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Balloon-Expandable versus Self-Expanding Transcatheter Aortic Valve Replacement: A Propensity-Matched Comparison from The France-TAVI Registry

Running Title: *Van Belle et al.; THV Design, Paravalvular Regurgitation and Mortality*

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Abstract

Background: No randomized study powered to compare balloon-expandable (BE) with self-expanding (SE) transcatheter heart valve (THV) on individual endpoints after transcatheter aortic valve replacement (TAVR) has been conducted to date.
Methods: From January 2013 to December 2015, the FRANCE-TAVI nationwide registry included 12,141 patients undergoing BE-THV (Edwards, n=8038) or SE-THV (Medtronic, n=4103) for native aortic stenosis (AS). Long-term mortality status was available in all patients (median 20 months, IQR:14-30). Patients treated with BE-THV (n=3910) were successfully matched 1:1 with 3910 patients treated with SE-THV by using propensity-score (25 clinical, anatomical and procedural variables) and by date of the procedure (within 3 months). The first co-primary outcome was the occurrence of paravalvular regurgitation (PVR)≥moderate and/or in-hospital mortality. The 2nd co-primary outcome was 2-year all-cause mortality.
Results: In matched-propensity analyses, the incidence of the 1st co-primary outcome was higher with SE-THV (19.8%) compared with BE-THV(11.9%; RR=1.68; 95%CI:1.46-1.91; p<0.0001). Each component of the outcome was also higher in SE-THV patients: PVR≥moderate (15.5% vs. 8.3%; RR=1.90; 95% CI:1.63-2.22; p<0.0001) and in-hospital mortality (5.6% vs 4.2%, RR=1.34; 95%CI:1.07-1.66; p=0.01). During follow-up, all-cause mortality occurred in 899 patients treated with SE-THV (2-year mortality was 29.8%) and in 801 patients treated with BE-THV (2-year mortality 26.6%; HR=1.17; 95% CI:1.06-1.29; p=0.003). Similar results were found using inverse probability of treatment weighting using propensity score analysis.
Conclusions: The present study suggests that use of SE-THV was associated with a higher risk of PVR and higher in-hospital and 2-year mortality as compared with BE-THV. These data strongly support the need for a randomized trial sufficiently powered to compare head-to-head the latest generation of SE and BE-THV.(Registry of Aortic Valve Bioprostheses Established by Catheter [FRANCE-TAVI]; NCT01777828)
Clinical Trial Registration: URL: https://clinicaltrials.gov Unique identifier: NCT01777828

Key Words: Transcatheter aortic valve replacement; Transcatheter heart valve design; Paravalvular regurgitation; Clinical outcome; Mortality

Abbreviations
AR: aortic regurgitation
AS: aortic stenosis
BE: Balloon-expandable
GEE: generalized estimating equations
IPTW: inverse probability treatment weighting
MDCT: multi-detector computed tomography
PVR: Paravalvular regurgitation
SAVR: surgical aortic valve replacement
SE: self-expanding
TAVR : transcatheter aortic valve replacement
THV: transcatheter heart valve
TTE: trans-thoracic echocardiography
VARC-2: Valve Academic Research Consortium 2

Clinical Perspective

What is new?

- We compared the outcomes of the Balloon-expandable (BE) and self-expanding (SE) transcatheter heart valves (THV) on a large nationwide registry (12,141 patients) after propensity-matching on 25 major clinical and anatomical variables and on the time of the procedure (within 3-months).
- SE-THV recipients had a higher risk of paravalvular regurgitation (PVR), mortality at 3 months and mortality at 2 years.
- The risk of mortality remained higher after multivariable adjustment including PVR severity and of other peri-procedural events.
- This study suggests that the two most widely used THV designs may not achieve the same clinical outcomes.

What are the clinical implications?

- As TAVR is moving to be the first-line treatment for patients with aortic stenosis, this study highlights:
- The urge for a randomized clinical study sufficiently powered to compare head-to-head on individual endpoints the efficacy of the SE and BE-THV.
- The need to simplify and optimize the grading of PVR and its long term clinical impact.

Introduction

Over the last years, several randomized studies comparing transcatheter aortic valve replacement (TAVR) to surgical aortic valve replacement (SAVR) have established TAVR as a treatment option in symptomatic patients with aortic stenosis (AS) [1,2,3,4,5,6].

Most transcatheter heart valves (THV) available are designed on either a balloon-expandable (BE) or a self-expanding (SE) concept. Despite major differences, both designs are recommended to be used indifferently in most of the clinical situations. It remains unclear however, whether these 2 very different THV concepts are achieving similar or different clinical outcomes. While there is an urgent clinical need to clarify this issue in an exponentially growing therapeutic field, to date no large randomized study powered to compare the 2 THV designs on individual endpoints has been conducted or initiated.

The occurrence of paravalvular regurgitation (PVR), in particular moderate or severe, has been associated with an increased long-term mortality risk[7]. Mild PVR have also been associated with higher mortality rate in some[8], but not in all studies[9]. Small randomized studies[10] and large registries[11,12] have suggested that PVR≥moderate was more frequent with SE- than with BE-THV.

Recently, a large-scale registry suggested higher in-hospital mortality with the use of SE as compared to BE-THV[13]. Whether this difference persists over time is unclear as the excess mortality was no longer statistically significant by 30 days and as no long-term follow-up was conducted[13]. In addition, no information on PVR was available and no clear explanation was provided to elucidate the association observed in that study.

FRANCE-TAVI is a nationwide registry collecting TAVR procedures performed in French TAVR centers and their follow-up[12]. The objective of this study was to evaluate the

impact of THV design (SE vs BE) on the risk of PVR, intra-hospital mortality, and 2-year mortality using a nationwide propensity score matched comparison.

Methods

FRANCE-TAVI registry and study population

Because of the sensitive nature of the data collected for this study, reasonable requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding authors.

Since January 2013, FRANCE-TAVI (NCT01777828) prospectively includes data for all patients who had undergone TAVR in 48 out of 50 TAVR centers in France and who volunteered to participate. This registry was designed in continuity with the FRANCE-2 registry[14,12] and is an initiative of the French Society of Cardiology and the French Working Group of Interventional Cardiology with the participation of the French Society of Thoracic and Cardiovascular Surgery. All patients included in the registry provided written informed consent before the procedure including consent for anonymous processing of their data. The registry was approved by the institutional review board of the French Ministry of Higher Education and Research (CCTIRS) and by the National Commission for Data Protection and Liberties (CNIL).

For the purposes of the present analysis, a database encompassing all patients (n=12,804) included in the France-TAVI registry from January 2nd 2013 to December 31st 2015 was locked. Patients with a previous SAVR (n=559; including those referred for a valve-in-valve procdures) and those treated with a different THV-design (n=104; including Lotus-THV, Boston Scientific; Directflow-THV, DirectFlow Medical; JenaValve-THV, JenaValve Technology) were excluded

from the analysis to achieve a total number of 12,141 patients treated with SE(Medtronic) or BE(Edwards Lifesciences) THV-design (Supplemental Figure 1).

