Relative survival following transcatheter aortic valve implantation: how do TAVI patients fare relative to the general population?

**Short title:** Martin et al. Relative Survival following TAVI

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# Abstract

## Background

Transcatheter aortic valve implantation (TAVI) is indicated for aortic stenosis patients who are intermediate-high surgical risk. While all-cause mortality rates following TAVI are established, survival attributable to the procedure is unclear due to competing causes of mortality. The aim was to report relative survival (RS) following TAVI, which accounts for background mortality risks in a matched general population.

## Methods and Results

National cohort data (n=6420) from the 2007-2014 UK TAVI registry were matched by age, sex and year to mortality rates for England and Wales (population 57.9 million). The Ederer II method related observed patient survival to that expected from the matched general population. We modelled RS using a flexible parametric approach that modelled the log cumulative hazard using restricted cubic splines. Relative survival of the TAVI cohort was 95.4%, 90.2% and 83.8% at 30-days, one year and three years, respectively. By one-year follow-up, mortality hazards in >85 age group were not significantly different to those of the matched general population and by three years survival rates were comparable. The flexible parametric RS model indicated that increasing age was associated with significantly less excess hazards after the procedure; for example, by two-years, a 5-year increase in age was associated with 20% lower excess mortality over the general population.

## Conclusions

RS following TAVI was high and survival rates in those aged >85 approximated those of a matched general population within three years. High rates of RS indicate that patients selected for TAVI tolerate the risks of the procedure well.

# Keywords

Aortic Stenosis; Relative Survival; Transcatheter Aortic Valve Implantation; Mortality

# Clinical Perspectives

## What is new?

* Relative survival (RS) adjusts observed mortality, for mortality rates expected within an age-, sex-, year- and region-matched general population.
* This is the first study to apply RS in transcatheter aortic valve implantation (TAVI), and demonstrates good long-term RS rates in patients selected for the procedure.
* RS was particularly high in elderly patients, where their observed mortality hazards returned to that seen in a matched general population by one-year post TAVI.
* High RS within elderly TAVI patients indicates that a large proportion of long-term deaths can be accounted for by the underlying mortality risks within the general population.

## What are the clinical implications?

* Elderly patients with severe aortic stenosis, who are selected to undergo TAVI, tolerate the risks of the procedure well, which has important implications from a resource allocation perspective.
* The careful selection applied to elderly TAVI candidates appears to control procedure related mortality rates, meaning that elderly patients should continue to be considered for TAVI, even with the potential expansion into lower risk patients.
* Future reporting of mortality rates from national TAVI registries should be presented in the context of the patient population, particularly when comparing rates across countries where underlying expected mortality may vary considerably.

# Introduction

Aortic Stenosis (AS) is the most common valve pathology in Europe and North America and occurs due to an age-related degeneration and calcification of the aortic valve. The onset of AS symptoms is associated with poor prognosis, with an estimated annual mortality rate of 25% 1. While surgical valve replacement is the mainstay treatment for AS, randomised controlled trials have demonstrated the efficacy of transcatheter aortic valve implantation (TAVI) for symptomatic AS patients considered to be at intermediate to high operative risk 2–5. Similarly, studies on several national TAVI registries have shown favourable short- and mid-term mortality 6–9. However, since TAVI is recommended in those at high-risk, the patients who undergo such a procedure are older and have more comorbid conditions than those undergoing alternative treatment options. Consequently, the long-term mortality profile is difficult to assess in TAVI patients since, by virtue of age and multi-morbidity, their risk of dying from other causes is high.

Administrative data on cause of death could be used to estimate the mortality profile associated with the disease or treatment in question, but such data are often unreliable 10. An alternative method is relative survival (RS), which adjusts the observed mortality for the expected mortality rates within a matched general population 11,12. Specifically, overall excess mortality attributable to the index AS and associated TAVI can be estimated as the difference between observed and expected mortality, which forms the RS estimate. Although RS is commonly used in studies of survival following cancer diagnosis 13 and is beginning to be used in cardiovascular disease 14,15, to date such methods have not been used to assess long-term mortality outcomes after TAVI.

The aim of this study was to investigate the survival of patients treated by TAVI in a national cohort, while adjusting for underlying expected mortality risks within a matched general population.

