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## **Outcomes Following Aortic Stenosis Treatment (Transcatheter vs Surgical Replacement) in Women vs Men (From a Nationwide Analysis)**

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## **Abstract**

Sex-differences in survival following transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) have been suggested. The objective of this study was to analyse outcomes following TAVR according to sex and to compare outcomes between TAVR and SAVR in women, at a nationwide level. Based on the French administrative hospital-discharge database, the study collected information for all consecutive patients treated with TAVR and SAVR between 2010 and 2019. Outcomes were analysed according to sex and propensity score matching was used for the analysis of outcomes. In total 71,794 patients were identified in the database. After matching on baseline characteristics, we analysed 12,336 women and 12,336 men treated with TAVR. In a second matched analysis, we compared 9,297 women treated with TAVR and 9,297 women treated with SAVR. Long term follow-up showed lower risk of all-cause death (12.7% vs. 14.8%, hazard ratio [HR] 0.85, 95% CI 0.81-0.90) in women than men. While the difference in cardiovascular death remained non-significant (5.8% vs. 6.0%, HR 0.96, 95% CI 0.88-1.05), non-cardiovascular death was less frequent in women than in men following TAVR (6.9% vs 8.8% HR 0.78, 95%CI 0.72-0.84). When TAVR was compared to SAVR in women, long-term follow-up with TAVR showed higher rates of all-cause death (11.2% vs. 6.5%, HR 1.91, 95%CI 1.78-2.05), cardiovascular death (5.0% vs. 3.2%, HR 1.44, 95%CI 1.30-1.59) and non-cardiovascular death (6.2% vs. 3.3%, HR 2.48, 95% CI 2.25-2.72). In conclusion, we observed that women undergoing TAVR have lower long-term all-cause mortality as compared to TAVR in men, driven by non-cardiovascular mortality. SAVR was associated with lower rates of long-term cardiovascular adverse events in women as compared to TAVR.

**Key words** TAVR, sex, women, SAVR

## **Introduction**

Continuous development has improved the results of transcatheter aortic valve replacement (TAVR) and this technique is considered to be the preferred treatment for severe aortic stenosis (AS) in high surgical risk patients (1). Recent data have also shown that TAVR is non-inferior to surgery in low- and intermediate-risk patients (2-4). Therefore, this technique has become a potential alternative to surgical aortic valve replacement (SAVR) in majority of patients with severe symptomatic AS. Sex-differences in adverse events following both TAVR and SAVR have been suggested (5-7). However, long-term data remain limited and results inconsistent in both fields. 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 (8). Therefore, based on this large, nationwide, administrative French database, we aimed to evaluate the long-term outcomes following TAVR versus SAVR in women and potential sex-differences in outcomes following TAVR.

## **Methods**

This longitudinal cohort study was based on the national hospitalization database covering hospital care from the entire French population, which have been previously described (8). 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. The PMSI contains individual pseudo anonymised 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 (8-9).

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, 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).

From 1 January 2010 to 30 June 2019, 520,662 adults (age  $\geq 18$  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). For the analysis of TAVR procedures, we included all adults with a single percutaneous procedure (Classification Commune des Actes Medicaux code: DBLF001). For the analysis of SAVR

procedures, we included all women with a single surgical isolated aortic valve replacement procedure (Classification Commune des Actes Medicaux code: DBKA006). 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. We also used the Charlson Comorbidity Index and the Claims-based Frailty Indicator to assess patient clinical status (10-12). Exclusion criteria were age <18 years.

Due to the evolution of TAVR technology during this analysis we planned to analyse we defined a first generation of prosthesis (Balloon expandable (BE) Sapiens and Sapiens XT and Self Expandable (SE) Corevalve) and a second generation of prosthesis (BE Sapiens 3 and SE Evolut R). BE Sapien 3 (approved in Europe and available since January 2014) and SE Evolut R (approved in Europe and available since November 2015) were differentiated with the use of their specific codes used for pricing.

Patients were followed until 30 June 2019 for the occurrence of outcomes. We aimed to evaluate the incidence of all-cause death, cardiovascular death, non-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 (13). The endpoints were evaluated with follow-up starting from date of either TAVR or SAVR 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. We also

report clinically relevant bleeding (defined as any bleeding considered relevant for reimbursement of the hospital stay or transfusion) and transfusion status. 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.

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 sex (i.e. male or female) and treatment (TAVR versus SAVR) as the dependent variable. The propensity score included all baseline characteristics listed in table 1. For each female patient treated with TAVR, a propensity score-matched male patient treated with TAVR 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.

For each female patient treated with TAVR, a propensity score-matched female patient treated with SAVR 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 1 and 2).

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 were compared using hazard ratios (HR). HRs and asymptotic two-sided 95% confidence intervals (CIs) were estimated using Cox proportional hazards model for death and the model by Fine and Gray for competing risks for 1) cardiovascular and non-cardiovascular death and 2) ischemic stroke and death. P values are reported without and with correction for multiple comparisons using Bonferroni correction.

A multivariable analysis for clinical outcomes during the whole follow-up in the unmatched cohort of patients was also performed using a Cox model with all baseline characteristics and reporting hazard ratio. All comparisons with  $p < 0.05$  were considered statistically significant. All analyses 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**

Between January 1, 2010 and June 30, 2019, 71,794 patients were identified in the database, including 22,380 female patients treated with TAVR, 21,414 men treated with TAVR and 28,000 female patients treated with SAVR.

In the unmatched population of women and men who underwent a TAVR women were older, had lower estimated EuroSCORE II and cardiovascular risk factors and had less

often a history of coronary artery disease or revascularization (Table 1). In the unmatched population of female patients who had either TAVR or SAVR, we observed that patients treated with TAVR were older and had more comorbidities such as previous cancer, coronary artery disease, stroke and renal or lung disease (Table 2).

After propensity score matching, there were 12,336 patients in each group. Baseline characteristics in these populations were well matched (Table 3, Supplemental Figure 1). In the matched population, follow-up was 521 (544) days, median 349 days (interquartile range (IQR)) (24-837).

