redo SAVR between 2010 to 2015, the opposite trend was reported during the second period (2015 to 2019). Regarding surgical risk, we found a significant interaction for cardiovascular death (p interaction 0.01), with TAVR associated with a lower risk than SAVR for patients at higher risk (estimated EuroSCORE II > 5%), and the opposite trend for patients at lower risk (Supplemental Table 3). Analysis according to previous coronary artery bypass graft is presented in Supplemental Table 4. A propensity score adjusted multivariable analysis for clinical outcomes during the whole follow-up in the unmatched cohort of patients is provided in Supplemental Table 5 and results were consistent with those obtained with 1:1 matching.

Discussion

In this propensity score-matched analysis, VIV TAVR was associated with lower rates of 30 days outcomes compared with redo SAVR for failed surgically implanted bioprosthetic aortic valve. However, in the long-term no significant difference on the incidence of the composite endpoint of cardiovascular death, all-cause stroke, myocardial infarction, rehospitalization for heart failure was observed between the two groups (**Central Illustration**). Our study is, to our knowledge, the largest one reporting outcomes with these two therapeutic options in this population of unselected patients seen at a nationwide level.

Bioprosthetic aortic valves are increasingly favored in comparison with mechanical devices for the surgical treatment of severe aortic valve disease. This worldwide trend is mainly driven by the possible avoidance of long-life anticoagulant in case of bioprosthesis (when not

needed for other reasons) (17). However, despite improvements in devices, the risk of structural valve degeneration of the current bioprostheses remains one of the main limitations in the long term (1-3). Because redo SAVR procedure carries significant risks, VIV TAVR has emerged as a less invasive option in case of failed surgical bioprosthesis. Initial experience has shown acceptable short-term clinical outcomes as well as satisfying echographic data during follow up (18-23). Therefore, new technics are under development to overpass challenges associated with the VIV procedure (24), and will need to be evaluated in a near future.

Our results showed that, in France, patients who underwent VIV TAVR had more frequent comorbidities and were older than patients treated with redo SAVR. Moreover, we observed a trend over time with more VIV TAVR cases in recent years, reflecting the clinical adoption of VIV TAVR at a nationwide level. Short-term outcomes (i.e. 30 days) showed that compared with SAVR, VIV TAVR was associated with lower rates of all cause death, cardiovascular death, new onset of atrial fibrillation and major clinical events. On the other hand, the need for pacemaker implantation was three-fold higher after VIV TAVR. Those rates of events after VIV TAVR were consistent with those seen in registries of selected patients with VIV procedures (18-23). The short-term mortality in the large PARTNER 2 VIV registry, STS/ACC registry and VIVID registry were respectively 2.7%, 2.9% and 7.6% at 30 days. Importantly, early mortality following redo SAVR was higher (7% at 30 days in our cohort), confirming the worse early prognosis previously suspected when indirectly comparing this surgery with standard primary SAVR or VIV TAVR (25). Importantly, our 30 days redo SAVR mortality were higher than reported in literature, likely reflecting the high population included in this analysis (mean EuroSCORE II 4.7% after matching).

Need for permanent pacemaker implantation remains one of the relative Achilles' heel of

TAVR procedure. Recent French data showed 20 to 25% of new pacemaker implantation after native aortic valve TAVR (12). Because the surgical bioprosthesis structure protects the conduction system (if not previously injured), VIV procedures may carry a lower risk of mechanical lesions during TAVR (26, 27). Meanwhile, redo SAVR is associated with significantly higher risk of definite pacemaker than primary SAVR (28, 29). Even if lower than in native aortic valve TAVR, our data showed slightly higher pacemaker implantation rates following VIV TAVR than reported in most of the registries (18, 20, 23, 30). Our analysis offers an exhaustive evaluation of unselected patients and their outcomes. Therefore, these real-life high rates of pacemaker implantation after VIV TAVR provide new and robust insights, which however may need to be further evaluated in other healthcare systems.

Lower risk of cerebral ischemic events on magnetic resonance imaging has been reported after VIV TAVR compared to native aortic valve TAVR (31). The per-procedural risk of stroke associated with TAVR is mainly related to embolization of either aorto-femoral or aortic valve material. Despite numerically higher rates, we did not observe significantly higher 30-day or long-term incidences of stroke after VIV TAVR. Higher rate of early new onset of atrial fibrillation observed after redo SAVR could mitigate those results. The markedly higher risk of atrial fibrillation after SAVR is also a relevant finding in our analysis, since it is known to be associated with a worse prognosis in these patients. This included, but was not limited to peri-procedural atrial fibrillation (32, 33).

Long term follow-up showed more frequent re hospitalization for heart failure in the VIV TAVR group. During the first year following intervention rehospitalization rates were lower in the VIV TAVR group compared to redo SAVR. Then, after this time period the incidence curves did cross and rehospitalization for heart failure increase over time in the VIV TAVR cohort. This

observation may result from more frequent patient prosthesis mismatch and valve thrombosis after VIV TAVR versus redo SAVR (22, 34). Moreover, higher rates of pacemaker need after VIV TAVR may participate in those findings, potentially related to pacing induced cardiomyopathy. Longer follow-up and larger cohorts are required to further evaluate these issues.

