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Five-year Outcomes of Self-Expanding Versus Balloon-Expandable Transcatheter Aortic Valves: *Insights from The OBSERVANT Study*

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ABSTRACT

Background. No robust data on clinical outcomes of balloon-expandable (BE) and self-expanding (SE) transcatheter aortic valves (TAVs) beyond 2 years are currently available.

Methods. A total of 1440 patients enrolled in the multicenter OBSERVANT study, underwent transfemoral transcatheter aortic valve replacement (TF-TAVR) with either the Medtronic CoreValve (MCV) SE (n=830, 57.6%) and the Edwards SAPIEN XT (ES) BE (n=610, 42.4%) valves. Clinical outcomes of the two groups were compared after adjustment using inverse probability of treatment weighting (IPTW) and confirmed by sensitivity analysis with propensity score matching. The primary endpoint was all-cause death at 5 years.

Results. Patients receiving MCV valve showed a higher all-cause mortality at 5 years [Kaplan-Meier estimates 52.3% vs. 47.7%; Hazard ratio (HR) 1.2, 95% confidence interval (CI) 1.0-1.4, p=0.04]. Landmark analyses showed that the MCV group had the highest excess of risk for all-cause mortality at 1 year (HR 1.17, 95% CI 1.00-1.36; p=0.05), whereas there was a reversal of risk excess against the ES group starting from 3 years after the procedure (HR 0.98 and 0.99 between 3-4 and 4-5 years, respectively; p=0.86 and p=0.96,respectively). Patients receiving the MCV TAV had also a higher rate of repeat hospitalization for any cardiac cause at 5 years (cumulative incidence 46.9% vs. 42.1%; sub-distribution HR 1.18, 95% CI 1.06-1.31; p<0.01) compared to those receiving ES valve. Post-procedural, moderate/severe paravalvular regurgitation (PVR) (HR 1.5, 95% CI 1.1-1.9; p<0.01) and AKI (HR 3.9, 95% CI 2.5-6.4; p<0.01) showed to be independent predictors of 5-year all-cause mortality in multivariable analysis.

Conclusions. Patients undergoing TF-TAVR with the MCV valve had a higher all-cause mortality compared to those receiving the ES valve at 5 years. A late catch up phenomenon of patients receiving the ES valve was observed beyond 3 years. Post-procedural moderate/severe PVR seems to play a crucial role in determining this finding. Comparative studies with longer follow-up of new generation devices are needed to evaluate the benefit of each specific TAV type.

INTRODUCTION

Transfemoral transcatheter aortic valve replacement (TAVR) is now being considered a valid alternative to surgery for patients with symptomatic severe aortic stenosis (AS), regardless pre-operative mortality risk (1,2). As a consequence, the focus of TAVR is now shifting towards younger patients with a significantly longer life-expectancy.

A number of studies have shown favorable up to long-term clinical outcomes of both early- and new-generation balloon-expandable (BE) and self-expanding (SE) transcatheter aortic valves (TAVs). However, head-to-head comparisons between these two device technologies are limited and most of them do not extend beyond 1 year follow-up (3–8). Considering such a paucity of evidence, it is crucial to assess whether any difference may emerge at longer-term period between BE and SE TAVs. The aim of this analysis from the OBservational Study of Effectiveness of SAVR-TAVR procedures for severe Aortic steNosis Treatment (OBSERVANT) Study is to compare long-term clinical outcomes of patients treated with TAVR using either the Medtronic CoreValve (MCV) SE (Medtronic Inc, Minneapolis) and the Edwards SAPIEN XT (ES) BE (Edwards Lifesciences, Irvine, CA) TAVs.

METHODS

Study design and population

Details of the OBSERVANT study have been previously published. Briefly, the OBSERVANT is a prospective, multicenter registry that enrolled consecutive patients having undergone SAVR or TAVR for aortic stenosis (AS) at 93 Italian centers (34 cardiology centers and 59 cardiac surgery centers) between January 2010 and December 2012. The study was performed by the Italian National Health Institution in cooperation with the Italian Ministry of Health, the National Agency for Regional Health Services, Italian Regions, and Italian scientific societies and federations representing Italian professionals involved in the treatment. The study protocol was approved by the local ethics committee of the coordinating institution (Policlinico San Donato). All patients gave an informed consent to participate to this study. For the purposes of this analysis, we considered only patients who underwent TAVR through a transfemoral approach and received either the ES BE or the MCV SE valve. Study participant flow is reported in **Figure 1**.