Patient's selection and TAVR procedure

The decision to perform TAVR, choices of vascular approach and THV-design were based on a heart-team assessment at each participating center. Procedures and post-procedural management were performed in accordance with each site's routine protocol. Thirty-day follow-up was recommended in the case-report form and performed either on-site or by telephone contact with the patient and their physician depending on each site's protocol. Both commercially available valves were used: the BE–THV SAPIEN-XT (Jan. 2013-last quarter 2014) or SAPIEN 3 (last quarter 2014-Dec. 2015) valves (Edwards Lifesciences) and the SE-THV Corevalve valve (Medtronic). For each device, 4 sizes were available (BE-THV: 20, 23, 26 and 29 mm, and SE-THV: 23, 26, 29 and 31mm).

Pre-procedural sizing was performed using multi-detector computed tomography (MDCT) imaging. The technical aspects of the TAVR procedure have been previously reported in detail[14,15].

Evaluation of aortic regurgitation on Trans-Thoracic Echocardiography

Pre-procedural trans-thoracic echocardiography (TTE) were performed in all patients and post-procedural TTE was performed before hospital discharge with a median at day 3 (IQR=2-4). Pre-TAVR native aortic regurgitation (AR)[16] and post-TAVR AR grading was site reported and not centrally adjudicated. AR grading was defined as "mild", "moderate" or "severe" as described in France 2[11]. The analysis was based on a multi-window, multi-parameter approach integrating the data of semi-quantitative and qualitative parameters, which include visual assessment of the number of jets, jet width, and the circumferential extent of PVR and evaluation

of regurgitant volume[17], following the European and American Society of Echocardiography guidelines[16,18] and Valve Academic Research Consortium(VARC)-2 recommendations[19].

Follow-up

Mortality data was acquired in all patients from an INSEE(Institut national de la statistique et des études économiques) query on April 12th 2016, with dates of death available, with a median follow-up of 20 months (IQR=14-30). Deaths were classified as cardiovascular unless a clear non-cardiovascular cause was identified. Other follow-up adverse events, including re-hospitalization, were site reported and assessed according to the VARC-2 classification[19].

Clinical Outcome

Two co-primary outcomes were defined. The 1st co-primary outcome of the study was the assessment of PVR at discharge. Because PVR can only be evaluated in patients alive, this was achieved by defining "the occurrence of either PVR≥moderate on TTE before discharge or in-hospital all-cause mortality" as estimate of PVR. The 2nd co-primary outcome of the study was 2-year all-cause mortality.

Secondary outcomes were: 1) each individual component of the 1st co-primary outcome, 2) procedural and in-hospital events (requirement for a second THV, stroke, myocardial infarction, major or life-threatening bleeding, major vascular complication, permanent pacemaker) and 3) post-procedural transprosthetic gradient by echocardiography. Follow-up events including hospitalization for acute cardiac event or for valve re-intervention, stroke, cardiovascular mortality and the composite of all-cause mortality, stroke or acute cardiac event were also reported.

Data collection and management (see Supplemental appendix)

Statistical analysis

Full details are available in Supplementary appendix. We assessed the effect of THV-design on short (PVR and/or intra-hospital all-cause mortality, mean and high residual gradient) and 2-year follow-up (all-cause and cardiovascular follow-up mortality, hospitalization for acute cardiac event or valve re-intervention) outcomes after taking into account the potential confounding factors by using pre-specified propensity-score methods[20,21]. As the primary analysis, propensity score was used to assemble well-balanced groups (propensity score-matched cohort) and, as a sensitivity analysis, propensity score was used to weight each subject by the inverse probability of treatment (stabilized inverse propensity score as weight) and generate an inverse probability treatment weighting (IPTW) cohort. Both analyses were performed to estimate the average treatment effect, namely the effect of treatment on the entire population eligible to TAVR. The propensity score was estimated using a non-parsimonious multivariable logistic regression model, with the THV-design (SE vs. BE) as the dependent variable and all of the baseline characteristics listed in Table 1 as the independent variables, since they were all considered potential confounders linked to clinical outcome. Patients treated with SE-THV were matched 1:1 to patients treated with BE-THV according to date of procedure and propensity score using the greedy nearest neighbor matching algorithm according to a caliper width of 0·2 standard deviation of logit of propensity score and using the procedural date which should be within 3 month of each other[22,23]. Because of missing baseline data (range 0-14%), leading to 24.5% of the study sample with at least 1 missing value among confounders included in propensity score calculation, treatment effect sizes were estimated using multiple imputation method.

In propensity-score matched cohort, between-group comparisons (SE vs. BE-THV) were done using a generalized estimating equations (GEE) model (binomial distribution, log function)

with a compound symmetry working correlation structure for binary outcomes, a linear mixed model with the matched blocks as random effect for continuous, Fine and Gray (by treating death as competing risk) and Cox's regression models for long-term outcomes with robust sandwich variance estimator to account the matched design. In IPTW cohort, comparisons were done using log-binomial (binary outcomes), linear mixed model (quantitative outcomes), Fine and Gray and Cox's regression models (long-term outcomes), using the stabilized inverse propensity score as weight, and including the year of intervention as covariate. Propensity-score matched and IPTW analyses were adjusted for center, by including center as random effect in log-binomial and linear mixed models and as stratification factors in Cox's and Fine and Gray models. We assessed the proportional hazard assumption using Schoenfeld residuals plots[24]; since the proportional hazard assumption was violated for all-cause and cardiovascular mortalities, the treatment effect size was modeled using time-dependent coefficients[25]. We further investigated the heterogeneity in treatment effect size for the occurrence of PVR≥moderate (and/or in-hospital all-cause mortality) across key subgroups. Finally, predictors of all-cause and cardiovascular mortalities were assessed using univariable and multivariable Cox's regression models. Falsification outcomes, including mortality for malignancy and infection (individual or combined criteria), were post-hoc analysed to acknowledge possible residuals confounding related to the non-randomized controlled design.

Statistical testing was conducted at the two-tailed α-level of 0·05. Data were analyzed using the SAS software version 9.3(SAS Institute).

Results

Population

From February 2013 to December 2015, a total of 12,141 patients with a severe native aortic stenosis were treated by TAVR in 48 centers and received either a BE-THV (n=8038) or a SE-THV (n=4103) (Supplemental Figure 1).

Baseline characteristics according to THV-design, before and after propensity score-matching and after handling missing values by multiple imputation are presented in Table 1. Baseline characteristics before matching and handling missing values are presented in Supplemental Table 1. The distributions of propensity score according to THV-design are reported in Supplemental Figure 2. Before matching, most characteristics were already well balanced (absolute standardized difference ≤10%), except that patients treated with a BE-THV had a lower mean aortic annulus diameter, were more often treated in hybrid room, by femoral approach, and in the second study period (after January 2015) than patients treated by SE-THV. These differences were controlled after propensity-score matching (Table 1, Supplemental Figure 3) where 3910 matched pairs could be found.

