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Two-year clinical outcomes after successful transcatheter aortic valve implantation with balloon-expandable versus self-expanding valves: A subanalysis of the GALILEO trial

Running title: BEV versus SEV in GALILEO

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Abstract

Background: Midterm data comparing clinical outcomes after successful implantation of self-expanding and balloon-expandable transcatheter heart valves (THV) are limited. We aimed to compare 2-year outcomes after successful transcatheter aortic valve implantation (TAVI) with the Edwards balloon-expandable or the Medtronic self-expanding THV.

Methods: Two-year outcomes were analyzed according to the implanted THV in the GALILEO trial. Major adverse cardiac and cerebrovascular events (MACCE) was a composite of all-cause death or thromboembolic events including stroke, myocardial infarction, symptomatic valve thrombosis, systemic embolism, deep-vein thrombosis, or pulmonary embolism.

Results: Among 1644 patients recruited in 136 centers across 16 countries between 2015 and 2018, 499 received a self-expanding and 757 patients received a balloon-expandable THV. Patients treated with a self-expanding THV were more likely 3ob e female, and had higher surgical risk, lower hemoglobin levels, and more frequent valve-in-valve procedures than those with a balloon-expandable THV. After multivariable adjustment, there were no significant differences in major clinical outcomes between self-expanding versus balloon-expandable THV: MACCE (17.0% vs. 13.4%, adjusted-hazard ratios [HR] 1.18, 95% confidence intervals [CI]: 0.82-1.69); all-cause death (11.4% vs. 9.3%, adjusted-HR 1.26; 95% CI: 0.78-2.05); cardiovascular

death (8.5% vs. 4.0%, adjusted-HR 1.53; 95% CI: 0.82-2.86), any stroke (5.1% vs. 3.7%, adjusted-HR 0.86; 95% CI: 0.43-1.73); major or life-threatening bleeding (5.9% vs. 6.8%, adjusted-HR 0.93; 95% CI: 0.53-1.63).

Conclusions: Two-year follow-up data from the GALILEO trial indicate that successful TAVI either with self-expanding or balloon-expandable THVs according to physician discretion did not show difference in rates of MACCE.

Clinical Trial Registration: https://www.clinicaltrials.gov. NCT02556203.

Keywords: aortic valve setenosis;balloon-expandable valve;GALILEO;major adverse cardiac and cerebrovascular events;self-expanding valve;successful implantation;transcatheter aortic valve implantation;transcatheter heart valve

Introduction

Transcatheter aortic valve implantation (TAVI) has become an alternative therapeutic option to surgical aortic valve replacement (SAVR) for elderly symptomatic patients with severe aortic valve stenosis (AS) irrespective of surgical risk(1). To optimize the TAVI procedure for individual patients, there are multiple device options with different technologies in bioprosthetic design (intra/supra-annular leaflet position, porcine/bovine leaflets, and cobalt-chromium/nitinol stent frame) and deployment systems (balloon-expandable or self-expanding)(2). As there is no definitive data to prioritize one device over another, device selection is mainly based on a local operator/heart team experience and the individual valve anatomy, focusing primarily on the successful implantation of the device with optimal outcome in terms of valve area, paravalvular regurgitation, coronary access, and conduction abnormalities. Both randomized and observational studies have provided insights into device selection aiming at successful implantation(3-10). In brief, balloon-expandable devices appear generally advantageous in terms of paravalvular regurgitation and atrio-ventricular conduction disturbances, while self-expanding devices appear generally advantageous in terms of valve hemodynamic performance and risk of annular rupture(11,12). However, it remains unclear whether there are any differences in long-term clinical outcomes between the devices once successfully implanted with intended valve performance.

GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) was a large scale, multinational, randomized clinical trial of patients without an established indication for long-term oral anticoagulation who had completed successful TAVI with any commercially available device(13,14). The present sub-analysis of the GALILEO trial was aimed to compare long-term clinical outcomes after successful implantation of the two most frequently implanted TAVI devices (Medtronic self-expanding and Edwards balloon-expandable transcatheter heart valves [THV]).