Endpoints and follow-up

The primary endpoint of this study was all-cause mortality at 5 years. Secondary endpoints were stroke, myocardial infarction (MI), repeat hospitalization for heart failure (HF), repeat hospitalization for any cardiac cause and repeat aortic valve intervention at 5 years.

An administrative follow-up has been performed for all patients through a record linkage with the National Hospital Discharged Records database, for in-hospital events, and with the Tax Registry Information System, for information on life status (data provided by Ministry of Health), allowing the completeness of follow-up for all patients at 5 years.

Statistical Analysis

Continuous and categorical variables were reported as mean ± standard deviation (SD), and frequencies, respectively. Continuous variables were compared with the t-test or Wilcoxon rank sum tests, and categorical variables were compared with the chi-square statistics or Fisher's exact test as appropriate. Inverse probability of treatment weighting (IPTW) based on propensity score (PS) was used as primary tool to adjust for baseline confounding variables between the TAV study groups. Variables included in the propensity score were sex, age, body mass index (BMI), diabetes, coronary artery disease (CAD), severe renal impairment on dialysis, chronic obstructive pulmonary disease (COPD), severe frailty (Geriatric Status Scale 2 or 3), severe dyspnea (NYHA classification 3 or 4), pulmonary hypertension, left ventricle ejection fraction (LVEF), EuroSCORE 2, active malignancy and critical status leading to emergent/urgent TAVR procedure. One-to-one PS matching with the nearest neighbor method and a caliper width of 0.1 the standard deviation (SD) of propensity score logit was used as sensitivity analysis. Balance between baseline characteristics was estimated as a standardized mean difference lower than 10%.

Time-to-event curve for primary outcome was constructed with the Kaplan-Meier estimates adjusted by the IPTW. Hazard ratio (HR) for all-cause death was calculated using the IPTW-adjusted Cox proportional-hazard regression model. Cumulative incidence functions of stroke, MI, repeat hospitalization for HF, repeat hospitalization for any cardiac cause and repeat aortic valve intervention were estimated using a competing-risk regression using Fine and Gray method adjusted by the IPTW. In these analyses, death has been considered a competing event because patients under observation might have died preventing the event of interest to occur.

Finally, independent predictors of all-cause death were assessed using IPTW-adjusted multivariable logistic regression model. All statistical tests were performed

two-tailed, and a p-value <0.05 was considered as the threshold for statistical significance. Statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM Corporation, New York, USA) and R 3.4 (https://www.R-project.org/) softwares.

RESULTS

Baseline characteristics and in-hospital outcomes

A total of 1781 TAVR patients were enrolled in the OBSERVANT study. Only patients who underwent transfemoral (TF) TAVR (n=1440, 80.9%) were considered for the present analysis (**Figure 1**). Mean age was 82.0±6.0 years and mean EuroSCORE II was 7.0±7.5%, respectively. Patients received the MCV TAV in 57.6% (n=830) and the ES TAV in 42.4% (n=610) of cases.

Before adjustment, several differences were encountered between baseline characteristics of the MCV and ES cohorts. Patients undergoing TAVR with the MCV were mostly male (48.9% vs. 30.0%, p<0.01), had more frequently COPD (33.5% vs. 20.8%, p<0.01), CAD (31.4% vs. 24.6%, p<0.01) and lower LVEF (50.9±12.6 vs. 53.9±11.2 mmHg, p<0.01).

After either IPTW and PS matching adjustment, all baseline characteristics were well balanced and no variable had a standardized mean difference greater than 10%. Baseline characteristics of the MCV and the ES cohorts, before and after adjustment, are summarized in **Table 1**.

Patients receiving the MCV had a higher in-hospital mortality (4.3% vs. 2.3%, p=0.03). No differences in stroke, MI, vascular complications and acute kidney injury (AKI) were encountered between MCV and ES groups. Patients receiving the MCV had a higher rate of permanent pacemaker implantation (PPI) (22.7% vs. 4.6%, p<0.01) and more-than-mild paravalvular regurgitation (PVR) (13.4% vs. 9.7%, p=0.05) as well as a lower mean transprosthetic gradient (9.1±6.1 vs. 10.6±5.3 mmHg, p<0.01). In-hospital outcomes of MCV and ES cohorts, before and after adjustment, are reported in **Supplementary Table 1**.