A time dependent relation between clinical outcomes and VIV TAVR was observed in our analysis. Indeed, the number of VIV TAVR had a steady rise since 2010 and it is likely that operators were able to improve their procedural outcomes over time. Our adjustment considered year of implantation (and experience of centers volume of TAVR implantation) for limiting a bias related to a possible time effect. A significant interaction between all-cause and cardiovascular death was observed between 2010 to 2015 and 2016 to 2019. In the last period, VIV TAVR was associated with non-significant lower rates of all-cause death than redo SAVR, while significantly lower incidences of cardiovascular death were reported. This supports the need for further and longer evaluation of outcomes with these procedures in these patients. Over these 2 periods (before and after 2015), indications for TAVR have been extended to patients at lower surgical risk (i.e. intermediate and recently low risk). However, the differences and interactions for outcomes were more present when comparing the different periods of the study (i.e. before and after 2015) than when comparing the lower or higher estimated risk of the intervention (i.e. EuroSCORE II < or ≥5).

Limitations

We acknowledge several limitations of our work. A main limitation is inherent to the retrospective, observational nature of the study and its potential biases. Further, the study was based on administrative data, with limitations inherent to such methodology. The PMSI database

contains diagnoses coded using ICD-10, which are obtained at hospital discharge and are the physician's responsibility. Data were not systematically externally checked and this could have caused information bias. However, the large scale of the database is likely to partly compensate this bias and, as coding of complications is linked to reimbursement and is regularly controlled, it is expected to be of good quality. Events included were only in-hospital and we were not able to analyse data for out-of-hospital deaths.

Our large population of patients admitted for either redo SAVR or VIV TAVR procedure likely represents a heterogeneous group of patients admitted with various kinds of illnesses and severities, which may have affected prognosis. We were not able to evaluate specific procedural risk factors such as size and model of primary aortic bioprosthesis, left ventricle ejection fraction, coronary height, graft patency in cases of previous coronary artery bypass or extent of coronary disease. We selected patients with AS or mixed aortic valve disease, and therefore excluded pure aortic regurgitation as SAVR or TAVR indication (lack of reimbursement in France).Further, the non-randomized design of the analysis leaves a risk of residual confounding factors. Definite conclusions for comparisons between groups may not be fully appropriate even though multivariable matching was done, as it cannot fully eradicate the possible confounding variables between these groups. We have been able to estimate the EuroSCORE II, which showed in our cohort satisfying correlation with early clinical outcomes. Moreover, the Charlson comorbidity index and Frailty index were used as risk predictors of all-cause death over a longer term. Another limitation is the lack of information on antithrombotic drug use, as drug therapies were not available in the database.

Our analysis was restricted to the variables present in the database, which meant that characteristics such as mean gradient, valve area, paravalvular leak and body surface area were

not available for analysis. Moreover, we were not able to evaluate post procedural echocardiography data. Recent data indicated that post intervention patient-prothesis mismatch was not associated with 1-year survival (35).

Conclusions

This analysis included the largest propensity matched comparison of VIV TAVR versus redo SAVR for patients with failed surgically implanted aortic bioprosthesis. At 30 days, VIV TAVR was associated with lower rates of outcomes; while in the long-term redo SAVR showed lower incidences of rehospitalization for heart failure. Those results seem to be time-dependent; VIV TAVR being associated with better outcomes in the most recent period (from 2015 to 2019).

Clinical perspectives

Competency in Patient Care and Procedural Skills: In a nationwide propensity matched analysis, all-cause and cardiovascular mortality were lower within 30 days after valve-in-valve (VIV) transcatheter aortic valve replacement (TAVR) than after re-operative surgical AVR, but long-term rehospitalization for heart failure was less frequent in those undergoing re-operative SAVR. Translational Outlook: Randomized trials are needed to determine the optimum approach to degenerated surgically implanted aortic valve bioprostheses, but the continued evolution of TAVR technology is likely to influence the comparative outcomes.

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Figure Legends

Figure 1: Incidences for all cause and cardiovascular death. Incidences for all-cause death (A) and cardiovascular death (B) in patients with a previous prosthesis valve treated with redo SAVR compared with VIV TAVR. VIV: valve in valve; TAVR: transcatheter aortic valve replacement; SAVR: surgical aortic valve replacement.

Figure 2: Incidences for new onset of atrial fibrillation, rehospitalization for heart failure, pacemaker implantation and combined endpoint. Incidences for new-onset atrial fibrillation (A), rehospitalization for heart failure (B) and pacemaker or defibrillator implantation (C) in patients with a previous prosthesis valve treated with redo SAVR compared with VIV TAVR. VIV: valve in valve; TAVR: transcatheter aortic valve replacement; SAVR: surgical aortic valve replacement.

Central Illustration: Incidence of the combined endpoint in long term follow-up. *combined endpoint: cardiovascular death, all-cause stroke, myocardial infarction, rehospitalization for heart failure. VIV: valve in valve; TAVR: transcatheter aortic valve replacement; SAVR: surgical aortic valve replacement.