At 30 days, no significant differences were observed between the two matched cohorts except for pacemaker implantations which were less frequent in women and clinically relevant bleeding fewer in men (Table 4). Long-term results are presented in Table 5. During the whole follow-up, all-cause death was reported in 2227 (12.7%) women and 2560 (14.8%) men following TAVR (HR 0.81, 95%CI 0.81-0.90) (Figure 1 top panel). Cardiovascular death (5.8% vs. 6.0%, HR 0.96, 95%CI 0.88-1.05) was not different between the two matched groups (Figure 1 lower panel), while non-cardiovascular death was less frequent in women (6.9% vs 8.8% HR 0.78, 95%CI 0.72-0.84). Hospitalization for heart failure was more frequent in women (17.8% vs. 16.2%, HR 1.09, 95%CI 1.03-1.15). New onset of atrial fibrillation was less frequently reported in women (5.6% vs. 6.6%, HR 0.84, 95%CI 0.77-0.92). Rates of all-cause stroke (4.1% vs. 4.0%), myocardial infarction (2.0% vs. 2.3%) and the combined endpoint (24.8% vs. 23.5%) were not significantly different between the two matched groups.

As a sensitivity analysis, the multivariable analysis for clinical outcomes at 30 days and during the whole follow-up in the unmatched cohort of patients is provided in Supplemental Tables 1 and 2 and results were consistent with those obtained with 1:1 matching.

After propensity score matching, there were 9,297 women in each group. Baseline characteristics in these populations were well matched (Table 6, Supplemental Figure 2). In the matched population, follow-up was 913 (928) days, median 637 days (IQR) (45-1522).

At 30 days, all-cause death (3.7% vs. 5.4%, OR 0.67 95%CI 0.57-0.79) and cardiovascular death (3.2% vs. 5.0%, OR 0.63 95%CI 0.54-0.75) were lower in matched women who underwent TAVR compared to SAVR (Table 7). Rate of new onset of atrial fibrillation was lower following TAVR (1.2% vs. 5.0%, OR 0.22 95%CI 0.18-0.28), while new pacemaker implantation (24% vs. 3.9%, OR 7.68 95%CI 6.84-8.63) was more frequent after TAVR in women.

Long-term follow-up showed higher rates of all-cause death (11.1% vs. 6.8%, HR 1.77, 95%CI 1.64-1.90) (Figure 2 top panel), cardiovascular death (5.0% vs. 3.4%, HR 1.26, 95%CI 1.14-1.40) (Figure 2 lower panel) and non-cardiovascular death (6.1% vs. 3.4%, HR 2.45, 95%CI 2.21-2.72) in matched women treated with TAVR compared to women treated with SAVR (Table 8).

All-cause stroke (3.8% vs. 2.1%, HR 1.98, 95%CI 1.74-2.26), myocardial infarction (1.9% vs. 1.0%, HR 2.03, 95% CI 1.69-2.45), hospitalization for heart failure (15.6% vs. 7.6%, HR 2.12, 95%CI 1.98-2.28) and the combined endpoint (21.9% vs. 11.6%, HR 1.73, 95%CI 1.63-1.83) were more frequently reported after TAVR than after SAVR in women.

Outcomes according to the generation of TAVR prosthesis are presented in Tables 9 and 10. We observed that there were some statistical interactions which indicated better results with TAVR in women in recent years and with more recent generations of device for cardiovascular death, and also for rehospitalization for heart failure in recent years.

Analysis according to EuroSCORE II (<4 vs. ≥4) are presented in Supplemental Table 3 and Supplemental Figures 3 and 4 and indicated better results with TAVR over a longer period in women with highest EuroSCORE II.

As a sensitivity analysis, the multivariable analysis for clinical outcomes at 30 days and during the whole follow-up in the unmatched cohort of women treated with TAVR or SAVR is provided in Supplemental Tables 4 and 5 and results were consistent with those obtained with 1:1 matching.

## **Discussion**

In this propensity score-matched analysis, we observed that: Sex had no impact on long-term cardiovascular outcomes after TAVR. We observed lower rates of all-cause death during follow-up in women, this difference being driven by lower incidences of non-cardiovascular death, while cardiovascular mortality was not different. TAVR was associated with better short-term outcomes versus SAVR in women, while after 2 years follow-up, curves tended to cross and rates of cardiovascular mortality, stroke and hospitalization for heart failure were more frequent in the TAVR group. Female sex has been shown to be associated with increased risk of adverse events after SAVR (14, 15). Moreover, women are more likely to receive smaller prosthetic valves, more frequently undergo aortic annular enlargement procedures, have greater technical difficulties associated with smaller anatomy, and may have more bleeding complications related to cardiopulmonary bypass (16). Therefore, sex is included in the surgical STS risk score calculator (6). Whether sex should have a place in the decision-making process for AS treatment at an individual basis remains under evaluated so far and dedicated clinical studies are required.

Largest studies evaluating sex-differences in TAVR patients were limited to 30 days and 1 year outcomes (5, 17). A recent meta-analysis of 40,861 patients found that women had lower long-term all-cause mortality and no difference in early mortality as compared to men (18). While procedure-related vascular complications do not affect long-term mortality, the reasons for a survival benefit in women compared with men after TAVR remained unclear and might be mainly related to longer life expectancy in women (5, 19). Interestingly, in our

nationwide analysis, we do not report significantly different rates of major or life-threatening bleeding in women, while we confirm higher rates of other bleeding events and transfusions on the short-term in women than in men from this cohort. In the long-term, our results confirm previous data reporting lower rates of all-cause death following TAVR in women. This trend was driven by lower rates of non-cardiovascular death in this population and possibly related to life expectancy which was in France in 2020 79.8 years for men and 85.7 years for women (<https://www.insee.fr/fr/statistiques/4277640?sommaire=4318291>).

Female sex has been demonstrated as an independent risk factor for adverse outcomes after SAVR. Most of the studies assessing sex-impact of AS treatment explored up to 2 years mortality following either TAVR or SAVR. This is a relevant point to be considered, while we showed that curves for cardiovascular death tended to cross at approximately 18 months in our nationwide cohort (and beyond the 24 months in women considered to be at higher risk for surgery), which provides the longest follow-up available. Therefore, it seems that the benefit derived from TAVR versus SAVR in women is relatively more prominent in a short-term perspective, which might have a strong impact while treating lower-risk women with longer life expectancy. Two recent meta-analysis from randomized trials showed that female patients who underwent TAVR had a substantial reduction in mortality compared to those undergoing SAVR, while no difference was observed in men (20, 21). Similarly, Siontis et al found that compared with SAVR, TAVR was associated with a significant survival benefit throughout 2 years of follow-up (22). Our observations emphasize the need for long and very long follow-up when comparing surgery versus interventional cardiology in such patients. Similarly, regarding revascularization of left main coronary artery disease, long-term follow-up of the EXCEL trial showed lower benefit of percutaneous strategy versus surgery (23). In this setting, death curves crossed after one year, while death, stroke or MI crossed between the second and third year. Taken together, those findings from TAVR and coronary fields,

are a plea for longer follow-up in clinical studies, before claiming benefit of one strategy over the other, and wide adoption in daily practice.