Methods

Study design

The GALILEO trial design has been published previously(13,15). In brief, patients without established indication for long-term anticoagulation and dual antiplatelet therapy were eligible for enrollment if they had undergone successful TAVI for treatment of symptomatic severe AS and were randomly assigned to either an antithrombotic treatment strategy (rivaroxaban 10 mg per day and aspirin 100 mg per day for three months followed by long-term rivaroxaban 10 mg per day monotherapy) or an antiplatelet strategy (dual antiplatelet therapy for three months followed by

aspirin monotherapy). Successful TAVI was defined as correct positioning of any single THV into the proper anatomical location with the intended valve performance and without periprocedural complications. The trial was conducted in compliance with the International Conference on Harmonization and the Declaration of Helsinki. The ethics committees and corresponding health authorities for all participating centers approved the study, and all patients provided informed written consent to participate.

In the trial, TAVI was performed by femoral or subclavian access with any approved (marketed) device type available in the specific enrolling site per country regulations. The choice of the primary access and device type were determined by a heart team assessment at each participating center, and the procedures were performed in accordance with each site's routine protocol based on established best practice guidelines. For the purpose of the present analysis, only patients who had undergone TAVI with a Medtronic self-expanding THV (CoreValve or Evolut R) and an Edwards balloon-expandable THV (SAPIEN XT or SAPIEN 3) were included; other valve types were utilized much less frequently; valve type did not affect the trial's primary endpoint analyses between the two randomized groups as previously reported[13].

Endpoints

The standardized follow-up was scheduled at 30, 90, 180 days, and every 180 days thereafter until the trial was (prematurely) terminated. Clinical endpoints of interest for the present study included major adverse cardiac and cerebrovascular events (MACCE), all-cause death, cardiovascular death, non-cardiovascular death, any stroke, myocardial infarction, and major or life-threatening bleeding. MACCE was defined as the composite of all-cause death or thromboembolic events including any stroke, myocardial infarction, symptomatic valve thrombosis, systemic embolism, deep-vein thrombosis, or pulmonary embolism. Death, stroke, myocardial infarction, and major or life-threatening bleeding were defined in accordance with the Valve Academic Research Consortium (VARC-2) criteria(16).

Statistical analysis

Categorical variables are represented as frequencies and percentages and the differences between groups are evaluated with the Chi-square test or Fisher's exact test. Continuous measures are presented as mean values ± standard deviation (SD) and compared between groups using t-test. Two-year clinical events are presented in a time-to-event manner using Kaplan-Meier methods and compared using the log-rank test. Patients were censored to the time of last known follow-up up to 720 days or death whichever came first. Univariable and multivariable Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% CIs for clinical outcomes. A

multivariable model included adjustments for baseline, procedural, and post-procedural variables: age, sex, arterial hypertension, diabetes mellitus, congestive heart failure, Society of Thoracic Surgeons (STS) risk score, coronary artery disease, peripheral artery disease, glomerular filtration rate <45 ml/min/1.73 m^2, chronic obstructive pulmonary disease, left ventricular ejection fraction, valve-in-valve procedure, and paravalvular regurgitation. The factors entered into the multivariable model for adjustment were predefined based on the presumed association with clinical outcomes of interest. All statistical analyses were performed using SAS (version 9.4, Cary, NC). Throughout the study, statistical significance was defined at two-sided p-value of <0.05.

Results

Studied population and baseline characteristics

The GALILEO trial enrolled 1,644 patients from 136 centers in 16 countries between December 2015 and May 2018. Of these enrolled patients, 499 received a Medtronic self-expanding THV (CoreValve: n=68, Evolut R: n=431) and 757 patients received an Edwards balloon-expandable THV (SAPIEN XT: n=26, SAPIEN 3: n=731), and were eligible for the present analysis (**Figure 1**).

Baseline demographics of the study population are summarized in **Table 1**. Patients treated with a self-expanding THV were less likely to be male ($p < 0.0001$) and had higher surgical risk scores (STS risk score: $p < 0.0001$, EuroSCORE II: $p = 0.0002$) and lower hemoglobin levels ($p = 0.0002$), and were more likely to have a previous permanent pacemaker implantation ($p = 0.0008$) than those with a balloon-expandable THV.

Procedural characteristics are shown in **Table 2**. The mean THV size was larger ($p < 0.0001$) and the proportion of valve-in-valve procedure was higher ($p = 0.0009$) in self-expanding than balloon-expandable THV procedures. After the procedure, a self-expanding THV was associated with a larger aortic valve area ($p = 0.0001$) and a lower mean transvalvular gradient ($p < 0.0001$), but had a higher rate of paravalvular regurgitation ($p < 0.0001$) compared with a balloon-expandable THV.