Table 1: Baseline characteristics in the overall (unmatched) population of patients with a previous prosthesis valve treated with VIV TAVR or redo SAVR.

	Redo SAVR (n=1773)	VIV TAVR (n=2554)	p	SMD, TAVR vs SAVR (%)
Age, years	68.7±12.2	80.6±8.0	<0.0001	114.7
Charlson comorbidity index	4.2±3.1	4.7±2.9	<0.0001	18.2
Frailty index	8.3±7.9	10.6±9.2	<0.0001	27.9
EuroSCORE II	4.4±1.1	4.9±1.0	<0.0001	54.0
Gender (male)	1066(60.1)	1298(50.8)	<0.0001	-19.0
Hypertension	1272(71.7)	2061(80.7)	<0.0001	20.8
Diabetes mellitus	489(27.6)	723(28.3)	0.6	0.7
Heart failure	1050(59.2)	1869(73.2)	<0.0001	30.5
History of pulmonary oedema	342(19.3)	206(8.1)	<0.0001	-32.3
Aortic regurgitation	581(32.8)	695(27.2)	0.0001	-11.9
Mitral regurgitation	416(23.5)	719(28.2)	0.001	11.6
Previous endocarditis	229(12.9)	104(4.1)	<0.0001	-32.0
Dilated cardiomyopathy	270(15.2)	521(20.4)	<0.0001	14.2
Coronary artery disease	907(51.2)	1626(63.7)	<0.0001	25.6
Previous myocardial infarction	219(12.4)	400(15.7)	0.002	9.8
Previous PCI	143(8.1)	695(27.2)	<0.0001	51.8

Previous CABG	410(23.1)	499(19.5)	0.004	-8.8
Vascular disease	581(32.8)	1026(40.2)	<0.0001	15.4
Atrial fibrillation	1045(58.9)	1505(58.9)	0.99	0.1
Previous pacemaker or Defibrillator	276(15.6)	743(29.1)	<0.0001	33.2
Ischemic stroke	92(5.2)	138(5.4)	0.76	1.1
Intracranial bleeding	31(1.7)	50(2.0)	0.62	1.4
Smoker	296(16.7)	283(11.1)	<0.0001	-16.4
Dyslipidaemia	849(47.9)	1331(52.1)	0.01	9.3
Obesity	482(27.2)	694(27.2)	0.99	0.3
Alcohol related diagnoses	113(6.4)	142(5.6)	0.26	-3.2
Abnormal renal function	181(10.2)	554(21.7)	<0.0001	31.7
Lung disease	402(22.7)	690(27.0)	0.001	9.4
Sleep apnoea syndrome	154(8.7)	280(11.0)	0.01	7.2
COPD	248(14.0)	426(16.7)	0.02	7.4
Liver disease	128(7.2)	175(6.9)	0.64	-1.5
Gastroesophageal reflux	70(3.9)	88(3.4)	0.39	-2.6
Thyroid diseases	210(11.8)	454(17.8)	<0.0001	16.8
Inflammatory disease	136(7.7)	294(11.5)	<0.0001	13.2
Anaemia	575(32.4)	940(36.8)	0.003	9.0
Previous cancer	201(11.3)	507(19.9)	<0.0001	23.4
VIH infection	4(0.2)	7(0.3)	0.76	0.8
Balloon-expandable TAVR	-	1118(43.8)	-	-

Self-expandable TAVR	-	1436(56.2)	-	-
Year of inclusion	2013(2011-2015)	2015(2013-2017)	<0.0001	114.7
Yearly number of TAVR by institution	160.3±101.3	158.3±90.7	0.51	18.2

Values are n (%), mean±SD or median (IQR) for year of inclusion. CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; PCI=percutaneous coronary intervention; SD=standard deviation; SMD=standardized mean difference; SAVR=surgical aortic valve replacement. TAVR=transcatheter aortic valve replacement.

Table 2: Baseline characteristics in the matched population of patients with a previous prosthesis valve treated with VIV TAVR or redo SAVR.

	Redo SAVR (n=717)	VIV TAVR (n=717)	p	SMD, TAVR vs SAVR (%)
Age, years	74.5±8.2	74.9±9.7	0.33	4.5
Charlson comorbidity index	4.5±3.1	4.7±3.0	0.18	7.1
Frailty index	9.2±8.3	9.7±8.7	0.23	6.3
EuroSCORE II	4.7±1.0	4.7±1.0	0.46	4.0
Gender (male)	414(57.7)	402(56.1)	0.52	-3.4
Hypertension	558(77.8)	569(79.4)	0.48	3.6
Diabetes mellitus	217(30.3)	227(31.7)	0.57	3.1
Heart failure	474(66.1)	472(65.8)	0.91	-0.6
History of pulmonary oedema	92(12.8)	115(16.0)	0.08	9.5
Aortic regurgitation	220(30.7)	223(31.1)	0.86	0.9
Mitral regurgitation	179(25.0)	190(26.5)	0.51	3.5
Previous endocarditis	67(9.3)	66(9.2)	0.93	-0.5
Dilated cardiomyopathy	122(17.0)	121(16.9)	0.94	-0.4
Coronary artery disease	409(57.0)	408(56.9)	0.96	-0.3
Previous myocardial infarction	107(14.9)	105(14.6)	0.88	-0.8
Previous PCI	97(13.5)	103(14.4)	0.65	2.3
Previous CABG	160(22.3)	178(24.8)	0.26	6.1