# Methods

## UK TAVI registry

 Prospective data on all consecutive TAVI procedures in the UK are collected in the UK registry through a Web-based interface provided by the National Institute of Cardiovascular Outcomes Research, where individual TAVI centres are contacted if there are data inconsistencies. Further details of the registry have been published previously 16. In summary, 95 variables are recorded, detailing patient demographics, risk factors for intervention, procedural details and adverse outcomes up to the time of hospital discharge. This study included all consecutive TAVI procedures conducted between January 2007 and December 2014 across the 32 centres running active TAVI programs in England and Wales.

All-cause mortality was obtained from the Office for National Statistics (ONS) providing the life-status of English and Welsh patients. Although mortality information was available in the majority of cases, we excluded patients with missing life status. Administrative censoring occurred at the end of follow-up on 31st May 2015. All survival times were defined as the number of days between the date of TAVI and either the date of death or date of last information regarding follow-up, up to a maximum of three years post procedure.

## Statistical Analysis

Relative survival was defined as the observed survival from the TAVI registry divided by the expected survival from a matched general population. Relative survival equal to one indicates that the observed survival is the same as that within the matched general population, while RS<1 means that the observed survival is worse than that expected within the general population. This study used the population life tables provided by the ONS to derive the population-expected survival; such life tables are stratified by age, sex, year and country (i.e. different tables for England and Wales). Although the life table mortality estimates will include those patients undergoing TAVI, the very low prevalence of such procedures undertaken across the general population means that the bias induced by this will be negligible 11. Further, while the UK TAVI registry had time-to-event information censored in 2015, the life tables were only available to 2014. Hence, the expected population mortality rates for 2015 were assumed the same as those from 2014. We excluded patients who were missing data on age, sex, year or country, which were used to match to the life tables. All analyses were conducted in the whole TAVI cohort and across the following subgroups: age (<80, 80-85 and >85 years), procedure year (2007-2010 and 2011-2014) and sex.

The Ederer II method was used to estimate RS 11, from which an estimate of the cumulative excess hazard could be obtained. An increasing (decreasing) cumulative excess hazard through time indicates that the mortality hazard in the TAVI population was higher (lower) than that expected from the matched general population. Constant cumulative excess hazards infer that the observed mortality hazard was the same as that expected from the general population (i.e. observed hazards of mortality “returned to baseline”); a cumulative excess hazard of zero means that observed survival equals the expected survival (i.e. RS equal to one).

Additionally, we calculated expected daily mortality hazards using the life tables, and observed daily mortality hazards using the Kaplan-Meier estimate. An estimated daily hazard ratio (HR) was then obtained by dividing the observed and expected daily hazard rates at each follow-up time within the first year of the procedure. Here, a daily HR of one implies the observed mortality hazards were the same as those in the general population, while HRs less (greater) than one imply that mortality hazards after TAVI were lower (higher) than the general population hazard. A smoother was applied to each of the daily HRs to estimate a trend through time 17.

An alternative estimation of RS was considered that uses a patient level approach, which has previously been described in detail 18. In short, the follow-up time (in days) for each patient was transformed to give the expected proportion of the matched general population that would have not survived that individual’s follow-up. For example, transforming the observed survival time for a given patient to 0.3 implies that individual survived longer than 30% of their matched general population. A Kaplan-Meier estimate and log-rank test can then be used directly on the transformed survival times to compare across strata.

Multivariable modelling of RS was undertaken using a flexible parametric RS model, which modelled the log cumulative hazard using restricted cubic splines, thereby allowing the baseline hazard to vary non-linearly with time 19,20. Covariates in the model included: age (continuous variable), procedure year (continuous variable) and sex. Other demographic and procedural variables were not entered into the model since our aim was not to identify a causal relationship of age, year or sex on RS; rather the aim was to explore associations of such variables. Interaction terms between log survival time and age, year and sex were included, to estimate time-varying excess hazard ratios. The degrees of freedom for the baseline and time-varying coefficients were selected to minimise the Akaike’s Information Criterion, with the knots of the splines placed at the centiles of the uncensored survival times.

R version 3.3.1 21 was used for all statistical analyses. Graphical plots were made using the “ggplot2” package 22, the package “rstpm2” was used to fit the flexible parametric RS models 23, and the package “relsurv” was used for the Ederer II RS analysis 24.