Clinical outcomes

Follow-up was complete for 96.8% of the patients, and vital status was available for 98.0%. The median follow-up duration for the study population was 17 months (interquartile range, 13 to 21). Throughout the period, there were no significant differences in the major outcomes of interest between the two THV groups (**Table 3**). Kaplan-Meier cumulative event rates for MACCE, all-cause death, and major or life-threatening bleeding are shown in **Figure 2**. At two years, MACCE occurred

in 17.0% of those with a self-expanding THV and in 13.4% of patients with a balloon-expandable THV (adjusted HR 1.18; 95% CI 0.82 to 1.69; p=0.382). The incidence of all-cause death was 11.4% in patients with a self-expanding THV and 9.3% in those with a balloon-expandable THV (adjusted HR 1.26; 95% CI 0.78 to 2.05; p=0.341). The incidence of cardiovascular death was 8.5% and 4.0%, respectively (adjusted HR 1.53; 95% CI 0.82 to 2.86; p=0.185). Rates of stroke were 5.1% and 3.7%, respectively (adjusted HR 0.86; 95% CI 0.43 to 1.73; p=0.673), and rates of myocardial infarction were 3.2% and 3.1%, respectively (adjusted HR 1.45; 95% CI 0.68 to 3.10; p=0.331). Major or life-threatening bleeding occurred in 5.9% of patients with a self-expanding THV and 6.8% of those with a balloon-expandable THV (adjusted HR 0.93; 95% CI 0.53 to 1.63; p=0.793).

A sensitivity analysis was conducted to compare the two most prevalent and contemporary device subtypes (Evolut R and SAPIEN 3) (**Table 4**). The results were qualitatively similar to the main analyses above.

Discussion

In the GALILEO trial, approximately half of the patients were treated with a SAPIEN type balloon-expandable THV, and one-third of the patients were treated with an Evolut type self-

expanding THV. Patients with a higher risk profile at baseline were more likely to have been selected for a self-expanding than a balloon-expandable THV. After successful TAVI, a self-expanding THV was associated with more favorable forward-flow hemodynamics but inferior outcomes in terms of paravalvular regurgitation compared with a balloon-expandable THV. Mortality, thromboembolic, and bleeding outcomes did not differ significantly up to two years after the successful implantation between a self-expanding and a balloon-expandable THV.

To date, there are two multicenter, randomized clinical trials comparing Medtronic self-expanding and Edwards balloon-expandable THVs for the treatment of severe symptomatic AS(3,4,17,18). The first randomized study compared the Medtronic CoreValve (n=121) versus the Edwards SAPIEN XT (n=120): the use of the former resulted in a lower rate of device success (77.5% versus 95.9%, P <0.001; defined as successful deployment with correct positioning of the device and intended valve performance) compared to the latter(3); this overall result was mostly driven by the rate of post-procedure paravalvular regurgitation. Despite this difference in device success rate, there were no significant differences in clinical outcomes up to five years between the two devices although the study was limited by the small sample size(17,18). The largest randomized clinical trial to date, compared newer generations of the two devices: the Medtronic Evolut R (n=219) versus the Edwards SAPIEN 3 (n=219). In this trial, the two devices appeared rather

equivalent in terms of the primary composite endpoint including all-cause mortality, stroke, moderate or severe paravalvular regurgitation, and new permanent pacemaker implantation at 30 days (28% vs. 26% respectively, P for equivalence = 0.04)(4). However, the rates of moderate or severe paravalvular regurgitation (3.4% versus 1.5%) and new permanent pacemaker implantation (23% versus 19%) were numerically higher in the Evolut R arm than the SAPIEN 3 arm. No long-term data has been reported so far from this trial.

Long-term comparative data of the two devices have been reported from multiple observational studies(9,10,19,20). In a large propensity score-matched analysis from the FRANCE-TAVI nationwide registry, 3,910 patients treated with a Medtronic self-expanding THV (CoreValve) were matched with 3,910 patients treated with an Edwards balloon-expandable THV (SAPIEN XT or SAPIEN 3). The use of a self-expanding THV was associated with a higher risk of paravalvular regurgitation as well as in-hospital and two-year mortality compared with the use of a balloon-expandable THV(9). Similarly, another large propensity score-matched study based on the French administrative hospital database including 10,459 matched pairs (the Medtronic Evolut R versus the Edwards SAPIEN 3) reported higher rates of all-cause death, cardiovascular death, rehospitalization for heart failure, and new permanent pacemaker implantation in the Evolut R than the SAPIEN 3 during the mean follow-up of one year(10). It remains unclear whether the long-term differences in

clinical outcomes were directly related to the valve design or the consequence of the procedural success and baseline patient characteristics due to residual confounding.