PVR and in-hospitality mortality according to BE- or SE-THV

In the propensity-score matched cohort, post-procedural PVR≥moderate and/or in-hospital mortality occurred more frequently in patients treated with SE-THV (19.8%, n=776) than in patients treated with BE-THV (11.9%, n=466; matched-RR:1.68; 95% CI:1.47-1.91, Table 2). A similar difference was found in the IPTW cohort (RR:1.74; 95%CI:1.57-1.92, Table 2) as well as in the sensitivity analysis performed before handling missing outcome (i.e. on patients with available data on PVR status by TTE) with a matched- and IPTW-RRs of 1.66 (95%CI:1.46-1.88) and 1.73 (95%CI:1.57-1.89) respectively.

Each component of the 1st co-primary outcome occurred more frequently in patients receiving the SE-THV. In the propensity-score matched cohort, PVR≥moderate was more frequent with SE- than BE-THV (15.5%, n=606; vs 8.3%, n=326; matched-RR=1.90; 95%CI:1.63-2·22, Table 2). In-hospital mortality was also higher in patients receiving a SE- than a BE-THV (5.6%, n=217; vs 4.2%, n=164; matched-RR=1.33; 95%CI:1.06-1.165, Table 2). A similar difference was observed in IPTW cohort (Table 2) as well as in sensitivity analysis performed before handling missing outcome with a matched- and IPTW-RR of 1.88(95%CI:1.16-2.20) and 2.04 (95%CI:1·81-2·31), respectively.

A similar difference was also observed when comparison was restricted to either older (before Sept. 2014) or newer (after Dec 2014) THV iterations (Supplemental Table 2 and 3).

Among procedural and in-hospital events, implantation of a 2nd THV during the procedure and need of new pacemaker were more frequently observed in patients treated with a SE- than a BE-THV in the propensity-score matched and IPTW cohorts (p<0·0001 for both events, Table 2). Higher rates of stroke and myocardial infarction were also found in patients receiving a SE-THV in both propensity-score matched and IPTW cohorts, although difference in stroke did not reach the significance level (Table 2). Conversely, mean transprosthetic gradient (p<0.0001 for propensity-score-matched and IPTW cohorts) and rate of patients with a mean gradient>20 mmHg (p=0.17 for propensity-score-matched cohort and p=0.004 for IPTW cohort) were higher in patients receiving the BE-THV device.

Two-year clinical outcome according to BE- or SE-THV-design

During follow-up (median duration 20 months, IQR:14-30), 2390 patients died (including 1828 from cardiovascular death, Supplemental Table 1). In the propensity-score matched cohort, all-cause mortality occurred in 899/3910 patients treated by SE-THV (24-month KM, 29·8%) and in

801/3910 patients treated by BE-THV (24-month KM, 26·6%), corresponding to a matched-HR of 1.17 (95%CI:1.06-1.28) (Figure 1 and Table 3; Supplemental Figure 4 for KM event curve in overall cohort before matching). However, proportional hazard assumption was not satisfied, since the excess mortality risk of SE-THV compared to BE-THV was only observed for the first-3 months period (HR=1.37, 95%CI=1.16-1.60, Table 3). Similar results were found in IPTW cohort, with an HR associated with SE-THV of 1.38(95% CI:1.21-1.58) for 3-month mortality. When only cardiovascular mortality was considered, SE-THV remained associated with higher short-term mortality both in matched- and IPTW cohorts (Table 3). The incidence of reported hospitalization for acute cardiac event or valve intervention was also higher in patients receiving SE-THV versus BE-THV (Supplemental Table 4).

Differences in clinical outcome persisted when comparisons were restricted to either older (before Sept. 2014) or newer (after Dec 2014) THV iterations (Supplemental Table 2 and 3, Supplemental Figure 5).

Subgroup analyses

In the propensity-score matched cohort, the relation between the occurrence of the primary outcome and THV-design was consistent across key subgroups, except for delivery approach and study period, in which a significant interaction was observed (Figure 2A).

The difference in the occurrence of the 1st co-primary outcome between SE-THV and BE-THV was stronger in patients treated via femoral approach (RR=1.82; 95%CI:1.56-2.13) than in those with a non-transfemoral access (RR=1.20; 95%CI:0.94-1.53, p for heterogeneity=0.004, Figure 2A). This was related to lower risk of events in patients treated via transfemoral as compared to non-transfemoral with a BE-THV (11.1% vs 15.1%) while the opposite was observed with a SE-THV(20.1% vs 17.6%).

The difference was also stronger in the second (≥01 January 2015, RR=2.23; 95%CI:1.71-2·94) as compared to the first-study period (<01 January 2015, RR=1.48; 95%CI:1.28-1.72; p for heterogeneity=0.006). This was related to a greater reduction of events between the first and second period in patients treated with BE-THV (14.3% vs. 7.9%) than in patients treated with SE-THV(21.0% vs. 18.0%). Similar heterogeneities were observed in IPTW cohort (Figure 2B, p for heterogeneity<0·001 for both). In addition, a significant heterogeneity across gender was found (p for heterogeneity=0.02), with a stronger THV-design difference in men (RR=1.92; 95%CI:1.68-2.19) than in women (RR=1.56; 95%CI:1.36-1.79). The same was true for the occurrence of a PVR≥moderate considered alone (Supplemental Figure 6).

PVR and 2-year mortality

As shown in Supplemental Table 5, PVR≥moderate was associated with a higher rate of 2-year all-cause and cardiovascular mortality, in the overall study population and in each THV-design. The other parameters associated with all-cause and cardiovascular mortalities by univariate analysis among baseline characteristics are presented in Supplemental Table 6. In multivariate analysis including univariate baseline predictors, both PVR severity and THV-design were independently associated with a higher risk of all-cause and cardiovascular mortality (Supplemental Table 7).

Falsification outcomes

Falsification outcomes (death from malignancy, death from infection or the composite of both) were observed at similar frequencies in patients treated with SE or BE-THV as observed in the propensity-score matched cohort and in the IPTW cohort (Supplemental Table 4).

Discussion

The present propensity-score matched comparison of 7,820 patients with native AS undergoing TAVR based on the nationwide FRANCE-TAVI registry is the largest observational study to date comparing SE-THV and BE-THV on PVR and 2-year clinical outcome including mortality. This study, in which patients were carefully matched on 25 major clinical and anatomical variables and on the time of the procedure (within 3-months), reports that use of SE-THV was associated with higher risk of PVR, PVR and/or in-hospital mortality and 2-year mortality as compared with use of BE-THV. The association of THV type with 2-year mortality remained after multivariable adjustment including PVR severity and other peri-procedural events.

THV-design and PVR

This study, reporting on patients treated during the 2013-2015 period, demonstrates a higher incidence of PVR with SE- as compared to BE-THV, irrespective of valve generation. Anatomical and procedural characteristics were included in the propensity score, in particular aortic annulus diameter as measured by MDCT and the procedural route of delivery. The date of the procedure (within 3 months) was also incorporated in the matching process. As the study was running on a 3-year inclusion period, this allowed comparing each patient with a patient treated during the same time window (same valve generation, same level of expertise). Analyses restricted to the "older" period and to the "newer" period provided similar results with the main analysis (Supplemental Table 2 and 3, Supplemental Figure 5).