# Results

Between January 2007 and December 2014, 6835 patients received TAVI in either England or Wales; patients with missing location information (n = 337) were removed from the analysis. Of the remaining 6498 patients, 56 had missing follow-up time and 22 patients had missing sex information, leaving 6420 (94%) patients available for analysis. Baseline characteristics of the whole TAVI cohort and across age groups are given in **Table 1**, while **Table 2** and **Table 3** present the procedure year and sex subgroup comparisons, respectively. The mean age of patients was 81.3 years and the majority of patients were male (53.7%). Older patients generally had fewer baseline risk factors (**Table 1**); for instance, the prevalence of renal failure (p<0.001), asthma/COPD (p<0.001), extra-cardiac arteriopathy (p<0.001) and LVEF<50% (p<0.001) were significantly less for older patients. The median follow-up time was 710 days (interquartile range 351 days to 1219 days) with 14627 person years of follow-up.

## Relative Survival

 In the TAVI cohort, all-cause 30-day, one year and three-year observed survival estimates were 94.7%, 83.4% and 64.5%, respectively, compared with corresponding RS rates of 95.4%, 90.2% and 83.8% (**Figure 1**). Hence, immediately following the procedure, the hazard of mortality in the TAVI cohort was approximately 50 times higher than that of the matched general population (**Figure 2 (A))**. However, the daily HR decreased rapidly, and by one year the observed mortality rate within the TAVI cohort was only 1.26 times higher than that of the matched general population (HR 1.26; 95% CI of 1.05-1.46). After one year, the cumulative excess hazard curve increased at an approximately constant rate; thus, the TAVI cohort had marginally higher mortality hazards compared with the general population up-to three years post procedure (**Figure 3 (A)**).

 RS was higher in 2011-2014 than for procedures conducted in 2007-2010 (**Figure 1**). In particular, the increase in mortality hazard over that in the general population immediately following the procedure was greater in 2007-2010 than in 2011-2014, with the daily HRs decaying quicker for the 2011-2014 group (**Figure 2 (B)**). By one year, the daily HR for both procedural year groups was similar. Consequently, after one year the cumulative excess hazard curves increased at a similar rate, meaning that the initial elevation in mortality risk for earlier procedures relative to the general population persisted throughout follow-up (**Figure 3 (B)**).

By 100 days after TAVI, the observed mortality rates within the >85 age group were the same as the expected mortality rates within the >85 matched general population (HR of one, **Figure 2 (C)**). Such a finding was not observed in the <80 or the 80-85 age groups, with the observed mortality hazard in these groups being higher than that expected from the matched general populations throughout follow-up (**Figure 3 (C)**). In contrast, for the >85 age group the cumulative excess hazard curve plateaued by one year (since the HR was one) and by three years, the cumulative excess hazard curve had decreased towards zero (**Figure 3 (C)**). Therefore, after surviving the initial high risk of the procedure, the observed survival rate in >85 age group was approximately similar to that in the >85 general population by three years (RS approximately one, as seen in **Figure 1**).

**Figure 4** shows the survival curves per age group after transforming each patient’s follow-up time (in days) to indicate population expected mortality. For example, when the expected mortality rate in each representative population was 20%, the observed cumulative mortality rate was approximately 25% in the >85 age group and 36% in the 80-85 age group. Hence, **Figure 4** indicates that, by the end of follow-up, the mortality rates observed within the >85 age group approximated those expected from the general population (dashed line), with RS significantly improved with increasing age group (log-rank test, p<0.001).

## Modelling Relative Survival

**Figure 5** gives the time-dependent excess HRs for age (per 5-year increase), procedure year (number of years from 2007) and sex from the flexible parametric RS model. Increasing age was associated with significantly less excess hazards after approximately 3 months post procedure. For example, at two-year follow-up the excess HR for age (per 5-year increase) was 0.80 (95% CI of 0.77-0.84) (**Figure 5**). Thus, on average, a given patient was experiencing 20% lower excess mortality over the general population as compared to a similar patient aged 5 years younger. Moreover, this model highlighted significant temporal improvements in RS for mid-term follow-up, with later procedure years having excess hazards significantly below one, until two years post procedure. The joint effects of age and procedure year on cumulative excess hazard are illustrated in **Figure 6**. RS was similar between male and female patients throughout follow-up (**Figure 5**).

# Discussion

This analysis of the UK TAVI registry aimed to compare the observed survival against that expected from a matched general population. We found that although the observed mortality hazard was high relative to that in the general population immediately following TAVI, the HR decayed rapidly within the first year of follow-up. After one-year, RS was significantly higher than all-cause survival, indicating that a large proportion of the long-term mortality can be accounted for by the underlying mortality risks within the general population. By one year, the most elderly patients were experiencing mortality hazards comparable to the general population and by three years, the excess hazard had reduced sufficiently for the observed survival to return to population-expected survival rates. Finally, our analysis shows that there were significant improvements in RS for those who underwent TAVI in 2011-2014 compared with 2007-2010.