We acknowledge several limitations of our work. One is inherent to the retrospective, observational nature of the study and its potential biases. Further, the study was based on administrative data, with limitations and information bias 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, but most of the major cardiovascular events analysed in our study are not managed out of hospitals. We were not able to evaluate specific procedural risk factors such as size and model of aortic bioprosthesis, left ventricle ejection fraction or extent of coronary disease. Further, the non-randomised 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. Our analysis was restricted to the variables present in the database, which meant that characteristics such as mean gradient, valve area, paravalvular leak were not available for analysis. Moreover, we were not able to evaluate post procedural echocardiography data. Prosthesis-patient mismatch may also be a predictor of adverse outcomes following TAVR and women had a higher mean gradient and lower valve area index when compared to men (24).

In conclusion, this sex-analysis of outcomes following aortic stenosis interventions found no impact of sex on major cardiovascular outcomes after TAVR, although all-cause

death was lower in women, which reflects a lower risk of non-cardiovascular death in women than in men treated with TAVR. When comparing TAVR versus SAVR in women, surgery was associated with more complications in the early stages, while after two years women who underwent a TAVR had significantly worse prognosis. Therefore, sex is a relevant parameter to be taken into account when assessing a patient with severe AS for intervention.

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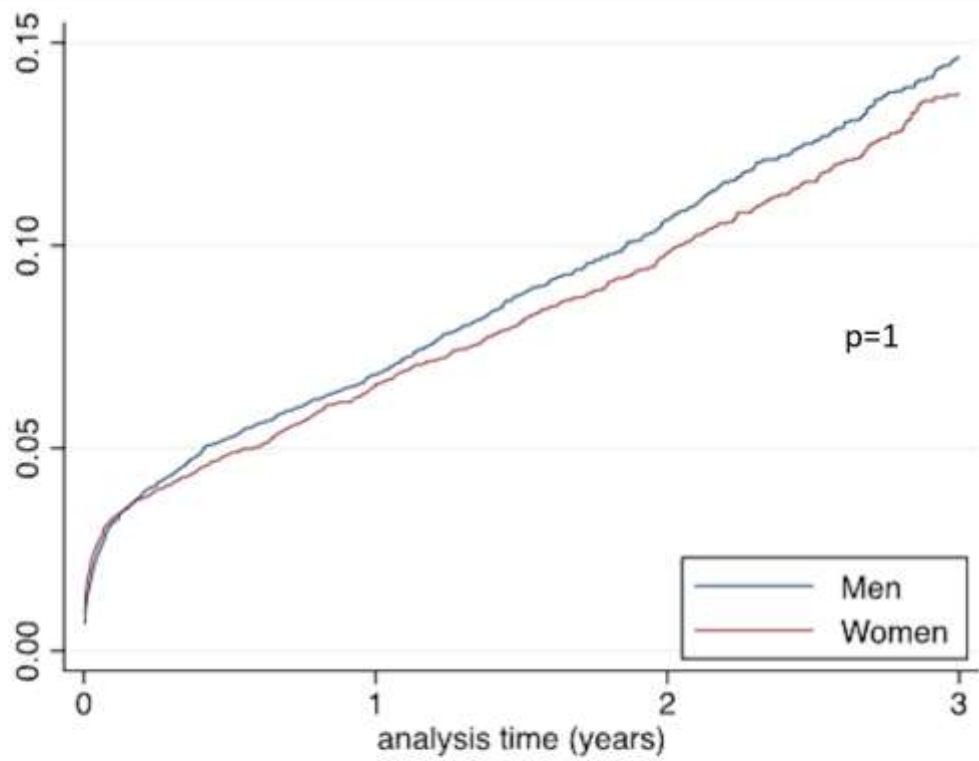
## Figures legends

**Figure 1.** Incidences for all-cause death (top panel) and cardiovascular death (lower panel) in matched women and men treated with TAVR.

TAVR: transcatheter aortic valve replacement.

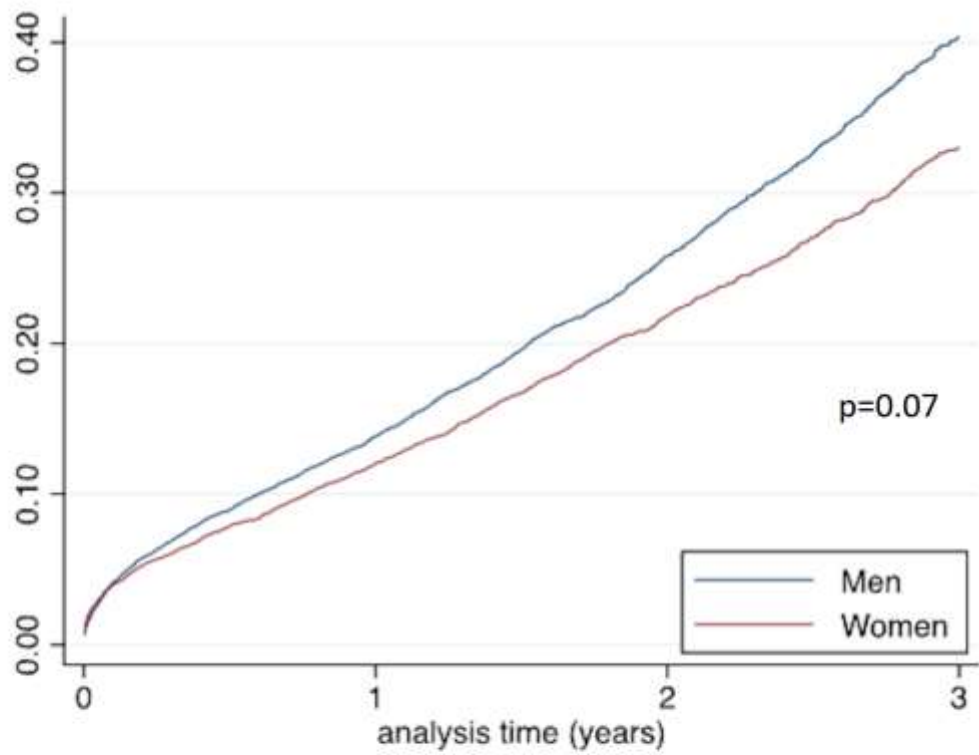
**Figure 2.** Incidences for all-cause death (top panel) and cardiovascular death (lower panel) in the matched population of women treated with TAVR or SAVR.

TAVR: transcatheter aortic valve replacement; SAVR: surgical aortic valve replacement.