The present sub-analysis of the GALILEO trial suggests that major clinical outcomes did not differ significantly between Medtronic self-expanding and Edwards balloon-expandable THVs up to two years once the device was successfully implanted. This observation significantly adds to the literature on TAVI device comparison with important clinical implications. In real-world clinical practice, the choice between balloon-expandable and self-expanding THVs is primarily based on the possibility for safe and successful implantation taking into consideration the individual anatomy rather than long-term outcomes(2). Some anatomical considerations, such as small annulus and left ventricular outflow tract calcification may result in preferential use of a self-expanding THV with a larger effective orifice area and passive radial force rather than a balloon-expandable THV(11,12). Due to the smaller diameter of the delivery system, a Medtronic self-expanding THV may also be preferred for patients with complex and small femoral access. Conversely, an Edwards balloon-expandable THV may be preferred in other settings to minimize the risk of paravalvular regurgitation and permanent pacemaker implantation. Our findings support the current real-world clinical practice where the optimal device is chosen for the individual patient anatomy to achieve the primary goal of successful implantation with optimal device and procedural outcome. The data of

this subanalysis of GALILEO are unique by focusing only on the population with successful TAVI implantation suggesting the absence of major between device differences during long-term follow-up.

Study Limitations

Several limitations should be acknowledged when interpreting the results of the present study. First, this was a post-hoc analysis based on a large-scale multinational randomized clinical trial, in which the selection of valve type was made by a treating heart team at each participating center in a non-randomized fashion. Thus, the findings may be confounded by unmeasured variables and need to be interpreted with caution. Second, the GALILEO trial only included patients who had successful TAVI, which allows us to provide long-term outcome data of successfully implanted balloon-expandable and self-expanding THV. In turn, potential differences in procedural complications and their long-term consequences could not be evaluated in the present analysis. Finally, the study included a small proportion of patients treated with previous generation devices that are no longer in clinical use. However, the findings were largely consistent in a sensitivity analysis excluding the early generation devices.

Conclusion

Two-year follow-up data from the GALILEO trial indicate that successful TAVI either with self-expanding or balloon-expandable THVs according to physician discretion results in comparable clinical outcomes.

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Figure Legends

Figure 1. Study flow chart.