These results of the period 2013-2015 are in line and confirm the observations made with the older generations of THV when optimal sizing using MDCT was not routinely implemented, in particular in the period 2010-2011 in the FRANCE-2 registry[11] and in the period 2012-2013 in the CHOICE Study[10]. The higher incidence of PVR with SE-THV was observed in all subgroups

but the magnitude was stronger when the procedure was performed via femoral delivery (+88%) as previously observed[11], and in those treated after January 2015 (+127%). The latter observation should be associated with the release during the last year of the study of the last generation of BE-THV (SAPIEN-3), featuring an anti-leak skirt, and of the newer generation of SE-THV. While the former allowed to decrease PVR rate from 9.2% to 6% compared with the previous years, the latter was not associated with a major impact on PVR (15.9% to 14.8%). Whether the newer iteration of SE-THV (Evolut-Pro) featuring an outer pericardial wrap will achieve to mitigate this major difference is unknown. A recent small non-randomized comparison did not show a significant difference in PVR rates between the two last iterations of SE-THV (Evolut vs Evolut-Pro)[26].

The remarkably low rate of PVR achieved in randomized clinical trials[9,3] was not replicated in an all-comers real-life registry irrespective of THV design (PVR rate>5%). This could be related to different characteristics of randomized clinical trials which cannot be replicated in everyday practice such as the contribution of only high-volume expert centers, the use of centralized CT core laboratory valve sizing or the exclusion of patients when results are anticipated to be suboptimal.

PVR and mortality

PVR≥moderate has been consistently associated with higher short-term and long-term mortality[27,14]. Although it has been suggested that the severity of PVR in SE-THV recipients could decrease over time or that PVR anatomy and grading differs between SE- and BE-THV, the present study confirms that a PVR≥moderate as measured at 3 days is associated with a similar 40% additional risk of death for both BE- and SE-THV, suggesting that if PVR could regress, it does at a similar rate for both devices and/or that the timing and the magnitude is not

sufficient to impact mortality differently at 2-years. While there are discordant results regarding the role of mild or mild-to-moderate PVR on mortality[27,28] , we observed that mild PVR was also associated with an additional risk of death (+13-18%). The potential deleterious long-term impact of mild PVR, which is observed in more than 30% in "low-risk" patients[29], will have to be further elucidated as the use of TAVR expands in this population.

THV-design and mortality

In the absence of head-to-head sufficiently-powered comparison the equipoise between the two THV designs is hypothetical. The small CHOICE[10] and SOLVE-TAVI(NCT02737150) randomized non-inferiority trials did not report mortality difference, but included only a few hundreds of patients and were not powered to investigate mortality as primary endpoint.

The present study demonstrates that the use of a SE-THV was associated with 16% higher risk of death at 2 years compared with the use of a BE-THV. This is explained by a 36% higher risk of death during the first 3 months with the 2 mortality curves remaining parallel after that period. These findings confirm the recent observation by the CENTER(Cerebrovacular-EvenNts-in-Patients-Undergoing-TranscathetER-aortic-valve-implatation)-collaboration initiative of a higher in-hospital mortality with SE-THV compared to BE-THV[13]. However, in that study in which the latest follow-up was at 30 days, the mortality difference was no longer present at that time (p=0.10), and the authors concluded that "there was no difference in 30-day mortality rates between both valve types". On the contrary, the present study, which is providing a much longer follow-up, demonstrates that the mortality difference observed between the 2 THV designs remains significant at 2 years (p=0.003).

The other limitations of the study by Vlastra include a very heterogeneous population originating from 10 different sources, the lack of information on PVR, and finally the lack of explanation for the "in-hospital mortality" finding which disappeared by 30 days.

Our study suggests that part of the additional risk of death observed with SE-THV may relate to a higher risk of PVR, and also to a higher risk of in-hospital events, including stroke, myocardial infarction and pacemaker implantation. However, the additional mortality risk observed with SE-THV persists after adjustment on all baseline and procedural characteristics and all peri-procedural complications, including PVR, which is highly suggestive of direct and specific effect related to valve design. In addition, this observation, combined to the early separation of survival curves could also suggest that PVR is partly acting as a marker rather than being the main driver of the mortality difference between the 2 THV designs. More granular registry data are needed to identify the parameters associated with higher mortality risk, such as occurrence and type of conduction disorders, valve calcium score, prosthesis hemodynamics, left ventricular dimensions, valve thrombosis, delayed coronary events.

Even if designs and clinical endpoints may have been slightly different between the landmarks trials evaluating BE-THV or SE-THV vs SAVR; transfemoral BE-THV was consistently superior to SAVR in high[2], intermediate[9] and low risk[5] patients whereas SE-THV achieved only superiority to SAVR in high-risk patients[3,4,6]. Our study sheds fresh light on these previous results and suggests that TAVR study findings should not be generalized as a class-effect regardless of the SE or BE-THV design.

Limitations

Observational registries are the only way to capture all-comers data on a national scale, but several limitations should be considered when interpreting the results. PVR grading are site-

reported and were not analyzed in a core laboratory, which may have resulted in potential reporting bias and heterogeneity in PVR grading among centers. Clinical events, including re-hospitalization are site-reported and not adjudicated, therefore exposing to the risk of under-reporting. However, mortality data are complete are they are obtained from an INSEE query. Furthermore, there is no reason to believe that under-reporting by the sites of some clinical events would differ according to type of THV. In addition, the lack of difference in PVR severity among centers once adjusted to the type of THV does not support presence of heterogeneity in PVR grading. This issue was further taken into account in multivariable analyses of predictors of PVR where adjustment for "participating centers" was done which reinforce interpretation of the main finding of this study.

It is not a randomized trial and potential differences in unmeasured variables might remain despite the risk-adjustment matching process. Among others the presence of extensive valve calcification, massively calcified aortic root, or small femoral vessel size were not measured and could be more frequent in patients receiving a SE-THV. Such residual confounders could explain all or part of the mortality difference. However, the baseline clinical, anatomical and procedural characteristics of this very large cohort were already well balanced between the 2 populations (Table 1). The propensity-score matching process involving>25 variables was able to further "balance" the very few variables which were not, in particular aortic annulus diameter and delivery approach. Further, the analysis of falsification endpoints found no signs of a hidden bias exaggerating the mortality difference observed between the 2 THV groups. Similar methodology using registry data and propensity-score analysis has previously been highly predictive of the results of randomized studies, as in the study by Thourani et al.[30]

predicting accurately the results of the PARTNER-2 study[9], or in the study by Makkar et al.[31] investigating the use of TAVR in patient with bicuspid vs tricuspid aortic stenosis.

It remains to be demonstrated whether the differences observed in the present study would still stand whether comparing the newer SE-THV (Evolut-Pro) to the SAPIEN-3. While the Evolut-Pro does not appear to be associated with a significantly lower risk of PVR compared to previous iterations of SE-THV[25], on multivariable analysis the significant difference between BE-THV and SE-THV with respect to mortality persisted despite comprehensive adjustment for several factors including PVR (Supplemental Table 7). Finally, the 4 THVs iterations (Corevalve, Evolut, SAPIEN-XT, SAPIEN-3) investigated in the present study are also those used in the randomized studies investigating the benefit of TAVR vs SAVR, including the most recent ones. In particular, the SAPIEN-3 was the BE-THV used in all patient undergoing TAVR in PARTNER 3[5], while the Corevalve and Evolut were used in the vast majority (80%) of patients undergoing TAVR in the "Evolut Low Risk Study"[6], the other 20% receiving the Evolut-Pro.