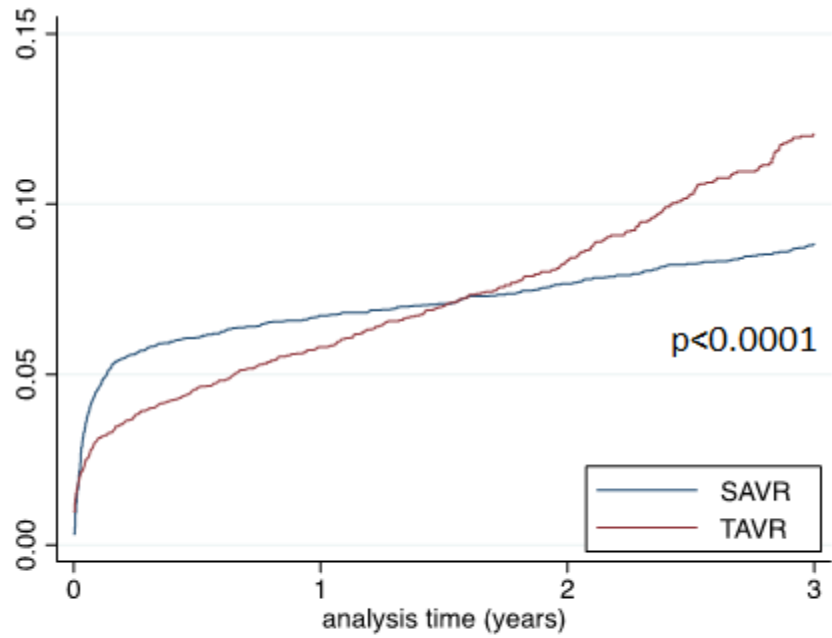
Number at risk

Men =	12336	7761	6106	4780	3626	2670	1914
Women =	12336	7556	6067	4792	3754	2875	2119



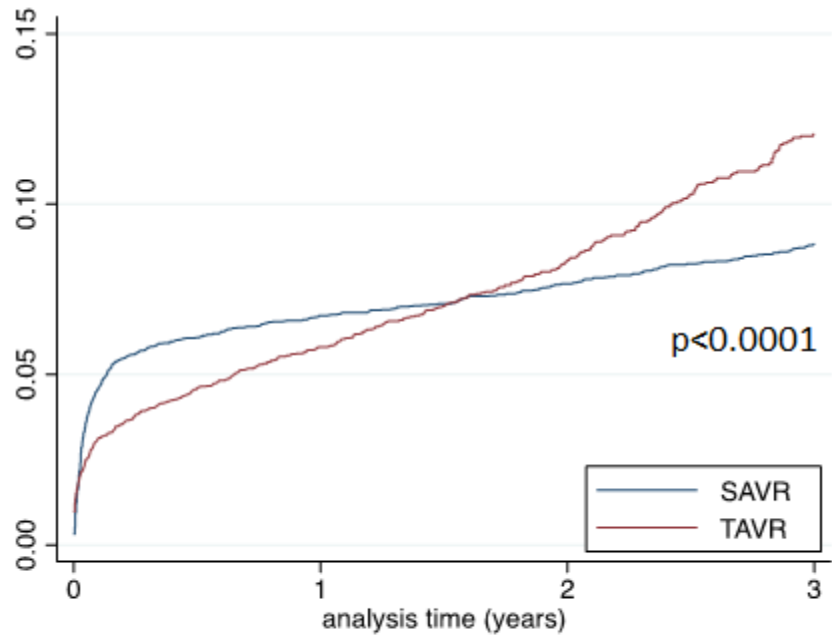
Number at risk

Men =12336	7761	6106	4780	3626	2670	1914
Women =12336	7556	6067	4792	3754	2875	2119



Number at risk

SAVR = 9297	6777	6321	5901	5452	4990	4556
TAVR = 9296	5237	4322	3539	2872	2329	1862



Number at risk

SAVR = 9297	6777	6321	5901	5452	4990	4556
TAVR = 9296	5237	4322	3539	2872	2329	1862

**Table 1: Baseline characteristics of women and men patients with aortic stenosis treated with TAVR.**

Variables	Women	Men	p	SMD,	Total
	(n=22380)	(n=21414)		Women vs Men (%)	
Age (years)	83.6±6.2	81.8±7.2	<0.0001	27.8	82.7±6.8
Charlson comorbidity index	3.8±2.8	4.6±3.0	<0.0001	-27.7	4.2±2.9
Frailty index	10.1±9.3	9.5±8.9	<0.0001	7.0	9.8±9.1
EuroSCORE II	3.7±0.9	3.8±1.1	<0.0001	-1.8	3.7±1.0
Hypertension	18171 (81.2%)	17183 (80.2%)	0.01	2.5	35354 (80.7%)
Diabetes mellitus	5876 (26.3%)	7038 (32.9%)	<0.0001	-14.5	12914 (29.5%)
Heart failure	12349 (55.2%)	12474 (58.3%)	<0.0001	-6.1	24823 (56.7%)
History of pulmonary edema	1083 (4.8%)	1231 (5.7%)	<0.0001	-4.3	2314 (5.3%)
Aortic regurgitation	2618 (11.7%)	2713 (12.7%)	0.002	-3.2	5331 (12.2%)
Mitral regurgitation	4499 (20.1%)	4001 (18.7%)	0.0002	3.6	8500 (19.4%)
Previous endocarditis	114 (0.5%)	196 (0.9%)	<0.0001	-5.8	310 (0.7%)
Dilated cardiomyopathy	3374 (15.1%)	3747 (17.5%)	<0.0001	-6.5	7121 (16.3%)
Coronary artery disease	11959 (53.4%)	15082 (70.4%)	<0.0001	-35.5	27041 (61.7%)
Previous myocardial infarction	2259 (10.1%)	4003 (18.7%)	<0.0001	-24.8	6262 (14.3%)
Previous PCI	5260 (23.5%)	7447 (34.8%)	<0.0001	-24.8	12707 (29.0%)
Previous CABG	782 (3.5%)	2980 (13.9%)	<0.0001	-37.5	3762 (8.6%)
Vascular disease	6875 (30.7%)	9212 (43.0%)	<0.0001	-25.9	16087 (36.7%)
Atrial fibrillation	9601 (42.9%)	10275 (48.0%)	<0.0001	-10.0	19876 (45.4%)
Previous pacemaker or ICD	3756 (16.8%)	5329 (24.9%)	<0.0001	-20.0	9085 (20.7%)
Ischemic stroke	1160 (5.2%)	1257 (5.9%)	0.002	-3.1	2417 (5.5%)
Intracranial bleeding	285 (1.3%)	369 (1.7%)	0.0001	-3.8	654 (1.5%)
Smoker	764 (3.4%)	2922 (13.6%)	<0.0001	-37.2	3686 (8.4%)
Dyslipidemia	9818 (43.9%)	10796 (50.4%)	<0.0001	-13.0	20614 (47.1%)
Obesity	5788 (25.9%)	5414 (25.3%)	0.16	1.6	11202 (25.6%)
Alcohol related diagnoses	405 (1.8%)	1465 (6.8%)	<0.0001	-25.2	1870 (4.3%)
Abnormal renal function	3600 (16.1%)	4074 (19.0%)	<0.0001	-7.8	7674 (17.5%)
Lung disease	4508 (20.1%)	5946 (27.8%)	<0.0001	-17.8	10454 (23.9%)
Sleep apnea syndrome	1343 (6.0%)	2571 (12.0%)	<0.0001	-21.1	3914 (8.9%)
COPD	2340 (10.5%)	4271 (19.9%)	<0.0001	-26.6	6611 (15.1%)
Liver disease	921 (4.1%)	1263 (5.9%)	<0.0001	-8.2	2184 (5.0%)
Gastroesophageal reflux	813 (3.6%)	685 (3.2%)	0.01	2.3	1498 (3.4%)
Thyroid diseases	4447 (19.9%)	1679 (7.8%)	<0.0001	35.4	6126 (14.0%)
Inflammatory disease	2201 (9.8%)	2265 (10.6%)	0.01	-2.6	4466 (10.2%)
Anaemia	6655 (29.7%)	5495 (25.7%)	<0.0001	9.1	12150 (27.7%)
Previous cancer	3250 (14.5%)	4958 (23.2%)	<0.0001	-22.2	8208 (18.7%)
Edwards Sapien XT	2334 (10.4%)	2093 (9.8%)	0.02	2.2	4427 (10.1%)
Edwards Sapien 3	10311 (46.1%)	11638 (54.3%)	<0.0001	-16.7	21949 (50.1%)
Medtronic Corevalve	2591 (11.6%)	2919 (13.6%)	<0.0001	-6.3	5510 (12.6%)
Medtronic Evolut	7144 (31.9%)	4764 (22.2%)	<0.0001	21.8	11908 (27.2%)