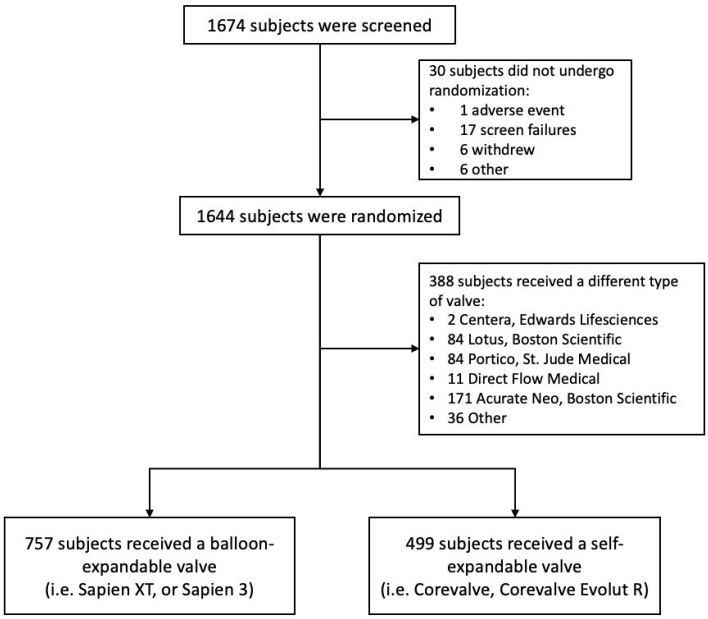
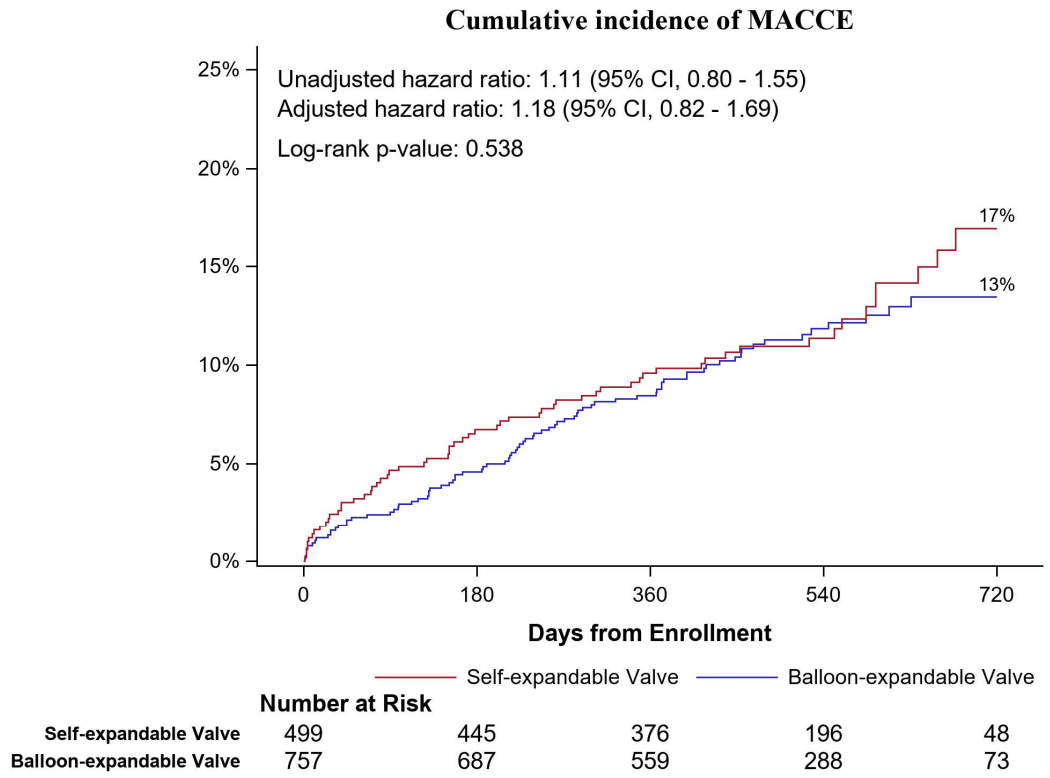
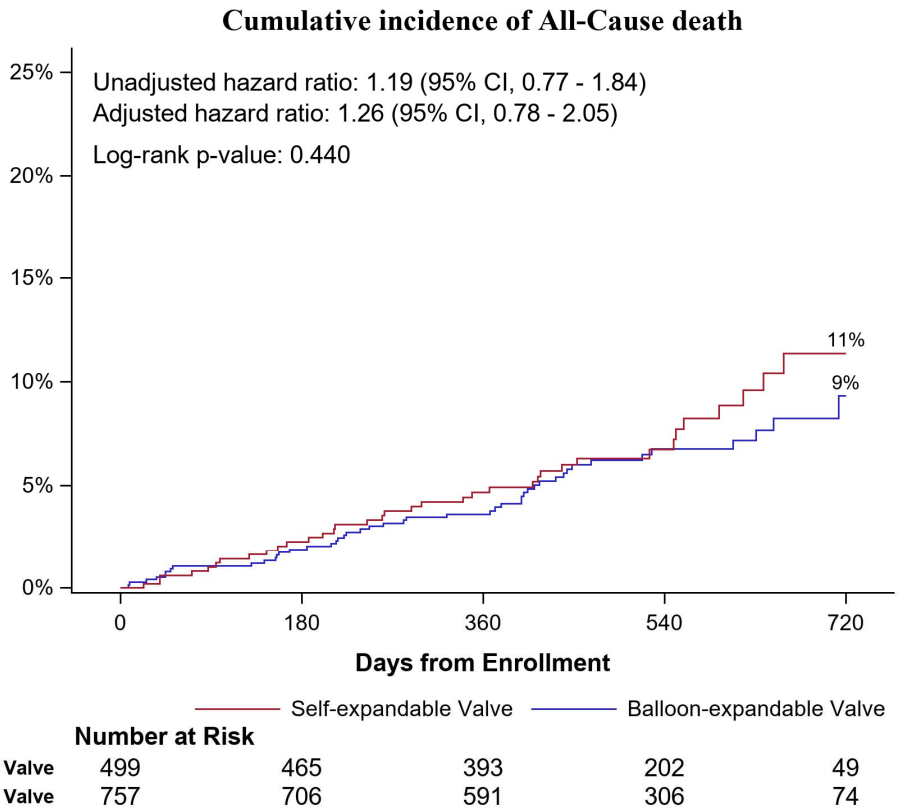


Figure 2. Kaplan-Meier Curves for major clinical outcomes.