The one year all-cause survival rates reported in this study compare with those from other national registries (7,9,25–27), but these do not account for competing causes of death. Without cause of death information, the expected mortality risks derived from the life tables are a suitable proxy for competing causes of death, given the low prevalence of TAVI procedures undertaken across the general population. We found that one-year and three-year RS estimates of 90.2% and 83.8%, respectively, were significantly higher than the corresponding all-cause survival rates of 83.4% and 64.5%. Thus, the initially high excess mortality, induced by the index AS and associated TAVI, decreased significantly within the first year. This supports previous work utilising cause of death information, which demonstrated that although the majority of short-term mortalities were cardiovascular and procedure related, beyond 24 months, non-cardiovascular causes became the leading cause of death 25. Moreover, the RS rates reported in this study approximately compare with the cardiovascular causes of death reported in the high-risk and intermediate-risk PARTNER trials 3,5. For example, the intermediate-risk PARTNER trial reported one-year cardiovascular death rate of 7.1% and the high-risk trial reported a corresponding rate of 14.3%; these values compare with our reported one-year RS mortality rate of 9.8% ($100\%-90.2\%$). Arguably, RS estimates are more useful to health-care users and providers than all-cause analyses, particularly given the decline in cardiovascular causes of death 26. By examining RS, this analysis suggests that the mortality risks observed following TAVI return to those expected within a general population, thereby supporting trial data showing the effectiveness of the procedure 2,3,5.

High rates of RS were particularly evident in the most elderly patients. Older age has previously been found to be a significant predictor of one year mortality after multivariable adjustment 9, with nonagenarians particularly being associated with increased risk 27. However, by adjusting for mortality risk within the underlying population, the present work demonstrates that elderly TAVI patients had better survival than younger patients did, relative to their matched general populations. Survival in the very oldest patients was equivalent to that of a matched general population by three years, which supports the work of Arsalan et al. 27, who demonstrated that despite the increased mortality risks of nonagenarians, the relative difference between the observed rates and an age-matched general population were less than for those aged <90. Although one needs to consider survival bias, the current work suggests that a large proportion of long-term deaths in elderly TAVI patients are unrelated to TAVI or the index AS. This has important clinical implications from a resource utilization perspective, but further studies on national registries that exploit administrative cause of death data are required.

Nevertheless, since TAVI is predominantly undertaken in patients who are considered high surgical risk, a patient aged <80 who undergoes TAVI is likely to have a range of co-morbidities that will influence subsequent survival. Hence, the RS estimates for young TAVI patients might be biased since we could not adjust for a correspondingly co-morbid young general population. Similarly, after surviving the initial high-risk period following TAVI, elderly patients are logically more robust than their counterparts in the general population. Hence, given octogenarians survive the initial high-risks it is unsurprising that they compare with the matched general population. Cardiac teams will select patients cautiously in the eldest age group and this could lead to selection bias. Paradoxically, the older TAVI patients had fewer baseline risk factors than the younger patients did, likely due to careful patient selection in such groups (**Table 1**). The current analysis suggests that given such careful selection practices, elderly patients should continue to be considered for TAVI, given that they appear to tolerate the risks of the procedure well and their mortality risks “return to baseline” within one year. Recent trial data highlights a potential expansion of TAVI into intermediate risk patients 5, and there is growing interest in identifying cases where TAVI will be futile 28. In terms of AS related mortality, the current study highlights that elderly patients are still viable and appropriate candidates. Arguably, one should consider improvements in quality of life and readmissions when debating if TAVI should be undertaken in the very elderly, particularly for cost effectiveness estimation. Such data were unavailable in the current analysis. Consequently, while the mortality risk in the elderly returned to that of the matched general population, we were unable to investigate if there were corresponding improvements in patient’s quality of life.

Finally, there have been rapid temporal developments of TAVI procedure technology and practice. This study found that the excess mortality, over that in the general population, immediately following TAVI was less for patients who underwent the procedure in 2011-2014. The reasons behind the faster decrease in excess hazards for 2011-2014 procedure years are unclear from the current work, but likely reflect the changes in patient selection/risk and advances in procedural techniques/valves. Mortality rates following diagnosis of AS are decreasing with time 29, with the current work suggesting similar temporal improvements following TAVI after accounting for competing causes of death.