Values are n (%) or mean±SD, SMD are before adjustment for propensity score.

CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD= implantable cardioverter defibrillator; PCI=percutaneous coronary intervention; SMD= standardized mean difference; TAVR=transcatheter aortic valve replacement.

**Table 2: Baseline characteristics of women with aortic stenosis treated with TAVR or SAVR.**

Variables	TAVR	SAVR	p	SMD, TAVR vs SAVR	Total
	(n=22380)	(n=28000)		(%)	(n=50380)
Age(years)	83.6±6.2	73.8±9.5	<0.0001	121.5	78.2±9.5
Charlson comorbidity index	3.8±2.8	3.1±2.7	<0.0001	26.4	3.4±2.8
Frailty index	10.1±9.3	7.4±8.0	<0.0001	28.7	8.6±8.7
EuroSCORE II	3.7±0.9	3.3±1.0	<0.0001	40.4	3.5±1.0
Hypertension	18171 (81.2%)	20208 (72.2%)	<0.0001	20.2	38379 (76.2%)
Diabetes mellitus	5876 (26.3%)	7110 (25.4%)	0.03	1.7	12986 (25.8%)
Heart failure	12349 (55.2%)	9824 (35.1%)	<0.0001	42.3	22173 (44.0%)
History of pulmonary edema	1083 (4.8%)	2248 (8.0%)	<0.0001	-11.6	3331 (6.6%)
Aortic regurgitation	2618 (11.7%)	2854 (10.2%)	<0.0001	4.6	5472 (10.9%)
Mitral regurgitation	4499 (20.1%)	4136 (14.8%)	<0.0001	14.4	8635 (17.1%)
Previous endocarditis	114 (0.5%)	357 (1.3%)	<0.0001	-8.2	471 (0.9%)
Dilated cardiomyopathy	3374 (15.1%)	3153 (11.3%)	<0.0001	11.0	6527 (13.0%)
Coronary artery disease	11959 (53.4%)	12364 (44.2%)	<0.0001	18.6	24323 (48.3%)
Previous myocardial infarction	2259 (10.1%)	1679 (6.0%)	<0.0001	14.9	3938 (7.8%)
Previous PCI	5260 (23.5%)	1383 (4.9%)	<0.0001	54.7	6643 (13.2%)
Previous CABG	782 (3.5%)	5740 (20.5%)	<0.0001	-53.6	6522 (12.9%)
Vascular disease	6875 (30.7%)	5645 (20.2%)	<0.0001	23.9	12520 (24.9%)
Atrial fibrillation	9601 (42.9%)	13649 (48.7%)	<0.0001	-11.6	23250 (46.2%)
Previous pacemaker or ICD	3756 (16.8%)	1511 (5.4%)	<0.0001	36.6	5267 (10.5%)
Ischemic stroke	1160 (5.2%)	613 (2.2%)	<0.0001	15.9	1773 (3.5%)
Intracranial bleeding	285 (1.3%)	126 (0.5%)	<0.0001	8.7	411 (0.8%)
Smoker	764 (3.4%)	1777 (6.3%)	<0.0001	-13.2	2541 (5.0%)
Dyslipidemia	9818 (43.9%)	12953 (46.3%)	<0.0001	-5.6	22771 (45.2%)
Obesity	5788 (25.9%)	7906 (28.2%)	<0.0001	-6.5	13694 (27.2%)
Alcohol related diagnoses	405 (1.8%)	436 (1.6%)	0.03	1.8	841 (1.7%)
Abnormal renal function	3600 (16.1%)	1432 (5.1%)	<0.0001	34.8	5032 (10.0%)
Lung disease	4508 (20.1%)	3894 (13.9%)	<0.0001	17.5	8402 (16.7%)
Sleep apnea syndrome	1343 (6.0%)	1144 (4.1%)	<0.0001	8.2	2487 (4.9%)
COPD	2340 (10.5%)	1871 (6.7%)	<0.0001	14.1	4211 (8.4%)
Liver disease	921 (4.1%)	838 (3.0%)	<0.0001	5.6	1759 (3.5%)
Gastroesophageal reflux	813 (3.6%)	869 (3.1%)	0.001	2.3	1682 (3.3%)
Thyroid diseases	4447 (19.9%)	4122 (14.7%)	<0.0001	13.0	8569 (17.0%)
Inflammatory disease	2201 (9.8%)	1496 (5.3%)	<0.0001	16.5	3697 (7.3%)
Anaemia	6655 (29.7%)	6876 (24.6%)	<0.0001	11.1	13531 (26.9%)
Previous cancer	3250 (14.5%)	2017 (7.2%)	<0.0001	22.9	5267 (10.5%)

Values are n (%) or mean±SD, SMD are before adjustment for propensity score.

CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD= implantable cardioverter defibrillator; PCI=percutaneous coronary intervention; SMD= standardized mean difference; SAVR=surgical aortic valve replacement. TAVR=transcatheter aortic valve replacement.

**Table 3: Baseline characteristics of matched women and men patients with aortic stenosis treated with TAVR.**

Variables	Women (n=12336)	Men (n=12336)	p	SMD, Women vs Men (%)
Age (years)	83.0±6.6	82.9±6.6	0.29	1.3
Charlson comorbidity index	4.2±2.9	4.1±2.7	0.56	0.7
Frailty index	9.8±9.2	9.6±8.9	0.08	0.7
EuroSCORE II	3.7±1.0	3.7±1.0	0.13	-0.2
Hypertension	9838 (79.8%)	9839 (79.8%)	0.99	0.0
Diabetes mellitus	3549 (28.8%)	3522 (28.6%)	0.7	0.5
Heart failure	6887 (55.8%)	6952 (56.4%)	0.4	-1.1
History of pulmonary edema	597 (4.8%)	645 (5.2%)	0.16	-1.7
Aortic regurgitation	1555 (12.6%)	1545 (12.5%)	0.85	0.2
Mitral regurgitation	2336 (18.9%)	2354 (19.1%)	0.77	-0.4
Previous endocarditis	75 (0.6%)	84 (0.7%)	0.47	-0.8
Dilated cardiomyopathy	2010 (16.3%)	1974 (16.0%)	0.53	0.8
Coronary artery disease	7698 (62.4%)	7573 (61.4%)	0.1	2.1
Previous myocardial infarction	1625 (13.2%)	1634 (13.2%)	0.87	-0.2
Previous PCI	3594 (29.1%)	3539 (28.7%)	0.44	1.0
Previous CABG	748 (6.1%)	762 (6.2%)	0.71	-0.4
Vascular disease	4391 (35.6%)	4408 (35.7%)	0.82	-0.3
Atrial fibrillation	5604 (45.4%)	5565 (45.1%)	0.62	0.6
Previous pacemaker or ICD	2524 (20.5%)	2506 (20.3%)	0.78	0.4
Ischemic stroke	666 (5.4%)	646 (5.2%)	0.57	0.7
Intracranial bleeding	185 (1.5%)	180 (1.5%)	0.79	0.3
Smoker	678 (5.5%)	791 (6.4%)	0.002	-3.3
Dyslipidemia	5679 (46.0%)	5684 (46.1%)	0.95	-0.1
Obesity	2982 (24.2%)	3000 (24.3%)	0.79	-0.3
Alcohol related diagnoses	343 (2.8%)	379 (3.1%)	0.17	-1.4
Abnormal renal function	2110 (17.1%)	2145 (17.4%)	0.56	-0.7
Lung disease	2707 (21.9%)	2754 (22.3%)	0.47	-0.9
Sleep apnea syndrome	955 (7.7%)	974 (7.9%)	0.65	-0.5
COPD	1668 (13.5%)	1707 (13.8%)	0.47	-0.9
Liver disease	555 (4.5%)	588 (4.8%)	0.32	-1.2
Gastroesophageal reflux	394 (3.2%)	395 (3.2%)	0.97	0.0
Thyroid diseases	1321 (10.7%)	1349 (10.9%)	0.57	-0.7
Inflammatory disease	1205 (9.8%)	1239 (10.0%)	0.47	-0.9
Anaemia	3273 (26.5%)	3340 (27.1%)	0.34	-1.2
Previous cancer	2277 (18.5%)	2244 (18.2%)	0.59	0.7
Edwards Sapien XT	1277 (10.4%)	1284 (10.4%)	0.88	-0.2
Edwards Sapien 3	6262 (50.8%)	6204 (50.3%)	0.46	0.9
Medtronic Corevalve	1609 (13.0%)	1561 (12.7%)	0.36	1.2
Medtronic Evolut	3188 (25.8%)	3287 (26.6%)	0.15	-1.8

Values are n (%), CABG=coronary artery bypass graft; COPD=chronic obstructive pulmonary disease; ICD=Implantable Cardioverter Defibrillator; PCI=percutaneous coronary intervention; SMD= standardized mean difference; TAVR=transcatheter aortic valve replacement.

**Table 4: Clinical outcomes at day 30 in the matched cohort of women and men treated with TAVR.**

<b>Outcomes</b>	<b>Women (n=12336)</b>	<b>Men (n=12336)</b>	<b>OR (95% CI) for Women vs Men</b>	<b>p (uncorrected)</b>	<b>p (Bonferroni correction)</b>
All-cause death	407 (4.3%)	404 (4.2%)	1.04 (0.91-1.20)	0.56	1
Cardiovascular death	349 (3.7%)	330 (3.4%)	1.10 (0.94-1.28)	0.24	0.97
All-cause stroke	108 (0.9%)	80 (0.7%)	1.35 (1.01-1.81)	0.04	0.16
Myocardial infarction	31 (0.3%)	31 (0.3%)	1.00 (0.61-1.65)	1.00	1
Major or life-threatening bleeding	303 (2.5%)	340 (2.8%)	0.89 (0.76-1.04)	0.14	0.56
Clinically relevant bleeding	829 (6.7%)	729 (5.9%)	1.15 (1.03-1.27)	0.009	0.04
Transfusion	357 (2.9%)	306 (2.5%)	1.17 (1.00-1.37)	0.05	0.18
Major clinical events*	801 (6.5%)	815 (6.6%)	0.98 (0.89-1.09)	0.72	1
New-onset atrial fibrillation	156 (1.3%)	147 (1.2%)	1.06 (0.85-1.33)	0.60	1
Permanent pacemaker implantation	2,534 (20.5%)	3,046 (24.7%)	0.79 (0.74-0.84)	<0.0001	<0.0001

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

**Table 5: Clinical outcomes during the whole follow-up (mean [SD] 521 [544], median [IQR] 357 [24-847] days) in the matched cohort of women and men treated with TAVR**