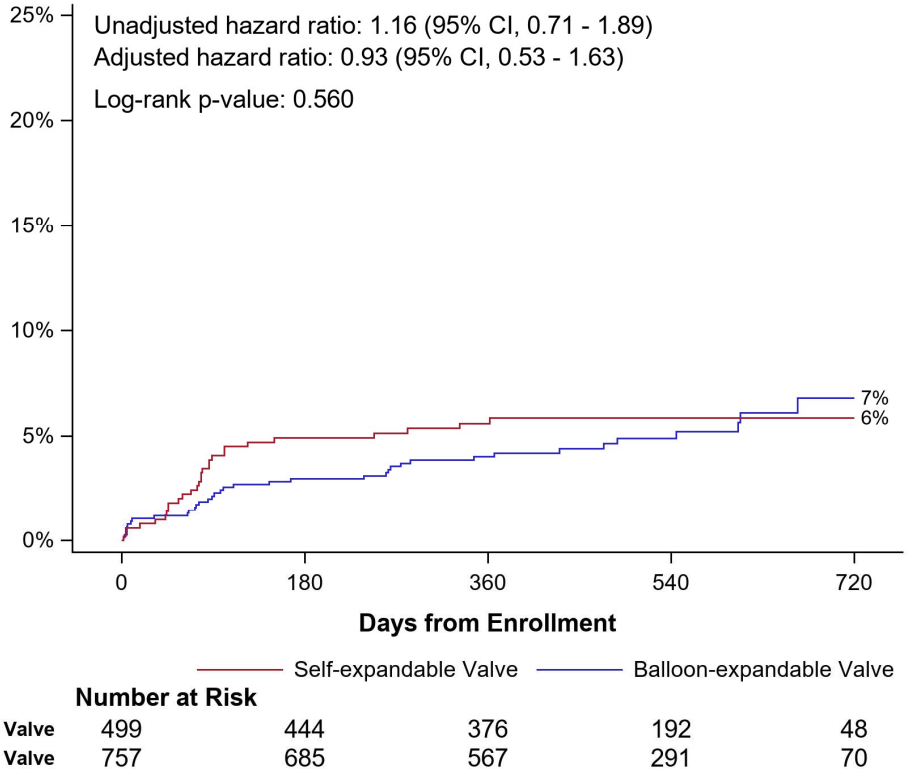



Cumulative incidence of All-Cause death
Unadjusted hazard ratio: 1.19 (95% CI, 0.77 - 1.84)
Adjusted hazard ratio: 1.26 (95% CI, 0.78 - 2.05)
Log-rank p-value: 0.440
25%
20%
15%
10%
5%
0%
11%
9%
0
180
360
540
720
Days from Enrollment
Self-expandable Valve
Balloon-expandable Valve
Number at Risk
Self-expandable Valve 499 465 393 202 49
Balloon-expandable Valve 757 706 591 306 74

8

9

Cumulative incidence of VARC-2 major, life-threatening or disabling bleeding



Number at Risk					
Self-expandable Valve	499	444	376	192	48
Balloon-expandable Valve	757	685	567	291	70

13 # Tables

14 **Table 1.** Baseline characteristics of the studied population

	Self-expanding THVs† (n=499)	**Balloon-expandable THVs‡ (n=757)**	**p-value**
Age - yr	81.0 ± 6.6	80.2 ± 6.8	0.0572
Male sex - no. (%)	203 (40.7%)	462 (61%)	<0.0001*
Baseline Body Mass Index (kg/m2)	28.0 ± 5.6	28.3 ± 5.7	0.4437
Current smoker (<1 year) - no. (%)	28 (5.6%)	32 (4.2%)	0.2604
Hypertension - no. (%)	431 (86.4%)	652 (86.2%)	0.9480
Diabetes mellitus - no. (%)	155 (31.1%)	214 (28.3%)	0.2944
EuroSCORE II	4.45 ± 3.89	3.97 ± 3.83	0.0002*
EuroSCORE II risk category - no. (%)			0.0571
Low Risk (<5%)	360 (72.1%)	587 (77.7%)	
Intermediate risk (>=5% - <=10%)	100 (20%)	114 (15.1%)	
High risk (>10%)	39 (7.8%)	54 (7.2%)	
STS risk score	4.76 ± 3.59	4.11 ± 3.58	<0.0001*