Five-year outcomes

Five-year outcomes after adjustment are presented in **Table 2** and **Figures 2-3**. Patients who underwent transfemoral TAVR with the MCV valve encountered a higher rate of all-cause death at 5 years [Kaplan-Meier estimates (KM est.) 52.3% vs. 47.7%; hazard ratio (HR) 1.2, 95% confidence interval (CI) 1.0-1.4, p=0.04] compared to those receiving ES TAV (**Figure 2**). These findings were confirmed in the sensitivity analysis in the matched population (KM est. 51.6% vs. 46.7% for the MCV and the ES, respectively; HR 1.2, 95%CI 1.0-1.4, p=0.04).

Landmark analyses showed that MCV group had the highest excess of risk for all-cause mortality at 1 year (HR 1.17, 95% CI 1.00-1.36; p=0.05), whereas there was a reversal of risk excess against the ES group starting from 3 years after the procedure (HR 0.98 and 0.99 between 3-4 and 4-5 years, respectively; p=0.86 and p=0.96 respectively) (**Table 3**).

Patients receiving the MCV TAV had also a higher rate of repeat hospitalization for any cardiac cause at 5 years (cumulative incidence 46.9% vs. 42.1%; sub-distribution HR [SHR] 1.18, 95% CI 1.06-1.31; p<0.01) compared to those receiving the ES valve. On the contrary, no excess risks of the MCV versus the ES valve for MI (SHR 1.16, 95% CI 0.81-1.65; p=0.42), stroke (SHR 1.03, 95% CI 0.79-1.33; p=0.84), repeat hospitalization for HF (SHR 1.10, 95% CI 0.98-1.23; p=0.12) and repeat aortic valve intervention (SHR 0.55, 95% CI 0.12-4.95; p=0.52) were observed (**Figure 3**). These findings were confirmed at sensitivity analysis (**Table 2**).

Multivariable, logistic regression adjusted by IPTW showed that post-procedural more-than-mild PVR (HR 1.5, 95% CI 1.1-1.9; p<0.01) and post-procedural AKI (HR 3.9, 95% CI 2.5-6.4; p<0.01) were independent predictors of 5-year all-cause mortality (**Table 4**).

Finally, the impact of moderate or severe grade of PVR on 5-year prognosis is showed by time-to-event curve for all-cause mortality stratified by post-procedural grade of PVR (KM est. 48.1% vs. 49.1% vs. 60.5% for none/trace, mild and moderate/severe PVR respectively, $p_{log\text{-}rank}$<0.01) (**Figure 4**).

DISCUSSION

Supported by the excellent results of latest randomized clinical trials involving low risk patients, TAVR is now expanding its indications to younger patients (1,2). As a consequence, patients' long-term perspectives are now being considered of primary importance. Either early- and new-generation BE and SE TAVs have shown similar acute and mid-term outcomes, but head-to-head comparisons remain scarce. The purpose of this analysis from the OBSERVANT study was to compare long-term (up to 5-year) clinical outcomes of patients undergoing TF-TAVR with either the MCV or the ES TAVs in a "real world" population.

The main findings of this study were: 1) during the study period (2010-2012), patients receiving the MCV prosthesis had a higher risk profile than patients who received the ES valve; 2) after multiple adjustments, patients who underwent TF-TAVR with the MCV valve showed a higher rate of all-cause mortality at 5 years; 3) the excess of mortality risk for patients treated with the MCV valve was confined during the first years after TAVR; afterwards a gradual "late catch up" phenomenon

of patients receiving the ES valve was observed, starting from 3 years after the procedure; 4) post-procedural AKI and more-than-mild PVR were found to be independent predictors of all-cause mortality at 5 years.

Baseline characteristics of TAVR patients enrolled in OBSERVANT study were rather different according the prosthesis received. Indeed, patients undergoing TF-TAVR with the MCV had a higher predicted mortality risk (EuroSCORE II 7.2% vs. 6.7%) compared to patients who received ES valve. Moreover, they had more frequently COPD, CAD, previous cardiac surgery and a lower LVEF. The reasons for this observation are unclear; one could argue that the choice of MCV for patients with a higher risk profile was related to the willingness to pursuit a better cost-benefit ratio, as MCV device cost was lower compared to ES valve at many Italian centers during the study period. However, this is just a hypothesis and this interpretation should be taken with caution.