<b>Outcomes</b>	<b>Women (n=12336)</b>	<b>Men (n=12336)</b>	<b>HR (95% CI) for Women vs Men</b>	<b>p (uncorrected)</b>	<b>p (Bonferroni correction)</b>
All-cause death	2227 (12.66%)	2560 (14.8%)	0.851 (0.805-0.901)	<0.0001	<0.0001
Cardiovascular death	1017 (5.78%)	1039 (6.01%)	0.962 (0.883-1.048)	0.38	1
Non-cardiovascular death	1210 (6.88%)	1521 (8.79%)	0.776 (0.720-0.836)	<0.0001	<0.0001
All-cause stroke	704 (4.12%)	666 (3.96%)	1.041 (0.937-1.157)	0.46	1
Myocardial infarction	350 (2.03%)	395 (2.33%)	0.866 (0.750-1.000)	0.05	0.20
Hospitalization for HF	2641 (17.77%)	2436 (16.23%)	1.093 (1.034-1.154)	0.002	0.008
Combined endpoint*	3583 (24.75%)	3435 (23.49%)	1.051 (1.004-1.102)	0.04	0.14
New-onset atrial fibrillation	931 (5.58%)	1071 (6.55%)	0.843 (0.773-0.921)	<0.0001	<0.0001

Values are n (incidence rate, %/year). CI=confidence interval; HF=heart failure; HR=hazard ratio; TAVR=transcatheter aortic valve replacement.

\*Cardiovascular death, all-cause stroke, myocardial infarction and rehospitalization for HF.

**Table 6: Baseline characteristics of matched women with aortic stenosis treated with TAVR or SAVR.**

Vaiables	TAVR (n=9297)	SAVR (n=9297)	p	SMD, TAVR vs SAVR (%)
Age (years)	79.6±7.3	79.4±5.8	0.04	2.5
Charlson comorbidity index	3.5±2.8	3.5±2.7	0.29	1.6
Frailty index	9.1±9.0	8.6±8.5	0.001	5.1
EuroSCORE II	3.5±1.0	3.5±0.9	0.02	3.4
Hypertension	7203 (77.5%)	7245 (77.9%)	0.46	-1.1
Diabetes mellitus	2455 (26.4%)	2465 (26.5%)	0.87	-0.2
Heart failure	4119 (44.3%)	4250 (45.7%)	0.05	-2.9
History of pulmonary edema	636 (6.8%)	639 (6.9%)	0.93	-0.1
Aortic regurgitation	1027 (11.0%)	1010 (10.9%)	0.69	0.6
Mitral regurgitation	1635 (17.6%)	1682 (18.1%)	0.37	-1.3
Previous endocarditis	75 (0.8%)	79 (0.8%)	0.75	-0.5
Dilated cardiomyopathy	1204 (13.0%)	1289 (13.9%)	0.07	-2.7
Coronary artery disease	3990 (42.9%)	3992 (42.9%)	0.98	0.0
Previous myocardial infarction	682 (7.3%)	652 (7.0%)	0.39	1.2
Previous PCI	840 (9.0%)	863 (9.3%)	0.56	-0.7
Previous CABG	775 (8.3%)	755 (8.1%)	0.59	0.7
Vascular disease	2254 (24.2%)	2232 (24.0%)	0.71	0.5
Atrial fibrillation	4473 (48.1%)	4296 (46.2%)	0.01	3.8
Previous pacemaker or ICD	922 (9.9%)	903 (9.7%)	0.64	0.7
Ischemic stroke	280 (3.0%)	297 (3.2%)	0.47	-1.0
Intracranial bleeding	56 (0.6%)	60 (0.6%)	0.71	-0.5
Smoker	386 (4.2%)	406 (4.4%)	0.47	-1.0
Dyslipidemia	4270 (45.9%)	4186 (45.0%)	0.22	1.8
Obesity	2587 (27.8%)	2537 (27.3%)	0.41	1.2
Alcohol related diagnoses	164 (1.8%)	160 (1.7%)	0.82	0.3
Abnormal renal function	782 (8.4%)	778 (8.4%)	0.92	0.1
Lung disease	1728 (18.6%)	1665 (17.9%)	0.23	1.8
Sleep apnea syndrome	480 (5.2%)	480 (5.2%)	1	0.0
COPD	849 (9.1%)	816 (8.8%)	0.4	1.3
Liver disease	350 (3.8%)	347 (3.7%)	0.91	0.2
Gastroesophageal reflux	307 (3.3%)	307 (3.3%)	1	0.0
Thyroid diseases	1587 (17.1%)	1590 (17.1%)	0.95	-0.1
Inflammatory disease	679 (7.3%)	673 (7.2%)	0.87	0.2
Anaemia	2434 (26.2%)	2390 (25.7%)	0.46	1.1
Previous cancer	993 (10.7%)	982 (10.6%)	0.79	0.4

Values are n (%) or mean±SD. CABG=coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ICD=Implantable Cardioverter Defibrillator; PCI=percutaneous coronary intervention; SMD= standardized mean difference; SAVR=surgical aortic valve replacement. TAVR=transcatheter aortic valve replacement.

**Table 7: Clinical outcomes at day 30 in the matched cohort of women treated with TAVR or SAVR.**

<b>Outcomes</b>	<b>TAVR (n=9297)</b>	<b>SAVR (n=9297)</b>	<b>OR (95% CI) for TAVR vs SAVR</b>	<b>p (uncorrected)</b>	<b>p (Bonferroni correction)</b>
All-cause death	250 (3.7%)	412 (5.4%)	0.67 (0.57-0.79)	<0.0001	<0.0001
Cardiovascular death	217 (3.2%)	380 (5.0%)	0.63 (0.54-0.75)	<0.0001	<0.0001
All-cause stroke	50 (0.6%)	43 (0.5%)	1.16 (0.77-1.75)	0.47	1
Myocardial infarction	15 (0.2%)	33 (0.4%)	0.45 (0.25-0.84)	0.01	0.04
Major or life-threatening bleeding	212 (2.4%)	243 (2.7%)	0.87 (0.72-1.05)	0.14	0.56
Clinically relevant bleeding	572 (6.2%)	2,134 (23.0%)	0.22 (0.20-0.24)	<0.0001	<0.0001
Transfusion	260 (2.8%)	436 (4.7%)	0.58 (0.50-0.68)	<0.0001	<0.0001
Major clinical events*	498 (5.5%)	713 (7.9%)	0.68 (0.60-0.77)	<0.0001	<0.0001
New-onset atrial fibrillation	104 (1.2%)	450 (5.0%)	0.22 (0.18-0.28)	<0.0001	<0.0001
Permanent pacemaker implantation	2,165 (24.0%)	356 (3.9%)	7.68 (6.84-8.63)	<0.0001	<0.0001