Vascular disease	263(36.7)	266(37.1)	0.87	0.9
Atrial fibrillation	436(60.8)	439(61.2)	0.87	0.9
Previous pacemaker or Defibrillator	152(21.2)	160(22.3)	0.61	2.7
Ischemic stroke	36(5.0)	38(5.3)	0.81	1.2
Intracranial bleeding	9(1.3)	11(1.5)	0.65	2.1
Smoker	109(15.2)	99(13.8)	0.45	-4.0
Dyslipidaemia	379(52.9)	388(54.1)	0.63	2.5
Obesity	201(28.0)	218(30.4)	0.32	5.3
Alcohol related diagnoses	45(6.3)	55(7.7)	0.3	5.9
Abnormal renal function	109(15.2)	114(15.9)	0.72	1.9
Lung disease	186(25.9)	193(26.9)	0.68	2.3
Sleep apnoea syndrome	84(11.7)	80(11.2)	0.74	-1.9
COPD	114(15.9)	117(16.3)	0.83	1.2
Liver disease	50(7.0)	60(8.4)	0.32	5.5
Gastroesophageal reflux	24(3.3)	31(4.3)	0.34	5.2
Thyroid diseases	101(14.1)	103(14.4)	0.88	0.8
Inflammatory disease	77(10.7)	67(9.3)	0.38	-4.7
Anaemia	262(36.5)	277(38.6)	0.41	4.4
Previous cancer	112(15.6)	112(15.6)	1	0.0
VIH infection	2(0.3)	3(0.4)	0.65	2.8
Balloon-expandable TAVR	-	335(46.7)	-	-
Self-expandable TAVR	-	382(53.3)	-	-

Year of inclusion	2014(2012-2016)	2014(2012-2016)	0.21	4.5
Yearly number of TAVR by institution	161.3±101.4	158.0±90.0	0.52	7.1

Values are n (%), mean±SD or median (IQR) for year of inclusion. CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; PCI=percutaneous coronary intervention; SD=standard deviation; SMD=standardized mean difference; SAVR=surgical aortic valve replacement. TAVR=transcatheter aortic valve replacement.

Table 3: Clinical outcomes at day 30 in the matched cohort of patients with a previous prosthesis valve treated with VIV TAVR or redo SAVR.

	Redo SAVR (n=717)	VIV TAVR (n=717)	OR (95% CI) for TAVR vs SAVR	p (uncorrected)	p (Bonferroni correction)
All-cause death	52(7.3)	26(3.6)	0.48 (0.30-0.78)	0.003	0.01
Cardiovascular death	47(6.6)	21(2.9)	0.43 (0.25-0.73)	0.002	0.008
All-cause stroke	3(0.4)	7(1.0)	2.35 (0.60-9.11)	0.22	0.87
Myocardial infarction	3(0.4)	1(0.1)	0.33 (0.03-3.20)	0.34	1
Major or life-threatening bleeding	34(4.7)	29(4.0)	0.85 (0.51-1.41)	0.52	1
Major clinical events*	90(12.6)	59(8.2)	0.62 (0.44-0.88)	0.008	0.03
New-onset atrial fibrillation	29(4.0)	4(0.6)	0.13 (0.05-0.38)	<0.0001	<0.0001
Permanent pacemaker implantation	41(5.7)	132(18.4)	3.72 (2.58-5.37)	<0.0001	<0.0001