Conclusion and clinical perspective

The present study suggests important differences in clinical outcome according to THV design, as use of SE-THV was associated with a higher risk of all-cause mortality at 2 years as compared with BE-THV. However, as the propensity-score matching-approach cannot rule out residual confounders, and as some of the most recent THV iterations were not part of the investigation, there is an urgent need to conduct a randomized trial sufficiently powered to compare head-to-head the latest generation of SE- and BE-THV on all-cause mortality. The present results also strengthen the need to refine the identification and grading of PVR and its long-term clinical impact[31,32].

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Table 1. Baseline Characteristics According to SE- or BE-THV Design Before and After Matching.

	Before Matching *			After Matching *†		
Characteristics	**SE-THV** (n=4103)	**BE-THV** (n=8038)	**ASD, %**	**SE-THV** (n=3910)	**BE-THV** (n=3910)	**ASD, %**
Clinical characteristics						
Age, y mean ± SD	83.5 ± 7.0	83.5 ± 7.1	0.4	83.5 ± 7.1	83.5 ± 9.0	0.5
Men	2027 (49.4)	3939 (49.0)	0.8	1922 (49.2)	1908 (48.8)	0.6
NYHA class						
I	210 (5.1)	325 (4.1)	7.8	189 (4.8)	161 (4.2)	7.5
II	1210 (29.5)	2232 (27.8)		1161 (29.7)	1099 (28.1)	
II	2257 (55.0)	4698 (58.4)		2152 (55.0)	2295 (58.7)	
IV	426 (10.4)	783 (9.7)		408 (10.4)	355 (9.1)	
Log.EuroSCORE, median (IQR)	14.0 (9.0 to 22.5)	15.0 (9.6 to 23.0)	5.8‡	14.0 (9.0 to 22.6)	15.0 (9.6 to 22.2)	4.1‡
High operative risk	1509 (36.8)	3193 (39.7)	6.1	1451 (37.1)	1471 (37.6)	1.1
BMI, kg/m^2, mean ± SD	26.5 ± 5.4	26.5 ± 5.3	0.6	26.5 ± 5.4	26.5 ± 6.6	0.5
Diabetes mellitus	1065 (25.9)	2106 (26.2)	0.6	1016 (26.0)	997 (25.5)	0.9
Hypertension	2722 (66.3)	5439 (67.8)	2.8	2604 (66.6)	2603 (66.6)	0.1
CAD	1830 (44.6)	3401 (42.3)	4.6	1724 (44.1)	1764 (45.1)	1.8
Previous stroke or TIA	467 (11.4)	873 (10.9)	1.6	444 (11.4)	441 (11.3)	0.1
PAD	965 (23.5)	1814 (22.6)	2.3	914 (23.4)	899 (23.0)	0.7
Atrial fibrillation	1016 (24.8)	1997 (24.8)	0.2	973 (24.9)	983 (25.2)	0.7
Permanent pacemaker	629 (15.3)	1093 (13.6)	4.9	586 (15.0)	607 (15.5)	1.3
Previous CABG	464 (11.3)	857 (10.7)	2.1	437 (11.2)	459 (11.8)	1.7
Respiratory insufficiency	871 (21.2)	1592 (19.8)	3.5	812 (20.8)	846 (21.6)	1.8
Renal insufficiency‖	210 (5.1)	421 (5.2)	0.5	197 (5.1)	206 (5.3)	0.7
Pre-procedural imaging						
Aortic annulus diameter, mm, mean± SD	24.2 ± 2.8	23.5 ± 2.7	27.9	24.1 ± 2.7	24.0 ± 2.7	2.2
LVEF, %, mean (SD)	54.7 ± 13.7	55.5 ± 13.7	5.6	54.9 ± 14.0	54.7 ± 15.3	1.9
<30%	186 (4.5)	334 (4.2)	4.6	170 (4.4)	185 (4.8)	1.9
30% to 49%	991 (24.1)	1805 (22.5)		926 (23.7)	931 (23.8)	
≥50%	2926 (71.3)	5898 (73.4)		2814 (72.0)	2794 (71.5)	
AVA, cm^2, median (IQR)	0.7 (0.5 to 0.8)	0.7 (0.5 to 0.8)	0.5‡	0.7 (0.5 to 0.8)	0.7 (0.5 to 0.8)	0.3‡
Trans-aortic gradient, mmHg, mean ± SD	47.1 ± 16.0	47.6 ± 16.0	2.8	47.3 ± 16.1)	47.2 ± 18.0	0.5

AR grade≥2	871 (21.2)	1442 (17.9)	8.3	798 (20.4)	825 (21.1)	1.6
MR grade≥2	941 (22.9)	1776 (22.1)	2.0	888 (22.7)	884 (22.6)	0.3
Procedural characteristics						
Room of intervention						
Catheterization laboratory	1607 (39.2)	2681 (33.4)	13.7	1501 (38.4)	1472 (37.7)	2.9
Hybrid Room	2343 (57.1)	4917 (61.2)		2260 (57.8)	2267 (58.0)	
Operating Room	154 (3.7)	440 (5.5)		149 (3.8)	171 (4.4)	
General anesthesia	2166 (52.8)	4085 (50.8)	3.9	2037 (52.1)	2111 (54.0)	3.4
Transfemoral approach	3287 (80.1)	6754 (84.0)	10.2	3183 (81.4)	3130 (80.1)	3.1
Years of intervention						
January 2013 to December 2014	2619 (63.8)	4123 (51.3)	25.6	1470 (37.6)	1475 (37.8)	0.3
January 2015 to December 2015	1484 (36.2)	3915 (48.7)		2440 (62.4)	2435 (62.3)	

Values expressed as numbers (%) unless otherwise indicated. *calculated after handling missing data using multiple imputation procedure (m=10). †matching on propensity score and date of TAVR procedure (± 3 month). ‡estimated using the rank-transformed data. ‖serum creatinine >200 µmol/L.
Abbreviations: AR=aortic regurgitation; ASD=Absolute standardized difference; AVA=aortic valve area; BE=Balloon-expandable; BMI=body mass index; CABG=coronary artery bypass grafting; CAD=coronary artery disease; LEVF=left ventricular ejection fraction; MR=mitral regurgitation; NYHA=New York Heart Association; PAD=peripheral arterial disease; SD=standard deviation; SE=self-expanding; TIA=transient ischemic attack; TTE=transthoracic echocardiography.

Table 2. Paravalvular Regurgitation, Intra-hospital Mortality and Other Procedural and in-hospital Clinical Events According to SE- or BE-THV Design in Propensity-Score Matched and IPTW Cohorts.