Values are n (%). CI=confidence interval; 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 8: Clinical outcomes during the whole follow-up (mean [SD] 913 [928], median [IQR] 637 [45-1522] days) in the matched cohort of women treated with TAVR or SAVR**

<b>Outcomes</b>	<b>TAVR (n=9297)</b>	<b>SAVR (n=9297)</b>	<b>HR (95% CI) for TAVR vs SAVR</b>	<b>p (uncorrected)</b>	<b>p (Bonferroni correction)</b>
All-cause death	1447 (11.1%)	2041 (6.76%)	1.77 (1.64-1.90)	<0.0001	<0.0001
Cardiovascular death	656 (5.03%)	1011 (3.35%)	1.26 (1.14-1.40)	<0.0001	<0.0001
Non-cardiovascular death	791 (6.07%)	1030 (3.41%)	2.45 (2.21-2.72)	<0.0001	<0.0001
All-cause stroke	483 (3.81%)	608 (2.08%)	1.98 (1.74-2.26)	<0.0001	<0.0001
Myocardial infarction	239 (1.87%)	303 (1.02%)	2.03 (1.69-2.45)	<0.0001	<0.0001
Hospitalization for HF	1751 (15.63%)	1995 (7.57%)	2.12 (1.98-2.28)	<0.0001	<0.0001
Combined endpoint*	2394 (21.93%)	2963 (11.55%)	1.73 (1.63-1.83)	<0.0001	<0.0001
New-onset atrial fibrillation	621 (5.01%)	1253 (4.68%)	0.95 (0.86-1.06)	0.36	1

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

**Table 9.** Clinical outcomes in matched women treated with TAVI or SAVR by period of intervention (<2015 vs ≥2015)

	<b>HR (95% CI) for TAVI vs SAVR</b>	<b>P</b>
<b>All-cause death:</b>		
<b>Intervention &lt;2015 (n= 9,096)</b>	2.06 (1.90-2.24)	<0.0001
<b>Intervention ≥2015 (n= 9,497)</b>	1.66 (1.42-1.94)	<0.0001
Intervention ≥2015 vs <2015 ratio 0.76 (0.64-0.90), p for interaction = 0.002		
<b>Cardiovascular death:</b>		
<b>Intervention &lt;2015 (n= 9,096)</b>	1.78 (1.58-2.00)	<0.0001
<b>Intervention ≥2015 (n= 9,497)</b>	1.19 (0.97-1.46)	0.10
Intervention ≥2015 vs <2015 ratio 0.63 (0.50-0.80), p for interaction = <0.0001		
<b>Non-cardiovascular death:</b>		
<b>Intervention &lt;2015 (n= 9,096)</b>	2.35 (2.10-2.63)	<0.0001
<b>Intervention ≥2015 (n= 9,497)</b>	2.41 (1.89-3.07)	<0.0001
Intervention ≥2015 vs <2015 ratio 0.98 (0.76-1.28), p for interaction = 0.90		
<b>All-cause stroke:</b>		
<b>Intervention &lt;2015 (n= 9,096)</b>	1.63 (1.38-1.92)	<0.0001
<b>Intervention ≥2015 (n= 9,497)</b>	1.84 (1.41-2.41)	<0.0001
Intervention ≥2015 vs <2015 ratio 1.11 (0.81-1.52), p for interaction = 0.51		
<b>Rehospitalization for HF:</b>		
<b>Intervention &lt;2015 (n= 9,096)</b>	2.17 (1.99-2.35)	<0.0001
<b>Intervention ≥2015 (n= 9,497)</b>	1.76 (1.53-2.03)	<0.0001
Intervention ≥2015 vs <2015 ratio 0.79 (0.67-0.93), p for interaction = 0.004		
<b>Combined endpoint:</b>		
<b>Intervention &lt;2015 (n= 9,096)</b>	1.89 (1.76-2.03)	<0.0001
<b>Intervention ≥2015 (n= 9,497)</b>	1.51 (1.35-1.69)	<0.0001
Intervention ≥2015 vs <2015 ratio 0.76 (0.67-0.87), p for interaction = <0.0001		

HF: Heart Failure; HR: Hazard Ratio; CI: confidence Interval. . SAVR=surgical aortic valve replacement; TAVI=transcatheter aortic valve implantation.

**Table 10.** Clinical outcomes in matched women treated with TAVI or SAVR by generation of TAVI device.

	<b>Adjusted HR (95% CI) for TAVI vs SAVR</b>	<b>P</b>
<b>All-cause death:</b>		
<b>SAVR or older TAVI device (n= 13,070)</b>	1.823 (1.679-1.980)	<0.0001
<b>SAVR or newer TAVI device (n= 14,820)</b>	1.443 (1.271-1.639)	<0.0001
Older vs newer device, p for interaction = 0.002		
<b>Cardiovascular death:</b>		
<b>SAVR or older TAVI device (n= 13,070)</b>	1.660 (1.472-1.872)	<0.0001
<b>SAVR or newer TAVI device (n= 14,820)</b>	1.180 (0.986-1.412)	0.07
Older vs newer device, p for interaction = 0.002		
<b>Non-cardiovascular death:</b>		
<b>SAVR or older TAVI device (n= 13,070)</b>	1.982 (1.770-2.219)	<0.0001
<b>SAVR or newer TAVI device (n= 14,820)</b>	1.793 (1.497-2.147)	<0.0001
Older vs newer device, p for interaction = 0.36		
<b>All-cause stroke:</b>		
<b>SAVR or older TAVI device (n= 13,070)</b>	1.159 (0.982-1.366)	0.08
<b>SAVR or newer TAVI device (n= 14,820)</b>	1.193 (0.959-1.484)	0.11
Older vs newer device, p for interaction = 0.84		
<b>Rehospitalization for HF:</b>		
<b>SAVR or older TAVI device (n= 13,070)</b>	1.729 (1.592-1.878)	<0.0001
<b>SAVR or newer TAVI device (n= 14,820)</b>	1.643 (1.458-1.852)	<0.0001
Older vs newer device, p for interaction = 0.49		
<b>Combined endpoint:</b>		
<b>SAVR or older TAVI device (n= 13,070)</b>	1.544 (1.440-1.655)	<0.0001
<b>SAVR or newer TAVI device (n= 14,820)</b>	1.378 (1.250-1.518)	<0.0001

Older vs newer device, p for interaction = 0.06

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HF: Heart Failure; HR: Hazard Ratio; CI: confidence Interval; SAVR=surgical aortic valve replacement; TAVI=transcatheter aortic valve implantation.

Since patients with older or newer device had different baseline characteristics, HR was adjusted on baseline characteristics from table 1.