Limitations

Several limitations need to be considered when interpreting the results of this study. One of the main limitations is that associations cannot be interpreted as casual but rather highlight those needing explanation. As discussed above, a limitation of the methodology is that there is selection bias in the entire TAVI cohort, which might have led to a false negative result in the younger patients. An assessment of all AS patients (treated surgically, by TAVI or conservatively) might negate such selection bias, but this data was unavailable; we recommend further work in this area. Similarly, it is impossible to determine what drives excess mortality since the RS could not be decomposed into that from AS, that from TAVI and that from co-morbidities that are correlated with AS. Indeed, the ONS life tables do not stratify by co-morbidities observed in the TAVI registry, which could influence the conclusions regarding the age and year subgroups. Additionally, the ONS population life tables lag the census information in the UK TAVI registry, with this analysis assuming the life tables in 2015 were the same as those in 2014. Although this could lead to bias in the calculation of expected mortality rates for 2015, the amount of variation in the life tables between years for any given age, sex and country stratum was minimal. Finally, we were only able to investigate mortality as an endpoint, without data on quality of life that is increasingly being used to identify TAVI effectiveness in the elderly.

## Conclusions

In conclusion, this study demonstrates good long-term RS in patients undergoing TAVI procedures in the UK. After surviving the initially high-risk period following TAVI, survival in elderly patients returned to that expected within the general population by three years.

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# Disclosures

None.

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# Figure Legends

## Figure 1. Kaplan-Meier curves of observed and relative survival. A relative survival of one implies the observed survival is the same as the expected survival in the matched general population.

## Figure 2. Daily hazard ratios for the whole TAVI cohort (A) and across subgroups of procedure year (B), age groups (C) and sex (D). Estimated daily hazard ratios were calculated as the observed hazard of mortality divided by the expected hazard from the matched general population. The lines are the smoother through each of the estimated daily hazard ratios, with 95% CIs shaded.

## Figure 3. Cumulative excess hazard curves for the whole TAVI cohort (A) and across subgroups of procedure year (B), age groups (C) and sex (D). An increasing (decreasing) cumulative excess hazard indicates worse (better) mortality hazard in the TAVI population compared with that expected of the general population. A cumulative excess hazard of zero implies that the observed survival is the same as the expected survival from the general population.

## Figure 4. Cumulative mortality curves on the transformed time scale per age category. The horizontal axis represents the mortality rate expected in each representative population, while the vertical axis shows the observed mortality on this transformed time-scale. The dashed line represents the null hypothesis that the matched background mortality rates apply.

## Figure 5. Time-dependent excess hazard ratios from the flexible parametric relative survival model. An excess hazard ratio of one means that the excess hazard (over that in the general population) was the same between groups.

## Figure 6. Predicted cumulative excess hazard curves for patients aged 75, 85 and 95 years, across increasing procedure year, obtained from the flexible parametric relative survival model. 95% confidence intervals are indicated by the shaded areas.