Different studies involving patients at higher surgical risk showed sustained clinical outcomes after TAVR with either the MCV and the ES TAVs at long-term follow-up (9–14). Nevertheless, head-to-head comparisons between these two types of TAVs are much more limited (3,15–17). A large, propensity-matched comparison from the FRANCE-TAVI registry, recently showed a higher overall mortality for patients undergoing TAVR with the MCV TAV (29.8% vs. 26.6% for patients receiving ES TAV; $p<0.01$) at 2 years. Beyond this landmark time, only the Comparison of Transcatheter Heart Valves in High Risk Patients with Severe Aortic Stenosis (CHOICE) randomized controlled trial reported outcomes of the two different TAV types up to 5 years. The authors of the CHOICE showed no differences in terms of overall mortality (47.6% vs. 53.4% for the MCV and the ES, respectively; $p= 0.38$), any stroke (16.5% vs. 17.5% for MCV and ES, respectively; $p= 0.73$), and HF re-hospitalization (22.5% vs. 28.9% for MCV and ES, respectively; $p= 0.75$) between patients receiving MCV or ES valve (17). Nevertheless, the study was not powered for these endpoints and its findings were limited by the small sample size.

In our analysis, we compared outcomes of more than one thousand patients undergoing TAVR with either MCV or ES valve from a real-world experience, with complete administrative-based follow-up data up to 5 years for mortality and several hard endpoints. We reported a higher all-cause mortality for patients receiving the MCV valve at 5 years (KM est. 52.3% vs. 47.7%; HR 1.2, 95% CI 1.0-1.4, $p=0.04$); this high excess of risk was encountered at 1 year from procedure. Beyond this landmark time, we observed a stepwise decrease of the mortality risk excess for patients who received MCV valve, and its reversal against patients who received ES valve beyond 3 years. This “late catch up” phenomenon by patients undergoing TAVR with ES valve could have different causes

and it virtually fills the gap between the differences reported by mid and long-term comparison studies. We might speculate that this finding could be related to the better long-term performances of MCV valve, whose supra-annular structure showed to guarantee lower residual gradients and larger effective orifice areas at follow-up (17). Moreover, valve thrombosis might have played a significant role in the difference between the two types of valve. Although in this regard currently available data are sparse, the CHOICE trial showed a higher, although not significant incidence of clinically evident thrombosis in patients receiving ES valve (7.3% vs. 0.8%, p=0.06) at 5 years. However, subclinical leaflet thrombosis evidenced as hypo-attenuated leaflet thickening (HALT) at CT scans, recently showed to increase over time and to have a much higher incidence (10% at 30 days and 24% at 1 year, in patients undergoing TAVR with SAPIEN 3 BE valve), and could have a relevant impact on long-term clinical outcomes (18). Unfortunately, the OBSERVANT study did not provide the collection of echocardiographic and CT assessment follow-up. In this context, long-term comparison study with echocardiographic and CT assessment follow-up are needed to reveal any difference between the two types of bioprostheses over years. We also speculate that non-cardiac causes of death might have been prevalent a few years after TAVR or more simply, in these very elderly, survival curves get closer because of the finite nature of the human beings.

Finally, post-procedural AKI and more-than-mild PVR were found to be independently associated with 5-year all-cause mortality, whereas the type of TAV itself did not affect long-term mortality. This finding is important and differs from the study by Van Belle et al., in which they observed an additional mortality risk at 2 years with SE-THV, persisting even after adjustment on all baseline and procedural characteristics and all periprocedural complications, including PVR.

Different studies have already demonstrated that either post-procedural AKI and more-than-mild PVR significantly impact on long-term mortality after TAVR (11,13,19–25). Our findings highlighted the importance of the acute results of TAVR procedure rather than TAV type used itself, although more-than-mild PVR is significantly associated with the use of MCV valve. The remarkable improvements in TAVR planning and new generation devices in recent years, have already showed to significantly improve early outcomes after TAVR, including PVR and are expected to have an important implication at long-term (27). Therefore, the findings of this analysis involving patients treated with early generation devices should be considered with caution and confirmed by long-term studies investigating new-generation TAVR devices, which demonstrated to significantly reduce the rates of PVR (27).