	Self-expanding THVs† (n=499)	Balloon-expandable THVs‡ (n=757)	p-value
STS risk category - no. (%)			0.0002*
Low (<3)	183 (36.7%)	352 (46.5%)	
Intermediate (>=3 - <=8)	249 (49.9%)	346 (45.7%)	
High (>8)	67 (13.4%)	59 (7.8%)	
Congestive heart failure - no. (%)	240 (48.1%)	390 (51.6%)	0.2261
NYHA class III or IV - no. (%)	150 (30.1%)	230 (30.4%)	0.8910
Coronary heart disease - no. (%)	193 (38.7%)	301 (39.8%)	0.7001
Previous stroke - no. (%)	25 (5%)	37 (4.9%)	0.9262
Peripheral artery disease - no. (%)	64 (12.8%)	71 (9.4%)	0.0547
Previous VTE - no. (%)	12 (2.4%)	14 (1.9%)	0.5009
Permanent pacemaker - no. (%)	62 (12.4%)	52 (6.9%)	0.0008*
COPD - no. (%)	62 (12.6%)	85 (11.5%)	0.5513
Baseline Creatinine - mg/dL	0.95 ± 0.30	0.96 ± 0.29	0.5528
Hemoglobin - g/dL	11.21 ± 1.46	11.53 ± 1.48	0.0002*
Glomerular filtration rate <45 - no. (%)	52 (10.4%)	70 (9.2%)	0.4918

† Self-expandable valves include: Corevalve, & Corevalve Evolut R.
‡ Balloon-expandable valves include: Sapien 3, & Sapien XT.

15 **Table 2.** Procedural characteristics of the studied population.

	Self-expanding THVs† (n=499)	**Balloon-expandable THVs‡ (n=757)**	**p-value**
Valve type - no. (%)			<0.0001*
Sapien XT, Edwards Lifesciences	0 (0%)	26 (3.4%)	
Sapien 3, Edwards Lifesciences	0 (0%)	731 (96.6%)	
Corevalve, Medtronic	68 (13.6%)	0 (0%)	
Corevalve Evolut R, Medtronic	431 (86.4%)	0 (0%)	
Aortic valve size - mm	28.3 ± 2.8	26.0 ± 2.4	<0.0001*
Valve-in-valve - no. (%)	41 (8.2%)	29 (3.8%)	0.0009*
Aortic valve area - cm^2	1.91 ± 0.60	1.80 ± 0.54	0.0001*
Mean aortic valve gradient - mmHg	8.7 ± 4.5	11.2 ± 4.7	<0.0001*
Left ventricular ejection fraction - %	57.7 ± 10.6	57.9 ± 12.1	0.7662
Paravalvular aortic regurgitation - no. (%)			<0.0001*
Absent	209 (42.1%)	455 (60.4%)	
Trace	130 (26.2%)	182 (24.2%)	

	Self-expanding THVs† (n=499)	Balloon-expandable THVs‡ (n=757)	p-value
Mild	144 (29%)	113 (15%)	
Moderate	13 (2.6%)	3 (0.4%)	
Mitral valve regurgitation			0.1496
None	146 (30.5%)	253 (34.7%)	
Grade I	267 (55.9%)	405 (55.5%)	
Grade II	50 (10.5%)	58 (7.9%)	
Grade III & IV	15 (3.1%)	14 (1.9%)	
Tricuspid valve regurgitation			0.5853
None	160 (34%)	244 (33.9%)	
Grade I	188 (39.9%)	294 (40.9%)	
Grade II	99 (21%)	156 (21.7%)	
Grade III & IV	24 (5.1%)	25 (3.5%)	

† Self-expandable valves include: Corevalve, & Corevalve Evolut R.
‡ Balloon-expandable valves include: Sapien 3, & Sapien XT.

16

17

Table 3. Clinical outcomes according to the valve design (balloon-expandable vs. self-expanding THVs).