# Tables

**Table 1**. Baseline and procedural characteristics of the UK TAVI dataset and across age subgroups.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** | **TAVI Cohort (n=6420)** | **Age <80 years (n=2213)** | **Age 80-85 years (n=1754)** | **Age ≥85 years (n=2453)** | **p-value\*** |
| Age, mean [range] | 81.3 [29-101] | 73.1 [29-79] | 82.2 [80-84] | 88.0 [85-101] | <0.001 |
| Females, n (%) | 2972 (46.3%) | 867 (39.2%) | 788 (44.9%) | 1317 (53.7%) | <0.001 |
| Diabetes |  |  |  |  | <0.001 |
|  Non-diabetic, n (%) | 4908 (76.4%) | 1520 (68.7%) | 1323 (75.4%) | 2065 (84.2%) |  |
|  Dietary control, n (%) | 282 (4.39%) | 105 (4.74%) | 78 (4.45%) | 99 (4.04%) |  |
|  Oral medicine, n (%) | 844 (13.1%) | 379 (17.1%) | 250 (14.3%) | 215 (8.76%) |  |
|  Insulin, n (%) | 351 (5.47%) | 198 (8.95%) | 91 (5.19%) | 62 (2.53%) |  |
| Current or ex-smoker, n (%) | 3313 (51.6%) | 1306 (59.0%) | 923 (52.6%) | 1084 (44.2%) | <0.001 |
| Creatinine, *µ*mol/L, mean [range] | 114.3 [29.0-1044.0] | 118.8 [39-1044] | 115.4 [38-681] | 109.4 [29-554] | <0.001 |
| Renal Failure †, n (%) | 390 (6.07%) | 169 (7.64%) | 118 (6.73%) | 103 (4.20%) | <0.001 |
| MI |  |  |  |  |  |
|  within 90 days of TAVI, n (%) | 145 (2.26%) | 51 (2.30%) | 39 (2.22%) | 55 (2.24%) | 0.984 |
|  within 30 days of TAVI, n (%) | 62 (0.97%) | 24 (1.08%) | 18 (1.03%) | 20 (0.82%) | 0.607 |
| Asthma/ COPD, n (%) | 1679 (26.2%) | 744 (33.6%) | 472 (26.9%) | 463 (18.9%) | <0.001 |
| Extracardiac Arteriopathy, n (%) | 1519 (23.7%) | 603 (27.2%) | 422 (24.1%) | 494 (20.1%) | <0.001 |
| Calcification of ascending aorta, n (%) | 1173 (18.3%) | 428 (19.3%) | 345 (19.7%) | 400 (16.3%) | 0.005 |
| Atrial Fibrillation/ flutter, n (%) | 1568 (24.4%) | 482 (21.8%) | 466 (26.6%) | 620 (25.3%) | <0.001 |
| Previous Cardiac Surgery, n (%) | 1999 (31.1%) | 1009 (45.6%) | 611 (34.8%) | 379 (15.5%) | <0.001 |
| Previous PCI, n (%) | 1300 (20.2%) | 475 (21.5%) | 371 (21.2%) | 454 (18.5%) | 0.020 |
| Weight (Kg), mean [range] | 74.0 [32.0-190.0] | 80.1 [32-190] | 74.0 [33-141.7] | 68.5 [32-163] | <0.001 |
| Height (m), mean [range] | 1.65 [1.10-2.36] | 1.67 [1.10-2.01] | 1.65 [1.15-1.97] | 1.63 [1.16-2.36] | <0.001 |
| Critical preoperative state, n (%) | 105 (1.64%) | 50 (2.26%) | 25 (1.43%) | 30 (1.22%) | 0.015 |
| CCS Class 4, n (%) | 77 (1.20%) | 30 (1.36%) | 19 (1.08%) | 28 (1.14%) | 0.698 |
| NYHA Class ≥ III | 5140 (80.1%) | 1776 (80.3%) | 1413 (80.6%) | 1951 (79.5%) | 0.593 |
| LVEF |  |  |  |  | <0.001 |
|  ≥ 50%, n (%) | 3907 (60.9%) | 1246 (56.3%) | 1066 (60.8%) | 1595 (65.0%) |  |
|  30 − 49%, n (%) | 1870 (29.1%) | 676 (30.5%) | 502 (28.6%) | 692 (28.2%) |  |
|  *<* 30%, n (%) | 585 (9.11%) | 272 (12.3%) | 165 (9.41%) | 148 (6.03%) |  |
| Procedure Urgency |  |  |  |  | 0.161 |
|  Elective, n (%) | 5624 (87.6%) | 1911 (86.4%) | 1550 (88.4%) | 2163 (88.2%) |  |
|  Urgent, n (%) | 749 (11.7%) | 280 (12.7%) | 193 (11.0%) | 276 (11.3%) |  |
|  Emergency/ Salvage, n (%) | 40 (0.62%) | 19 (0.86%) | 8 (0.46%) | 13 (0.53%) |  |
| Valve Type |  |  |  |  | 0.248 |
|  Edwards SAPIEN, n (%) | 3496 (54.5%) | 1179 (53.3%) | 938 (53.5%) | 1379 (56.2%) |  |
|  Medtronic CoreValve, n (%) | 2680 (41.7%) | 948 (42.8%) | 745 (42.5%) | 987 (40.2%) |  |
|  Other valve type, n (%) | 215 (3.35%) | 75 (3.39%) | 64 (3.65%) | 76 (3.10%) |  |
| Access Route |  |  |  |  | <0.001 |
|  TF Access, n (%) | 4795 (74.7%) | 1583 (71.5%) | 1309 (74.6%) | 1903 (77.6%) |  |
|  TA Access, n (%) | 1009 (15.7%) | 402 (18.2%) | 279 (15.9%) | 328 (13.4%) |  |
|  Other Access, n (%) | 604 (9.41%) | 225 (10.2%) | 161 (9.18%) | 218 (8.89%) |  |
| Logistic EuroSCORE, mean [range] ‡ | 21.9 [1.51-93.6] | 18.4 [1.51-86.0] | 23.2 [5.83-91.1] | 24.0 [7.96-93.6] | <0.001 |
| STS score, mean [range] ‡ | 5.06 [0.46-55.4] | 3.78 [0.46-44.6] | 5.04 [1.15-55.4] | 6.22 [1.49-44.8] | <0.001 |