Outcomes	SE-THV	BE-THV	Effect size (95%CI)	*P*-Value
Propensity-Score Matched Cohort	N=3910	N=3910		
PVR≥moderate and/or Intra-hospital mortality*	776 (19.8)	466 (11.9)	1.68 (1.47 to 1.91)†	<0.0001
PVR≥moderate	606 (15.5)	326 (8.3)	1.90 (1.63 to 2.22)†	<0.0001
Intra-hospital mortality	217 (5.6)	164 (4.2)	1.33 (1.06 to 1.65)†	0.01
Other procedural and intra-hospital events				
Second THV	143 (3.7)	38 (1.0)	3.79 (2.40 to 5.99)†	<0.0001
Stroke	96 (2.5)	70 (1.8)	1.38 (0.98 to 1.94)†	0.058
Myocardial infarction‡	14 (0.4)	7 (0.2)	2.07 (1.11 to 3.88)†	0.02
Major or life-threatening bleeding	398 (10.2)	356 (9.1)	1.03 (0.89 to 1.19)†	0.68
Major vascular complication	292 (7.5)	270 (6.9)	1.02 (0.85 to 1.22)†	0.81
Permanent pacemaker implantation	871 (22.3)	431 (11.0)	2.08 (1.83 to 2.35)†	<0.0001
Post-procedural transprosthetic echocardiography gradient				
Mean gradient (median, IQR)	7 (5 to 10)	10 (7 o 13)	-0.21 (-0.24 to -0.19)‖	<0.0001
Mean gradient>20 mmHg	75 (1.9)	102 (2.6)	0.75 (0.48 to 1.16)‖	0.17
IPTW Cohort	N=4103	N=8038		
PVR≥moderate and/or Intra-hospital mortality*	817 (19.9)	871 (10.8)	1.74 (1.57 to 1.92)#	<0.0001
PVR≥moderate	640 (15.6)	605 (7.5)	2.05 (1.80 to 2.33)#	<0.0001
Intra-hospital mortality	229 (5.6)	307 (3.8)	1.33 (1.12 to 1.58 #	0.001
Other procedural and Intra-hospital events				
Second THV implantation	151 (3.7)	66 (0.8)	4.26 (3.18 to 5.71 #	<0.0001
Stroke	99 (2.4)	143 (1.8)	1.31 (0.99 to 1.71)#	0.051
Myocardial infarction‡	15 (0.4)	11 (0.1)	2.51 (1.14 to 5.46)#	0.02
Major or life-treating bleeding	418 (10.2)	651 (8.1)	1.10 (0.97 to 1.24)#	0.13
Vascular complications	299 (7.3)	518 (6.4)	0.98 (0.84 to 1.13)#	0.74
Permanent pacemaker implantation	903 (22.0)	895 (11.1)	2.06 (1.88 to 2.25)#	<0.0001
Post-procedural transprosthetic echocardiography gradient				
Mean gradient (median, IQR)	7 (5 to 10)	10 (7 to 13)	-0.23 (-0.25 to -0.21)**	<0.001
Mean gradient>20 mmHg	79 (1.9)	245 (3.1)	0.65 (0.49 to 0.88)**	0.004

Values are n(%) or median (IQR). Effect sizes are relative risk or mean difference ($\log_e$) in mean transprothetic gradient calculated using BE-THV as reference group.

*pre-specified as 1st co-primary outcome. †calculated using a GEE model for binary data with a log link function to account the matched sets and including center as random effect. ‡ST-elevation myocardial infarction related to acute coronary obstruction. ‖calculated using a linear mixed model (on log-transformed data) including matched sets and center as random effects. #calculated using a log-binomial regression model weighted by inverse probability of treatment using propensity score, including center as random effect and year of intervention as fixed effect. **calculated using a linear mixed model (on log-transformed data) weighted by inverse probability of treatment using propensity score, including center as random effect and year of intervention as fixed effect. Values and effect sizes were calculated after handling missing values for variables included in the propensity score and outcomes by multiple imputation.

Abbreviations: AR=aortic regurgitation, BE=balloon-expandable, CI=confidence intervals, GEE=Generalized Estimating Equations, IPTW=inverse probability of treatment weighting, SE=self-expanding.

Table 3. Follow-up 2-year Mortality according to the SE- vs BE-THV-design In Propensity-Score Matched and IPTW Cohorts.

Outcomes	**SE-THV**	**BE-THV**	**HR (95%CI)**	***P-V*alue**
Propensity-Score Matched Cohort	**N=3910**	**N=3910**		
Follow-up all-cause mortality	899 (29.8)	801 (26.6)	1.17 (1.06 to 1.28)*	0.002
0 to 3 months	*381*	*286*	*1.37 (1.16 to 1.60)**	*0.0001*
3 to 6 months	*104*	*92*	*1.23 (0.88 to 1.70)**	*0.22*
6 month to end of follow-up	*414*	*423*	*1.00 (0.85 to 1.18)**	*0.89*
Follow-up cardiovascular mortality	675 (23.3)	612 (20.9)	1.18 (1.03 to 1.32)*	0.001
0 to 3 months	*270*	*192*	*1.47 (1.19 to 1.82)**	*0.0004*
3 to 6 months	*77*	*77*	*1.15 (0.80 to 1.65)**	*0.44*
6 month to end of follow-up	*328*	*343*	*1.01 (0.82 to 1.20)**	*0.86*
IPTW Cohort	N=4103	N=8038		
Follow-up all-cause mortality	958 (29.9)	1432 (25.7)	1.18 (1.08 to 1.29)†	<0.0001
0 to 3 months	*402*	*541*	*1.38 (1.21 to 1.58)†*	*<0.0001*
3 to 6 months	*112*	*183*	*1.21 (0.93 to 1.56)†*	*0.19*
6 month to end of follow-up	*444*	*708*	*1.03 (0.90 to 1.17)†*	*0.66*
Follow-up cardiovascular mortality	721 (23.4)	1107 (20.5)	1.19 (1.05 to 1.34)†	0.001
0 to 3 months	*286*	*374*	*1.46 (1.24 to 1.73)†*	*<0.0001*
3 to 6 months	*84*	*155*	*1.14 (0.85 to 1.53)†*	*0.37*
6 month to end of follow-up	*351*	*578*	*1.00 (0.86 to 1.5)†*	*0.88*

Values in brackets in columns 2 and 3 are cumulative incidence at 2-year expresses as % (calculated using Kalbfleisch and Prentice for follow-up hospitalizations by treating death as competing risk, or using Kaplan-Meier method for mortality) * calculated using a Fine and Gray or Cox's regression model stratified by center with the robust sandwich variance estimate to account the matched sets. † calculated using a Fine and Gray or Cox's regression model stratified by center, weighted by inverse probability of treatment using propensity score and including year of intervention as covariable. Number of events, cumulative incidence and HRs were calculated after handling missing values for variables included in the propensity score by multiple imputation. Abbreviations: BE=balloon-expandable, CI=confidence intervals, HR=hazard ratio, IPTW=inverse probability of treatment weighting, SE=self-expanding.

Figure Legends

Figure 1. Kaplan-Meier Curves of All-cause Mortality (A) and Cardiovascular Mortality (B) According to SE- vs BE-THV design in Matched-propensity score cohort.

Kaplan-Meier estimates and number of patients at risk were calculated after handling missing values for variables included in the propensity score by multiple imputation (using a complementary log-log as normalizing transformation for survival probabilities).