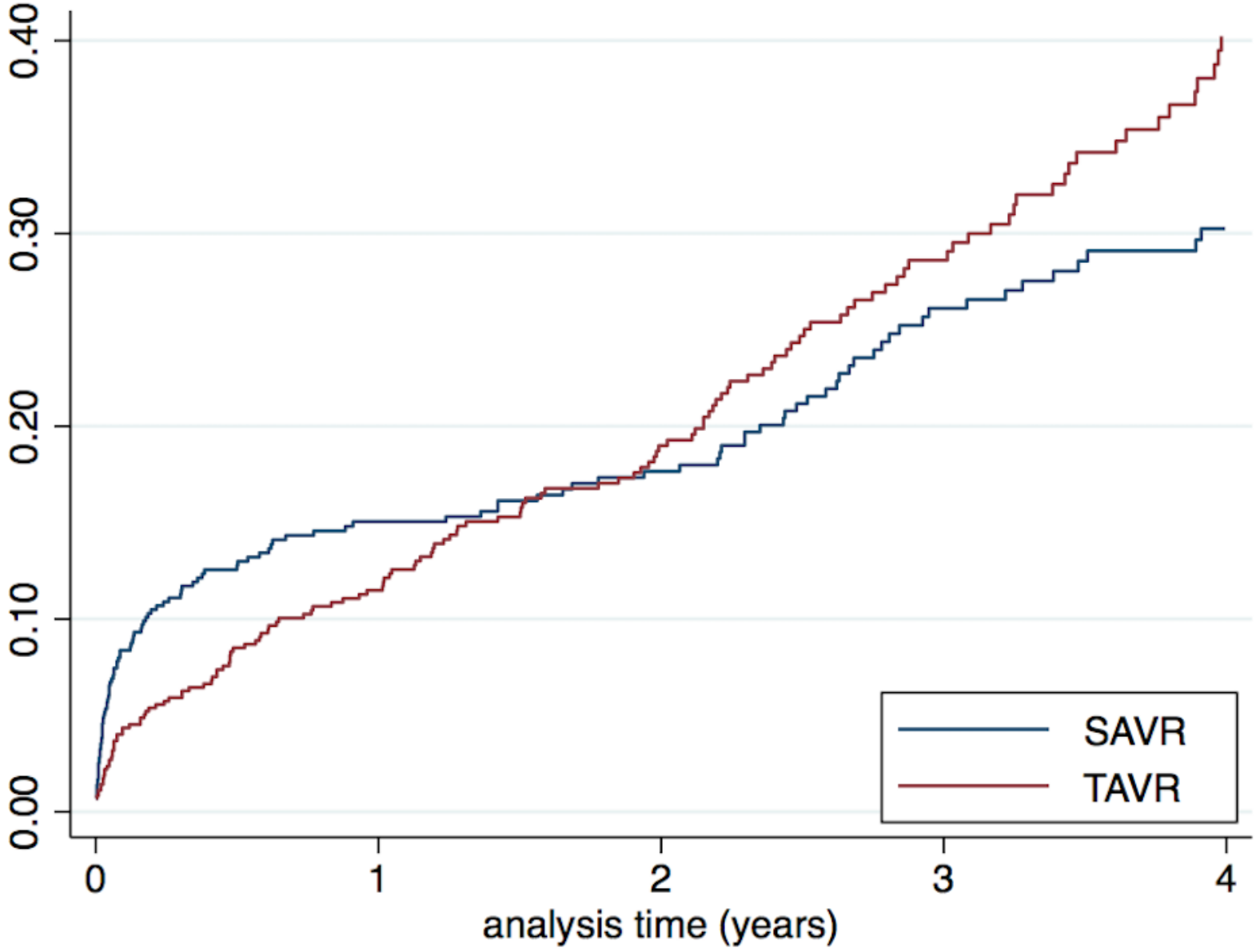
Values are n (%). CI=confidence interval; HF=heart failure; OR=odds ratio; SAVR=surgical aortic valve replacement; TAVR=transcatheter aortic valve replacement. *all-cause mortality, all-cause stroke, myocardial infarction, major or life-threatening bleeding.

Table 4: Clinical outcomes during the whole follow-up (mean [SD] 790 [751], median [IQR] 615 [79-1310] days) in the matched cohort of patients with a previous prosthesis valve treated with VIV TAVR or redo SAVR.

	Redo SAVR (n=717)	VIV TAVR (n=717)	IRR (95% CI) for TAVR vs SAVR	p (uncorrected)	p (Bonferroni correction)
All-cause death	147 (9.5)	170 (10.9)	1.14 (0.91-1.44)	0.23	0.92
Cardiovascular death	78 (5.1)	82 (5.3)	1.04 (0.75-1.44)	0.80	1
All-cause stroke	34 (2.3)	46 (3.0)	1.34 (0.84-2.15)	0.20	0.80
Myocardial infarction	17 (1.1)	24 (1.6)	1.41 (0.72-2.79)	0.28	1
Hospitalization for HF	144 (11.0)	199 (15.1)	1.37 (1.10-1.71)	0.004	0.02
Combined endpoint*	234 (18.6)	275 (21.9)	1.18 (0.99-1.41)	0.07	0.34
New-onset atrial fibrillation	70 (5.0)	62 (4.2)	0.85 (0.59-1.21)	0.35	1
Negative control analysis:					
Non-cardiovascular death	69 (4.5)	88 (5.6)	1.26 (0.91-1.76)	0.15	0.59