*\*: p-value indicates the age group comparison. †: Defined as creatinine>200µmol/L or dialysis for renal failure. ‡: The logistic EuroSCORE and the Society of Thoracic Surgeons (STS) score predict the risk of 30-day mortality using a range of risk factors known before the operation. LVEF: Left Ventricular Ejection Fraction, MI: Myocardial Infarction, NYHA: New York Heart Association Functional Classification, TA: Transapical Access route, TF: Transfemoral Access Route*

## Table 2. Baseline characteristics across procedure year subgroups.

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Procedure Year 2007-2010 (n=1528)** | **Procedure Year 2011-2014 (n=4892)** | **p-value** |
| Age, mean [range] | 81.5 [44-99] | 81.2 [29-101] | 0.217 |
| Females, n (%) | 721 (47.2%) | 2251 (46.0%) | 0.440 |
| Diabetes |  |  | 0.184 |
|  Non-diabetic, n (%) | 1188 (77.7%) | 3720 (76.0%) |  |
|  Dietary control, n (%) | 74 (4.84%) | 208 (4.25%) |  |
|  Oral medicine, n (%) | 178 (11.6%) | 666 (13.6%) |  |
|  Insulin, n (%) | 86 (5.63%) | 265 (5.42%) |  |
| Current or ex-smoker, n (%) | 846 (55.4%) | 2467 (50.4%) | 0.021 |
| Creatinine, *µ*mol/L, mean [range] | 118.5 [37-736] | 113.0 [29-1044] | 0.004 |
| Renal Failure\*, n (%) | 109 (7.13%) | 281 (5.74%) | 0.073 |
| MI |  |  |  |
|  within 90 days of TAVI, n (%) | 39 (2.55%) | 106 (2.17%) | 0.452 |
|  within 30 days of TAVI, n (%) | 18 (1.18%) | 44 (0.90%) | 0.424 |
| Asthma/ COPD, n (%) | 421 (27.6%) | 1258 (25.7%) | 0.112 |
| Extracardiac Arteriopathy, n (%) | 418 (27.4%) | 1101 (22.5%) | <0.001 |
| Calcification of ascending aorta, n (%) | 372 (24.3%) | 801 (16.4%) | <0.001 |
| Atrial Fibrillation/ flutter, n (%) | 359 (23.5%) | 1209 (24.7%) | 0.338 |
| Previous Cardiac Surgery, n (%) | 483 (31.6%) | 1516 (31.0%) | 0.795 |
| Previous PCI, n (%) | 332 (21.7%) | 968 (19.8%) | 0.136 |
| Weight (Kg), mean [range] | 72.2 [33-153] | 74.6 [32-190] | <0.001 |
| Height (m), mean [range] | 1.64 [1.10-1.90] | 1.64 [1.14-2.36] | 0.054 |
| Critical preoperative state, n (%) | 25 (1.64%) | 80 (1.64%) | 0.999 |
| CCS Class 4, n (%) | 26 (1.70%) | 51 (1.04%) | 0.057 |
| NYHA Class ≥ III | 1249 (81.7%) | 3891 (79.5%) | 0.161 |
| LVEF |  |  | 0.322 |
|  ≥ 50%, n (%) | 954 (62.4%) | 2953 (60.4%) |  |
|  30 − 49%, n (%) | 423 (27.7%) | 1447 (29.6%) |  |
|  *<* 30%, n (%) | 138 (9.03%) | 447 (9.14%) |  |
| Procedure Urgency |  |  | <0.001 |
|  Elective, n (%) | 1385 (90.6%) | 4239 (86.7%) |  |
|  Urgent, n (%) | 136 (8.90%) | 613 (12.5%) |  |
|  Emergency/ Salvage, n (%) | 7 (0.46%) | 33 (0.67%) |  |
| Valve Type |  |  | <0.001 |
|  Edwards SAPIEN, n (%) | 760 (49.7%) | 2736 (55.9%) |  |
|  Medtronic CoreValve, n (%) | 762 (49.9%) | 1918 (39.2%) |  |
|  Other valve type, n (%) | 0 (0%) | 215 (4.39%) |  |
| Access Route |  |  | <0.001 |
|  TF Access, n (%) | 1029 (67.3%) | 3766 (77.0%) |  |
|  TA Access, n (%) | 389 (25.5%) | 620 (12.7%) |  |
|  Other Access, n (%) | 110 (7.20%) | 494 (10.1%) |  |