Outcomes	Self-expanding THVs* (n=499)	Balloon-expandable THVs* (n=757)	Unadjusted Hazard Ratios (95% CI)	p-value	Adjusted Hazard Ratios† (95% CI)	p-value
MACCE	60 (17.0%)	82 (13.4%)	1.11 (0.80 - 1.55)	0.538	1.18 (0.82 - 1.69)	0.382
All-cause death, MI, or stroke	56 (16.2%)	76 (13.4%)	1.12 (0.79 - 1.58)	0.520	1.21 (0.83 - 1.76)	0.326
All-Cause death	36 (11.4%)	46 (9.3%)	1.19 (0.77 - 1.84)	0.440	1.26 (0.78 - 2.05)	0.341
Cardiovascular death	24 (8.5%)	25 (4.0%)	1.46 (0.83 - 2.55)	0.186	1.53 (0.82 - 2.86)	0.185
Non-Cardiovascular death	12 (3.2%)	21 (5.6%)	0.87 (0.43 - 1.76)	0.693	0.95 (0.44 - 2.06)	0.898
Stroke	15 (5.1%)	24 (3.7%)	0.95 (0.50 - 1.81)	0.879	0.86 (0.43 - 1.73)	0.673
Ischemic stroke	13 (4.7%)	22 (3.3%)	0.90 (0.45 - 1.78)	0.760	0.77 (0.36 - 1.61)	0.486
Myocardial infarction	15 (3.2%)	20 (3.1%)	1.13 (0.58 - 2.21)	0.713	1.45 (0.68 - 3.10)	0.331
VARC-2 major, life-threatening or disabling bleeding	28 (5.9%)	37 (6.8%)	1.16 (0.71 - 1.89)	0.560	0.93 (0.53 - 1.63)	0.793

** n (%) are Kaplan-Meier Estimates.*
† Hazard ratios were adjusted for age, sex, arterial hypertension, diabetes mellitus, congestive heart failure, STS risk score, coronary artery disease, peripheral artery disease, glomerular filtration rate <45, chronic obstructive pulmonary disease, left-ventricular ejection fraction, valve-in-valve procedure, & paravalvular aortic regurgitation.

Table 4. Clinical outcomes according to the two most prevalent valve sub-types (Medtronic Evolut R versus Edwards SAPIEN 3).

Outcomes	Evolut R, Medtronic* (n=431)	Sapien 3, Edwards Lifesciences* (n=731)	Unadjusted Hazard Ratios (95% CI)	p-value	Adjusted Hazard Ratios† (95% CI)	p-value
MACCE	51 (17.1%)	79 (13.6%)	1.10 (0.77 - 1.56)	0.607	1.17 (0.79 - 1.72)	0.433
All-cause death, MI, or stroke	48 (16.4%)	74 (13.7%)	1.11 (0.77 - 1.59)	0.588	1.21 (0.82 - 1.81)	0.340
All-Cause death	32 (12.0%)	45 (9.6%)	1.21 (0.77 - 1.91)	0.403	1.35 (0.82 - 2.24)	0.243
Cardiovascular death	22 (9.6%)	24 (4.0%)	1.56 (0.88 - 2.79)	0.127	1.71 (0.89 - 3.28)	0.105
Non-Cardiovascular death	10 (2.7%)	21 (5.9%)	0.81 (0.38 - 1.73)	0.588	0.93 (0.41 - 2.12)	0.856
Stroke	13 (5.1%)	23 (3.7%)	0.96 (0.49 - 1.90)	0.917	0.88 (0.42 - 1.84)	0.729
Ischemic stroke	11 (4.6%)	21 (3.3%)	0.89 (0.43 - 1.85)	0.760	0.75 (0.34 - 1.66)	0.479
Myocardial infarction	13 (3.3%)	19 (3.0%)	1.16 (0.57 - 2.34)	0.687	1.46 (0.65 - 3.25)	0.357
VARC-2 major, life-threatening or disabling bleeding	25 (6.1%)	36 (6.9%)	1.19 (0.71 - 1.98)	0.503	0.95 (0.53 - 1.71)	0.871

** n (%) are Kaplan-Meier Estimates.*

† Hazard ratios were adjusted for age, sex, arterial hypertension, diabetes mellitus, congestive heart failure, STS risk score, coronary artery disease, peripheral artery disease, glomerular filtration rate <45, chronic obstructive pulmonary disease, left-ventricular ejection fraction, valve-in-valve procedure, & paravalvular aortic regurgitation.