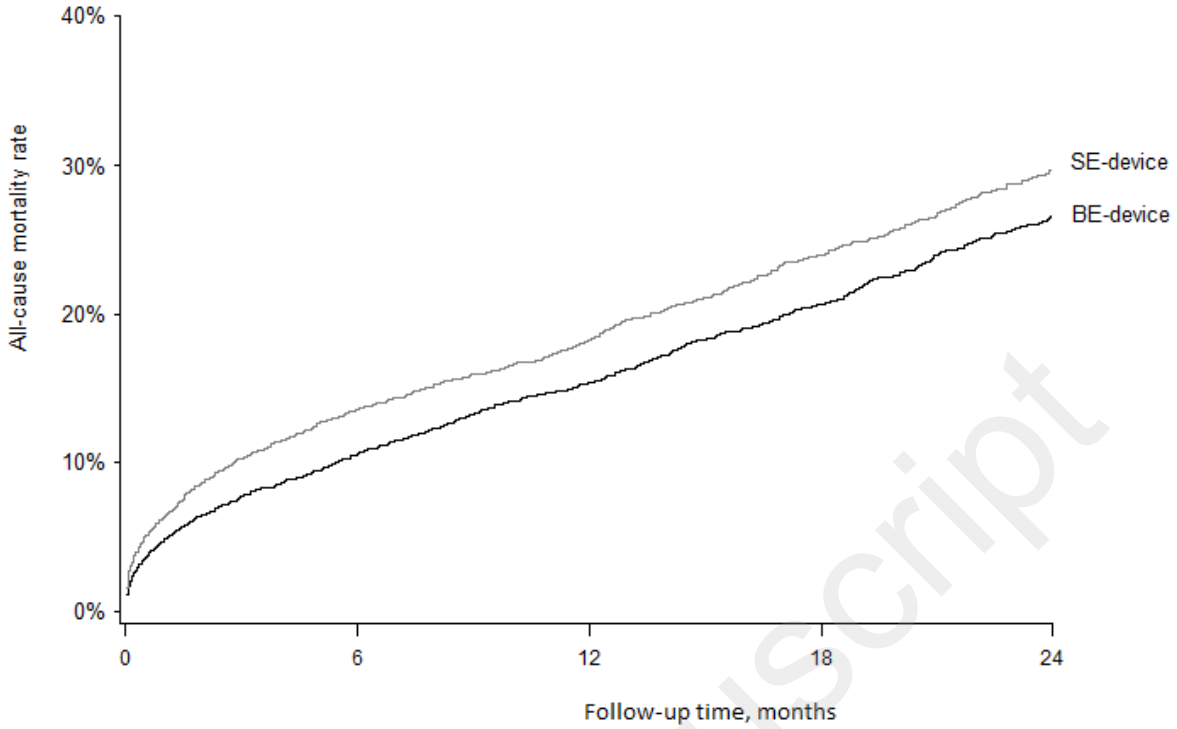
Figure 2. Comparisons of the occurrence of the 1st co-Primary Outcome (PVR≥moderate and/or in-hospital mortality) Between SE- and BE-THV design according to key subgroups In Propensity-Score Matched (A) and IPTW (B) Cohorts.

Panel A: RRs were calculated using a GEE model for binary data (with a log link function) to account the matched sets and after adjustment for center (random effect). P het indicates p-value for heterogeneity. Number of events (%), and RRs were calculated after handling missing values for variables included in the propensity score by multiple imputation. Abbreviations: AR=aortic regurgitation, BE=balloon-expandable, CI=confidence intervals, GEE=Generalized Estimating Equations, MR=mitral regurgitation, RR=relative risk, SE=self-expanding.

Panel B: RRs were calculated using a binary log-binomial regression model before and after inverse probability of treatment weighting using propensity score, adjustment for center (random effect) and year of intervention (fixed effects). P het indicates p-value for heterogeneity. Number of events (%), and RRs were calculated after handling missing values for variables included in the propensity score by multiple imputation. Abbreviations: AR=aortic regurgitation,

BE=balloon-expandable, CI=confidence intervals, IPTW: Inverse probability of treatment weighting, MR=mitral regurgitation, RR=relative risk, SE=self-expanding.

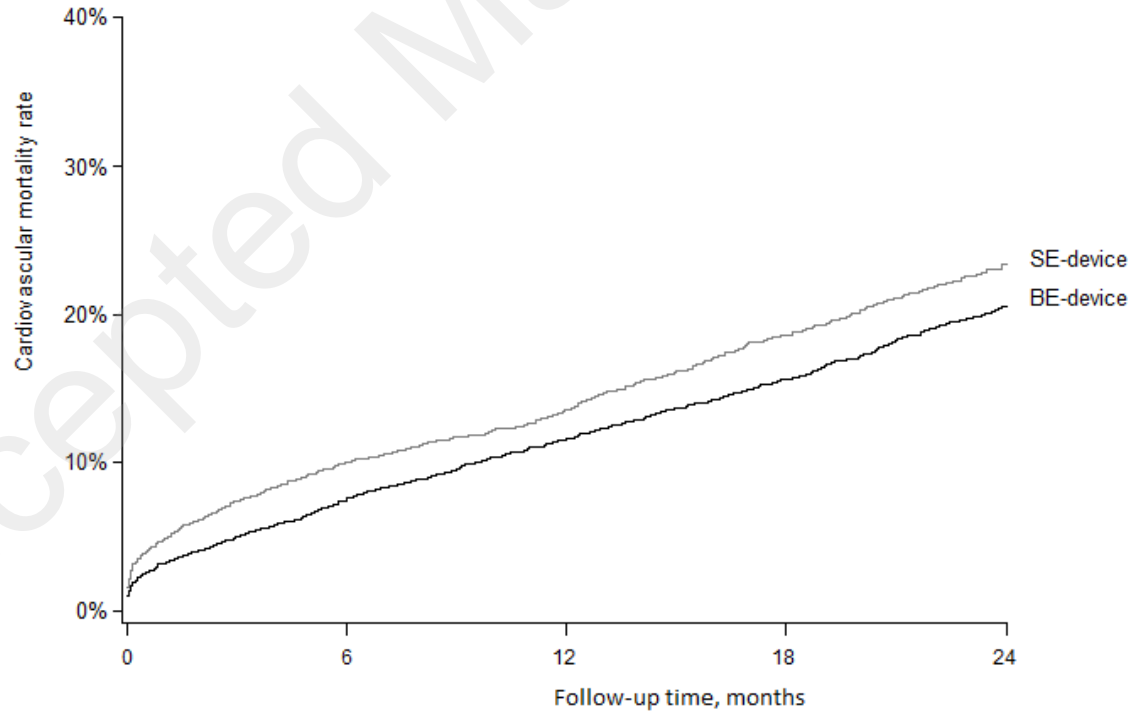
A)



Number of patients at risk :

SE-device	3910	2704	2077	1333	859
BE-device	3910	2843	2156	1405	888

B)

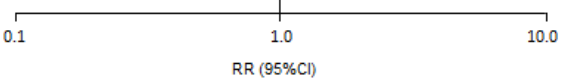


Number of patients at risk :