*\*: Defined as creatinine>200µmol/L or dialysis for renal failure.*

*LVEF: Left Ventricular Ejection Fraction, MI: Myocardial Infarction, NYHA: New York Heart Association Functional Classification, TA: Transapical Access route, TF: Transfemoral Access Route*

## Table 3. Baseline characteristics across sex subgroups.

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Female (n=2972)** | **Male (n=3448)** | **p-value** |
| Age, mean [range] | 82.3 [30-100] | 80.4 [29-101] | <0.001 |
| Diabetes |  |  | <0.001 |
|  Non-diabetic, n (%) | 2358 (79.3%) | 2550 (74.0%) |  |
|  Dietary control, n (%) | 119 (4.00%) | 163 (4.73%) |  |
|  Oral medicine, n (%) | 338 (11.4%) | 506 (14.7%) |  |
|  Insulin, n (%) | 142 (4.78%) | 209 (6.06%) |  |
| Current or ex-smoker, n (%) | 1095 (36.8%) | 2218 (64.3%) | <0.001 |
| Creatinine, *µ*mol/L, mean [range] | 100.2 [29-649] | 126.4 [39-1044] | <0.001 |
| Renal Failure\*, n (%) | 109 (3.67%) | 281 (8.15%) | <0.001 |
| MI |  |  |  |
|  within 90 days of TAVI, n (%) | 60 (2.02%) | 85 (2.47%) | 0.262 |
|  within 30 days of TAVI, n (%) | 22 (0.74%) | 40 (1.16%) | 0.112 |
| Asthma/ COPD, n (%) | 743 (25.0%) | 936 (27.1%) | 0.044 |
| Extracardiac Arteriopathy, n (%) | 560 (18.8%) | 959 (27.8%) | <0.001 |
| Calcification of ascending aorta, n (%) | 578 (19.4%) | 595 (17.3%) | 0.029 |
| Atrial Fibrillation/ flutter, n (%) | 676 (22.7%) | 892 (25.9%) | 0.003 |
| Previous Cardiac Surgery, n (%) | 521 (17.5%) | 1478 (42.9%) | <0.001 |
| Previous PCI, n (%) | 487 (16.4%) | 813 (23.6%) | <0.001 |
| Weight (Kg), mean [range] | 67.5 [32-153] | 79.6 [38-190] | <0.001 |
| Height (m), mean [range] | 1.57 [1.10-1.94] | 1.71 [1.15-2.36] | <0.001 |
| Critical preoperative state, n (%) | 43 (1.45%) | 62 (1.80%) | 0.307 |
| CCS Class 4, n (%) | 35 (1.18%) | 42 (1.22%) | 0.972 |
| NYHA Class ≥ III | 2413 (81.2%) | 2727 (79.1%) | 0.041 |
| LVEF |  |  | <0.001 |
|  ≥ 50%, n (%) | 2067 (69.5%) | 1840 (53.4%) |  |
|  30 − 49%, n (%) | 731 (24.6%) | 1139 (33.0%) |  |
|  *<* 30%, n (%) | 147 (4.95%) | 438 (12.7%) |  |
| Procedure Urgency |  |  | 0.460 |
|  Elective, n (%) | 2613 (87.9%) | 3011 (87.3%) |  |
|  Urgent, n (%) | 340 (11.4%) | 409 (11.9%) |  |
|  Emergency/ Salvage, n (%) | 15 (0.50%) | 25 (0.73%) |  |
| Valve Type |  |  | 0.546 |
|  Edwards SAPIEN, n (%) | 1607 (54.1%) | 1889 (54.8%) |  |
|  Medtronic CoreValve, n (%) | 1244 (41.9%) | 1436 (41.6%) |  |
|  Other valve type, n (%) | 107 (3.60%) | 108 (3.13%) |  |
| Access Route |  |  | 0.013 |
|  TF Access, n (%) | 2270 (76.4%) | 2525 (73.2%) |  |
|  TA Access, n (%) | 430 (14.5%) | 579 (16.8%) |  |
|  Other Access, n (%) | 267 (8.98%) | 337 (9.77%) |  |

*\*: Defined as creatinine>200µmol/L or dialysis for renal failure.*

*LVEF: Left Ventricular Ejection Fraction, MI: Myocardial Infarction, NYHA: New York Heart Association Functional Classification, TA: Transapical Access route, TF: Transfemoral Access Route*