Limitations

The present study has some limitations. First, observational studies can lead to less strong conclusions than using an RCT because treatment was not randomly assigned and because of potential residual confounding. In the present study, an IPTW adjustment and a PS matching sensitive analysis were used to taken into account any difference between treatment groups. However, residual confounding variables cannot be excluded. Second, the lack of a centralized echocardiographic corelab is another important limitation of this study, and it remains unknown whether the valve performance contributed to the main outcome of difference in 5-year all-cause mortality. Third, the cause of death and information regarding New York Heart Association functional class and quality of life parameters at long term were not available.

CONCLUSION

Patients undergoing TAVR with MCV valve had a higher all-cause mortality compared to those receiving ES valve at 5 years. Nevertheless, a late catch up phenomenon of patients receiving ES valve was observed beyond 3 years. Patients receiving the MCV had also a higher rate of repeat hospitalization for any cardiac cause at 5 years. Post-procedural more-than-mild PVR, which was significantly more frequent in patients receiving MCV, seems to play the most important role in determining this finding. Longer comparison studies between the newest generation of these two TAV types are needed to confirm these findings and to evaluate the benefit of a specific type of bioprosthesis at long term.

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Conflict of Interest statement

C. Tamburino: Consultant for Medtronic; speaker honoraria for Meril;

M. Barbanti: Consultant for Edwards Lifesciences; Advisory board member for Medtronic and Biotronik;

The other coauthors do not have any conflict of interest related to this study.

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TABLES

Table 1. Baseline, echocardiographic and procedural characteristics before and after adjustment.

Abbreviations: AVA, Aortic Valve Area; **BMI**, Body mass Index; **CABG**, Coronary Artery Bypass Graft; **CAD**, Coronary Artery Disease; **COPD**, Chronic Obstructive Pulmonary Disease; **ES**, Edwards SAPIEN XT; **GSS**, Geriatric Status Scale; **IPTW**, Inverse Probability of Treatment Weighting; **LVEF**; Left Ventricular Ejection Fraction; **MCV**, Medtronic CoreValve; **MI**, Myocardial Infarction; **NYHA**, New York Heart Association; **PCI**, Percutaneous Coronary Intervention; **PSM,** Propensity Score Matching; **SD**, standard deviation.