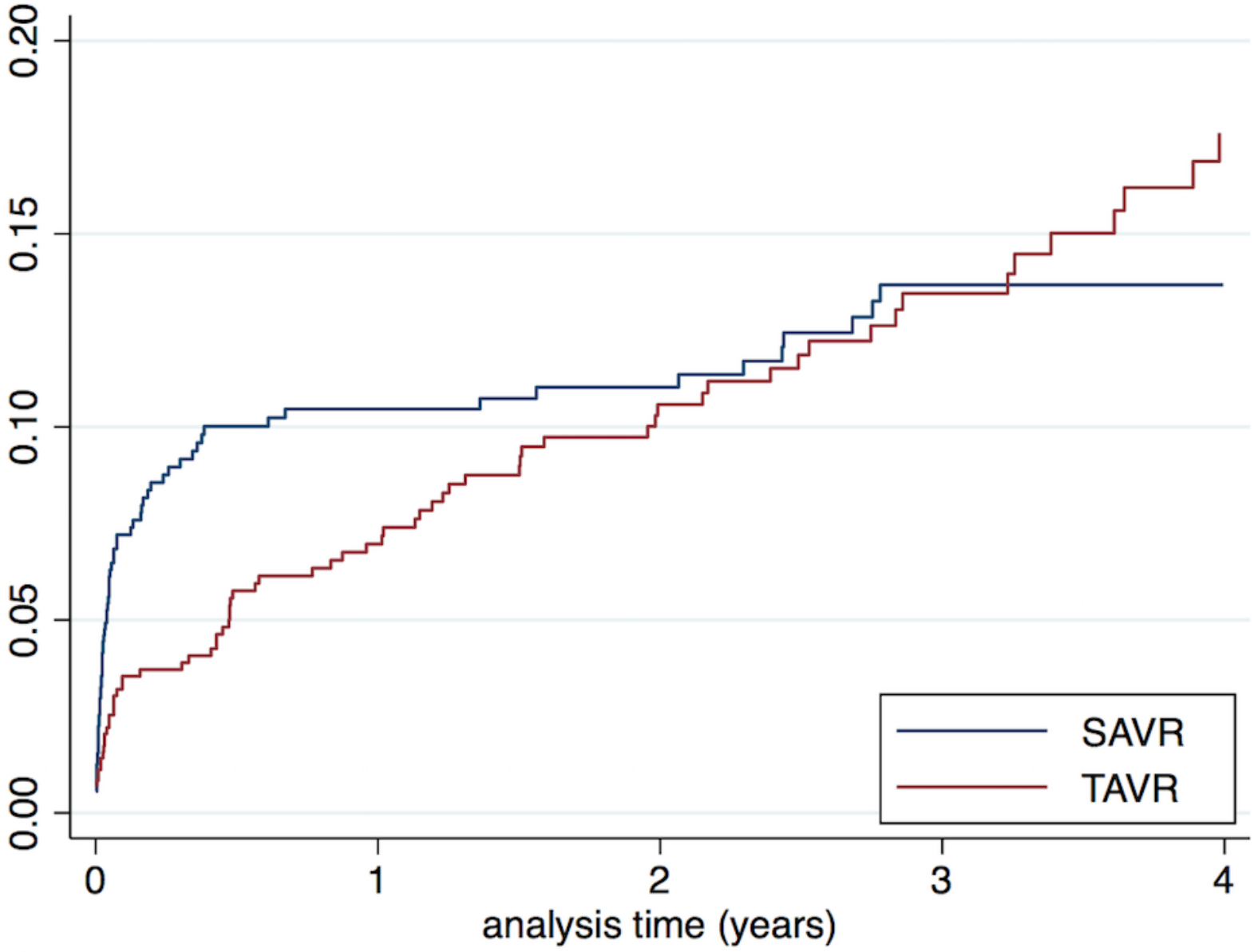
Cancer	69 (4.8)	52 (3.5)	0.72 (0.49-1.04)	0.07	0.28
Urinary infection	51 (3.5)	58 (3.9)	1.11 (0.75-1.64)	0.60	1

Values are n (incidence rate, %/year). CI=confidence interval; HF=heart failure; IRR=incidence rate ratio; SAVR=surgical aortic valve replacement; TAVR=transcatheter aortic valve replacement. *Cardiovascular death, all-cause stroke, myocardial infarction and rehospitalization for HF.