SE-device	3910	2704	2077	1333	859
BE-device	3910	2843	2156	1405	888

A)

Subgroups	SE-device (n=3910)	BE-device (n=3910)	Matched propensity-score RR (95%CI)	*P*	*P* Het
Overall	776/3910 (19.8)	466/3910 (11.9)	1.67 (1.46 to 1.91)	<0.001	-
Age, yr					
<70	49/223 (22.0)	19/199 (9.5)	2.49 (1.36 to 4.54)	0.003	0.92
71 to 80	111/665 (16.6)	66/696 (9.5)	1.75 (1.27 to 2.40)	<0.001	
81 to 90	485/2487 (19.5)	299/2498 (12.0)	1.63 (1.38 to 1.93)	<0.001	
≥90	131/535 (24.5)	82/517 (15.8)	1.56 (1.16 to 2.09)	0.003	
Gender					
Women	365/1988 (18.3)	238/2002 (11.9)	1.55 (1.30 to 1.85)	<0.001	0.23
Men	411/1922 (21.4)	228/1908 (11.9)	1.79 (1.50 to 2.13)	<0.001	
Diabetes					
No	587/2894 (20.3)	364/2913 (12.5)	1.63 (1.41 to 1.88)	<0.001	0.53
Yes	189/1016 (18.6)	102/997 (10.2)	1.79 (1.34 to 2.39)	<0.001	
Pre-procedural AR grade ≥2					
No	575/3112 (18.5)	333/3087 (10.8)	1.71 (1.44 to 2.02)	<0.001	0.63
Yes	200/798 (25.1)	133/825 (16.1)	1.59 (1.26 to 2.02)	<0.001	
Pre-procedural MR grade ≥2					
No	548/3023 (18.1)	338/3026 (11.2)	1.63 (1.40 to 1.89)	<0.001	0.53
Yes	228/887 (25.7)	128/884 (14.5)	1.77 (1.38 to 2.28)	<0.001	
Delivery approach					
Non-femoral	128/727 (17.6)	117/780 (15.1)	1.20 (0.94 to 1.53)	0.14	0.004
Femoral	648/3183 (20.3)	348/3130 (11.1)	1.82 (1.56 to 2.13)	<0.001	
Aortic annulus diameter, mm					
<22.0	143/697 (20.5)	88/709 (12.5)	1.63 (1.21 to 2.18)	0.001	0.91
22.0 to 23.9	187/988 (18.9)	130/1077 (12.0)	1.58 (1.25 to 2.00)	<0.001	
24.0 to 25.9	209/1061 (19.7)	112/988 (11.3)	1.76 (1.39 to 2.22)	<0.001	
≥26.0	237/1164 (20.3)	136/1136 (12.0)	1.70 (1.37 to 2.08)	<0.001	
Year of intervention					
<2015	512/2440 (21.0)	349/2435 (14.3)	1.48 (1.28 to 1.72)	<0.001	0.006
>2015	264/1470 (18.0)	117/1475 (7.9)	2.23 (1.71 to 2.91)	<0.001	



B)

Subgroups	SE-device (n=4103)	BE-device (n=8038)	Unadjusted RR (95%CI)	*P*	IPWT propensity score RR (95%CI)	*P*	*P* Het
Overall	817/4103 (19.9)	871/8038 (10.8)	1.84 (1.67 to 2.03)	<0.001	1.74 (1.57 to 1.92)	<0.001	-
Age, yr							
<70	50/235 (21.1)	41/426 (9.6)	2.21 (1.49 to 3.27)	<0.001	2.14 (1.47 to 3.11)	<0.001	0.66
71 to 80	123/709 (17.3)	129/1393 (9.2)	1.87 (1.46 to 2.41)	<0.001	1.82 (1.43 to 2.30)	<0.001	
81 to 90	504/2593 (24.2)	559/5158 (10.8)	1.79 (1.58 to 2.03)	<0.001	1.69 (1.49 to 1.92)	<0.001	
≥90	140/566 (24.8)	142/1061 (13.4)	1.85 (1.47 to 2.33)	<0.001	1.74 (1.39 to 2.16)	<0.001	
Gender							
Women	378/2076 (18.2)	449/4099 (11.0)	1.66 (1.45 to 1.91)	<0.001	1.56 (1.36 to 1.79)	<0.001	0.020
Men	439/2027 (21.7)	422/3939 (10.7)	2.02 (1.77 to 2.31)	<0.001	1.92 (1.68 to 2.19)	<0.001	
Diabetes							
No	617/3038 (20.3)	681/5932 (11.5)	1.77 (1.58 to 1.98)	<0.001	1.67 (1.49 to 1.87)	<0.001	0.17
Yes	200/1065 (18.8)	190/2106 (9.0)	2.09 (1.72 to 2.54)	<0.001	1.94 (1.60 to 2.34)	<0.001	
Pre-procedural AR grade ≥2							
No	597/3232 (18.5)	656/6596 (9.9)	1.86 (1.65 to 2.09)	<0.001	1.73 (1.54 to 1.95)	<0.001	0.58
Yes	220/871 (25.3)	221/1472 (14.9)	1.70 (1.38 to 2.07)	<0.001	1.62 (1.32 to 1.98)	<0.001	
Pre-procedural MR grade ≥2							
No	577/3162 (18.2)	631/6262 (10.1)	2.05 (1.71 to 2.45)	<0.001	1.71 (1.51 to 1.92)	<0.001	0.72
Yes	240/941 (25.5)	240/1776 (13.5)	2.04 (1.59 to 2.63)	<0.001	1.78 (1.45 to 2.17)	<0.001	
Delivery approach							
Non-femoral	147/816 (18.0)	185/1284 (14.4)	1.25 (1.02 to 1.53)	0,031	1.27 (1.04 to 1.55)	0.019	<0.001
Femoral	670/3287 (20.4)	686/6754 (10.2)	2.01 (1.80 to 2.23)	<0.001	1.86 (1.66 to 2.08)	<0.001	
Aortic annulus diameter, mm							
<22.0	144/706 (20.3)	229/1915 (8.8)	1.70 (1.39 to 2.08)	<0.001	1.59 (1.30 to 1.93)	<0.001	0.60
22.0 to 23.9	190/997 (19.0)	261/2435 (10.7)	1.77 (1.46 to 2.14)	<0.001	1.65 (1.36 to 2.00)	<0.001	
24.0 to 25.9	213/1083 (19.6)	190/1950 (9.7)	2.02 (1.65 to 2.47)	<0.001	1.92 (1.57 to 2.35)	<0.001	
≥26.0	272/1317 (20.6)	191/1738 (11.0)	1.88 (1.56 to 2.25)	<0.001	1.69 (1.40 to 2.05)	<0.001	
Year of intervention							
<2015	550/2619 (21.0)	572/4123 (13.9)	1.51 (1.35 to 1.70)	<0.001	1.53 (1.36 to 1.72)	<0.001	<0.001
>2015	267/1484 (18.0)	299/3915 (7.6)	2.36 (1.98 to 2.81)	<0.001	2.29 (1.93 to 2.71)	<0.001