	Before adjustment				After IPTW adjustment				After PSM adjustment			
	MCV (n=830)	ES (n=610)	SMD (%)	p-val	MCV (n=830)	ES (n=610)	SMD (%)	p-val	MCV (n=548)	ES (n=548)	SMD (%)	p-val
Age (years), mean±SD	81.9±6.09	82.23±5.91	5.5	0.30	82.02±5.98	81.94±5.92	1.2	0.83	82.2±5.9	82.3±5.6	1.1	0.85
Female, n (%)	424 (51.1)	427 (70.0)	39.4	<0.01	489 (58.9)	354 (58.1)	1.6	0.78	361 (65.9)	367 (67.0)	2.3	0.65
BMI, mean±SD	26.25±4.89	26.13±4.73	2.3	0.66	26.18±4.95	26.18±4.66	<0.1	0.99	26.2±5.2	26.1±4.7	2.6	0.67
NYHA class III-IV, n (%)	549 (66.1)	403 (66.1)	0.2	0.97	546 (65.8)	407 (66.8)	2.0	0.72	365 (66.6)	359 (65.5)	2.3	0.70
EuroScore 2, mean±SD	7.25±7.92	6.66±6.96	7.9	0.13	7.02 (7.56)	7.31 (8.05)	3.6	0.59	7.0±7.7	6.7±7.0	3.8	0.53
GSS 2-3, n (%)	212 (25.5)	158 (25.9)	0.8	0.88	211 (25.4)	152 (25)	1.1	0.84	131 (23.9)	148 (27)	7.1	0.24
Dialysis, n (%)	21 (2.5)	11 (1.8)	5.0	0.36	1 (2.2)	13 (2.1)	0.6	0.92	9 (1.6)	11 (2)	2.7	0.65
Prior MI, n (%)	29 (3.5)	25 (4.1)	3.0	0.57	213 (3.6)	26 (4.3)	3.5	0.54	22 (4.1)	25 (4.6)	2.6	0.67
COPD, n (%)	278 (33.5)	127 (20.8)	28.8	<0.01	237 (28.5)	181 (29.7)	2.8	0.64	135 (24.6)	125 (22.8)	4.3	0.48
Prior Cardiac Surgery, n (%)	144 (17.3)	82 (13.5)	10.7	<0.05	136 (16.4)	88 (14.5)	5.1	0.36	84 (15.3)	73 (13.3)	5.7	0.35
Diabetes, n (%)	235 (28.3)	153 (25.1)	7.3	0.17	227 (27.3)	169 (27.7)	0.9	0.88	152 (27.7)	145 (26.5)	2.9	0.63
Active Cancer, n (%)	36 (4.3)	18 (3)	7.4	0.17	31 (3.7)	23 (3.8)	0.2	0.97	28 (5.1)	18 (3.3)	9.1	0.13
CAD, n (%)	261 (31.4)	150 (24.6)	15.3	0.01	237 (28.5)	177 (29)	0.9	0.87	144 (26.3)	141 (25.7)	1.2	0.84
Prior PCI, n (%)	222 (26.8)	152 (25)	4.2	0.44	213 (25.7)	170 (27.8)	4.8	0.41	142 (26.0)	143 (26.1)	0.4	0.94
Prior CABG, n (%)	109 (13.1)	51 (8.4)	15.5	0.01	99 (11.9)	56 (9.2)	8.6	0.13	56 (10.2)	46 (8.4)	6.3	0.30
Pulmonary hypertension, n (%)	144 (17.3)	119 (19.5)	5.6	0.29	154 (18.2)	272 (18.7)	1.3	0.82	91 (16.6)	100 (18.2)	4.3	0.47
Critical status, n (%)	37 (4.5)	14 (2.3)	12.0	0.03	31 (3.7)	32 (5.2)	7.6	0.30	15 (2.7)	12 (2.2)	3.5	0.56
Echocardiographic assessment												
LVEF, %±SD	50.9±12.6	53.9±11.2	24.9	<0.01	52.1±12.3	51.9±12.1	<0.1	0.99	52.8±11.8	53.2±11.1	3.7	0.54
AVA, cm^2±SD	0.66±0.27	0.64±0.21	8.6	0.12	0.65±0.27	0.65±0.21	1.7	0.77	0.6±0.3	0.6±0.2	5.9	0.36
Mean gradient, mmHg±SD	48.6±15.0	50.8±14.3	14.6	0.01	49.28±15	49.6±14.3	2.5	0.66	49.7±15.1	50.6±14.4	5.9	0.33

Table 2. Five-year outcomes after either inverse probability of treatment weighting (IPTW) and propensity score matching (PSM) adjustment.

Five-year outcomes	MCV	ES	HR (95% CI)[#]	p-value
IPTW adjustment	**(n=830)**	**(n=610)**		
All-cause death, n (%)	434 (52.3)	291 (47.7)	1.2 (1.0-1.4)	0.04
Heart Failure, n (%)	334 (40.3)	231 (37.8)	1.1 (0.9 – 1.2)*	0.12
MI, n (%)	37 (4.5)	24 (3.9)	1.2 (0.8 – 1.6)*	0.42
Stroke, n (%)	66 (7.9)	46 (7.6)	1.0 (0.8 – 1.3)*	0.84
Rehospitalization for any cardiac cause, n (%)	389 (46.9)	257 (42.1)	1.2 (1.1-1.3)*	<0.01
Rehospitalization for re-intervention, n (%)	2 (0.3)	2 (0.3)	0.6 (0.1-4.9)*	0.52
PSM adjustment	**(n=548)**	**(n=548)**		
All-cause death, n (%)	283 (51.6)	256 (46.7)	1.2 (1.0 – 1.4)	0.04

Heart Failure, n (%)	221 (40.3)	203 (37.0)	1.1 (0.9 – 1.4)*	0.20
MI, n (%)	28 (5.1)	23 (4.2)	1.2 (0.7 – 2.1)*	0.47
Stroke, n (%)	43 (7.8)	46 (8.4)	0.9 (0.6 – 1.4)*	0.74
Rehospitalization for cardiac cause, n (%)	262 (47.8)	229 (41.8)	1.2 (1.0 - 1.5)*	0.02
Rehospitalization for re-intervention, n (%)	2 (0.4)	2 (0.4)	0.5 (0.1 - 2.7)*	0.42

Abbreviations: AKI, Acute Kidney Injury; **ES**, Edwards SAPIEN XT; **IPTW**, Inverse Probability of Treatment Weighting; **HR**, Hazard Ratio; **MCV**, Medtronic CoreValve; **MI**, Myocardial Infarction; **PSM,** Propensity Score Matching.