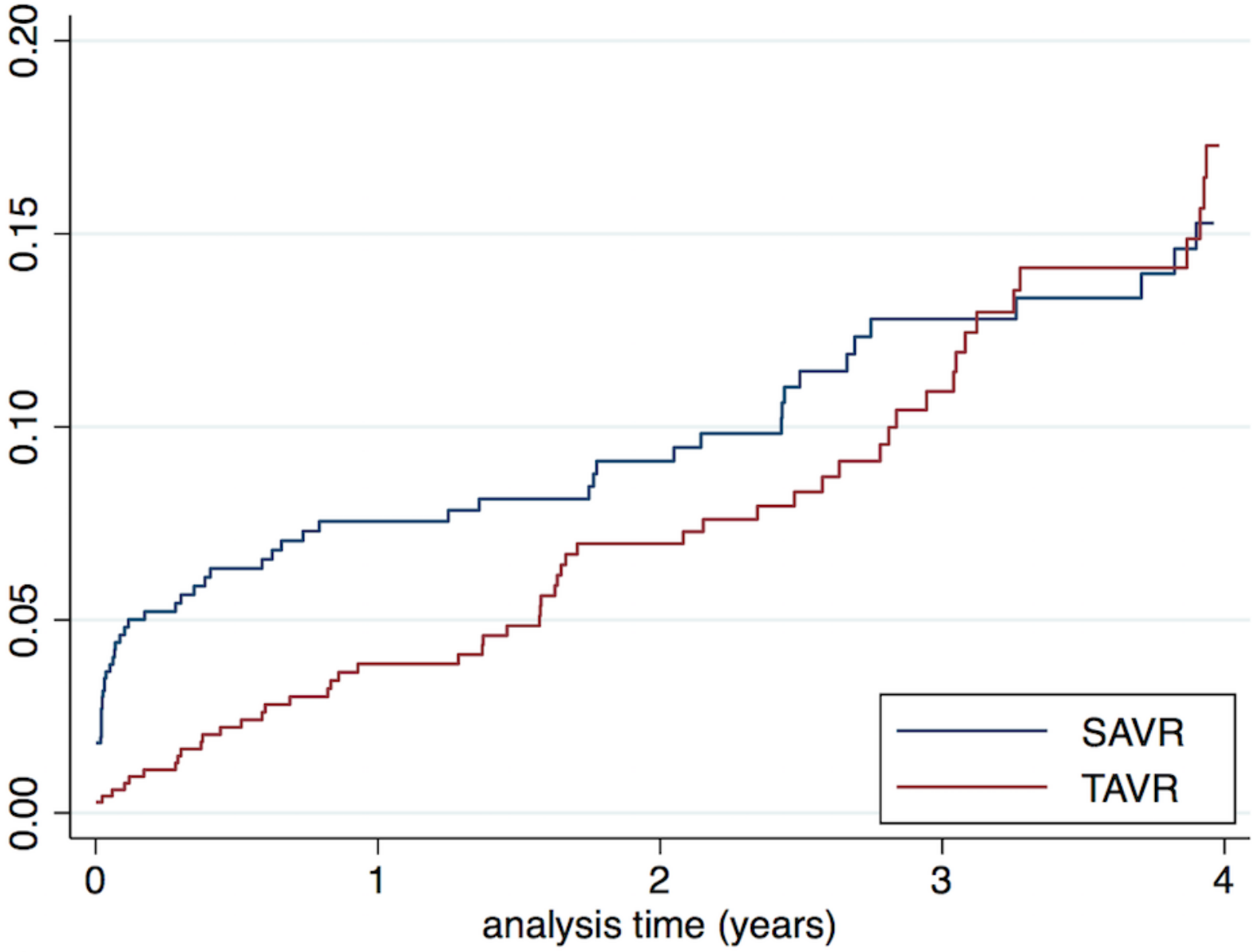
Number at risk

SAVR =	717	459	404	348	307	265	223	191	165
TAVR =	717	527	466	410	349	282	220	174	135



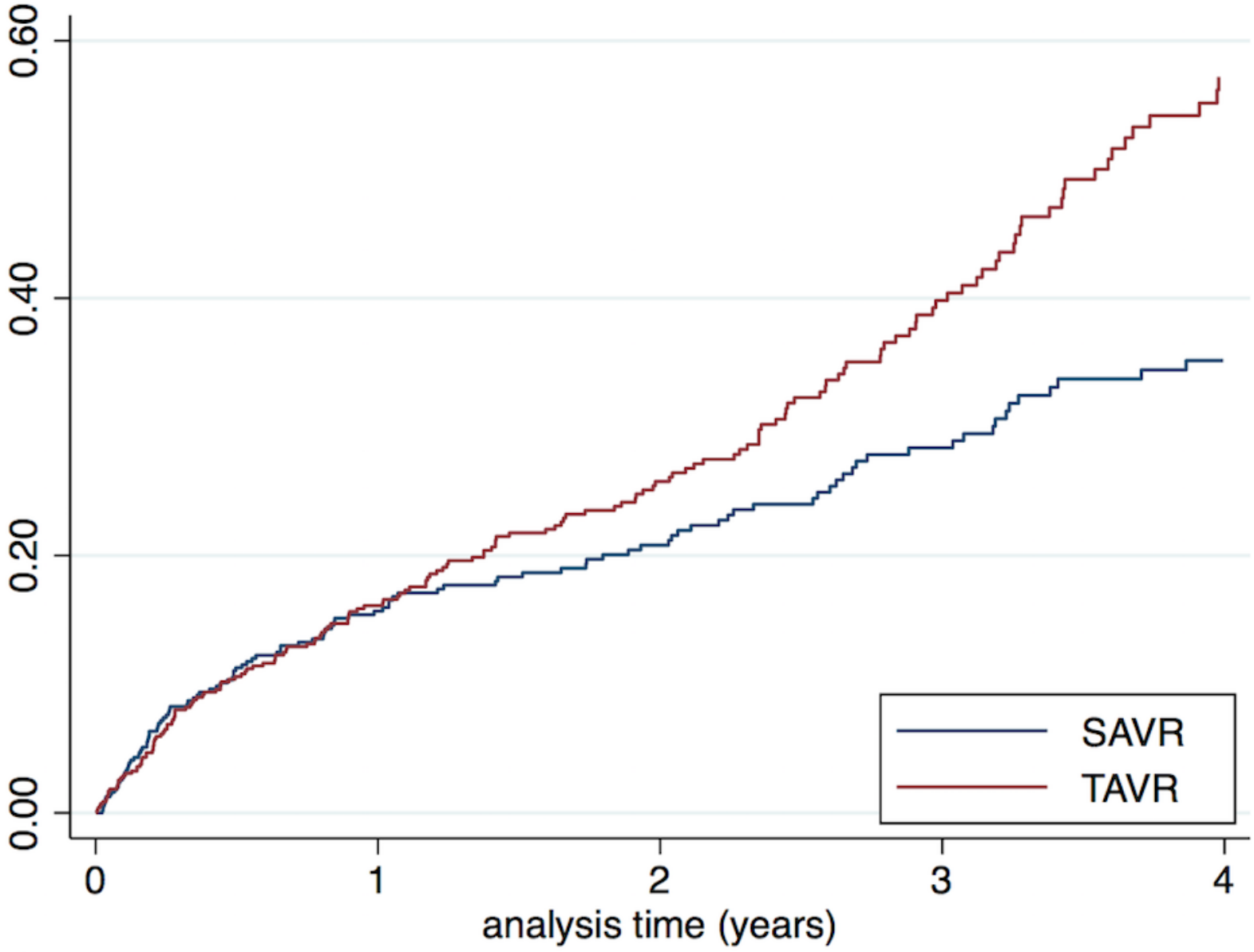
Number at risk

SAVR =	717	459	404	348	307	265	223	191	165
TAVR =	717	527	466	410	349	282	220	174	135



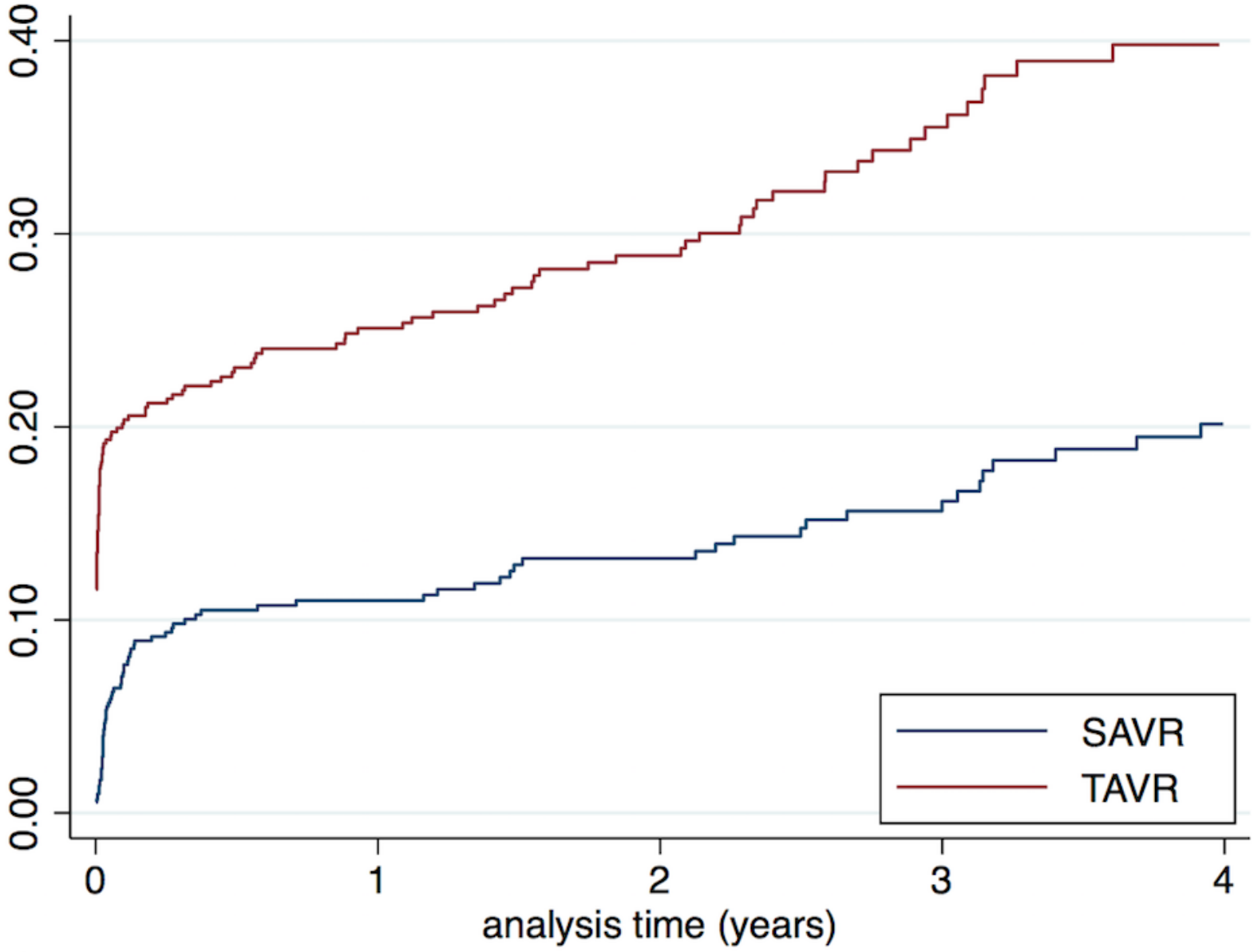
Number at risk

SAVR =	717	431	378	324	284	242	202	169	144
TAVR =	717	518	452	392	331	264	202	156	118



Number at risk

SAVR =	717	417	356	304	263	222	184	151	129
TAVR =	717	487	417	358	300	229	173	128	97



Number at risk

SAVR =	717	413	364	305	274	235	194	168	143
TAVR =	717	416	364	315	268	206	157	120	94