[#] Excess risk for CoreValve versus SAPIEN XT transcatheter aortic valve groups

* Subdistribution hazard ratio (HR) obtained with Fine-Gray method to consider the competing risk of death

Table 3. Landmark analyses for all-cause death risk per each year of follow-up.

IPTW-adjusted Landmark analyses	HR (95% CI)*	p-value
All-cause death at 5 years	1.18 (1.01-1.38)	0.04
0-1 year	1.17 (1.00-1.36)	0.05
1-2 years	1.07 (0.89-1.28)	0.48
2-3 years	1.01 (0.82-1.25)	0.89
3-4 years	0.98 (0.76-1.26)	0.86
5 years	0.99 (0.70-1.40)	0.96

*Excess risk for CoreValve versus SAPIEN XT transcatheter aortic valve groups

Table 4. Multivariable logistic regression adjusted by inverse probability of treatment weighting, of procedural and post-procedural factors associated with all-cause mortality at 5 years.

Multivariate analysis		
Predictor	**Adjusted HR (95% CI)**	**p-value**
Mean gradient >20 mmHg	1.2 (0.7-2.0)	0.48
More-than-mild PVR	1.5 (1.1-1.9)	<0.01
MCV	1.1 (0.9-1.3)	0.22
In-hospital AKI	3.9 (2.5-6.4)	<0.01
In-hospital vascular complications	1.0 (0.7-1.3)	0.78
In-hospital stroke	1.2 (0.6-2.7)	0.62
In-hospital MI	1.3 (0.5-3.3)	0.61

In-hospital PPI	1.2 (1.0-1.5)	0.10

Abbreviations: AKI, Acute Kidney Injury; **HR**, Hazard Ratio; **MCV**, Medtronic CoreValve; **MI**, Myocardial Infarction; **PPI**, Permanent Pacemaker Implantation; **PVR**, ParaValvular Regurgitation.

Supplementary Table 1. In hospital outcomes before and after adjustment.

Abbreviations: AKI, Acute Kidney Injury; **ES**, Edwards SAPIEN XT; **IPTW**, Inverse Probability of Treatment Weighting; **MCV**, Medtronic CoreValve; **MI**, Myocardial Infarction; **PPI**, Permanent Pacemaker Implantation; **PVR**, ParaValvular Regurgitation; **SD**, standard deviation.

	Before adjustment			After IPTW adjustment		
	MCV (n=830)	ES (n=610)	p-val	MCV (n=830)	ES (n=610)	p-val
Death from any cause, n (%)	36 (4.3)	16 (2.7)	0.10	36 (4.3)	14 (2.3)	0.03
MI, n (%)	5 (0.6)	6 (1.0)	0.37	5 (0.6)	7 (1.2)	0.24
Vascular complications, n (%)	58 (7.0)	56 (9.4)	0.09	63 (7.6)	55 (9.0)	0.35
PPI, n (%)	190 (23.0)	29 (4.9)	<0.01	188 (22.7)	28 (4.6)	<0.01
Stroke, n (%)	12 (1.4)	5 (0.8)	0.30	13 (1.6)	4 (0.7)	0.12
AKI, n (%)	30 (3.7)	28 (4.9)	0.25	31 (3.8)	29 (4.7)	0.43
More-than-mild PVR, n (%)	111 (13.7)	56 (9.8)	0.03	111 (13.4)	59 (9.7)	0.05
Mean gradient, mmHg±SD	9.2 (6.1)	10.9 (5.4)	<0.01	9.1 (6.1)	10.6 (5.3)	<0.01
Mean gradient >20 mmHg, n (%)	17 (2.1)	18 (3.1)	0.22	18 (2.2)	18 (3.0)	0.32

Figure 1. Study participant flow

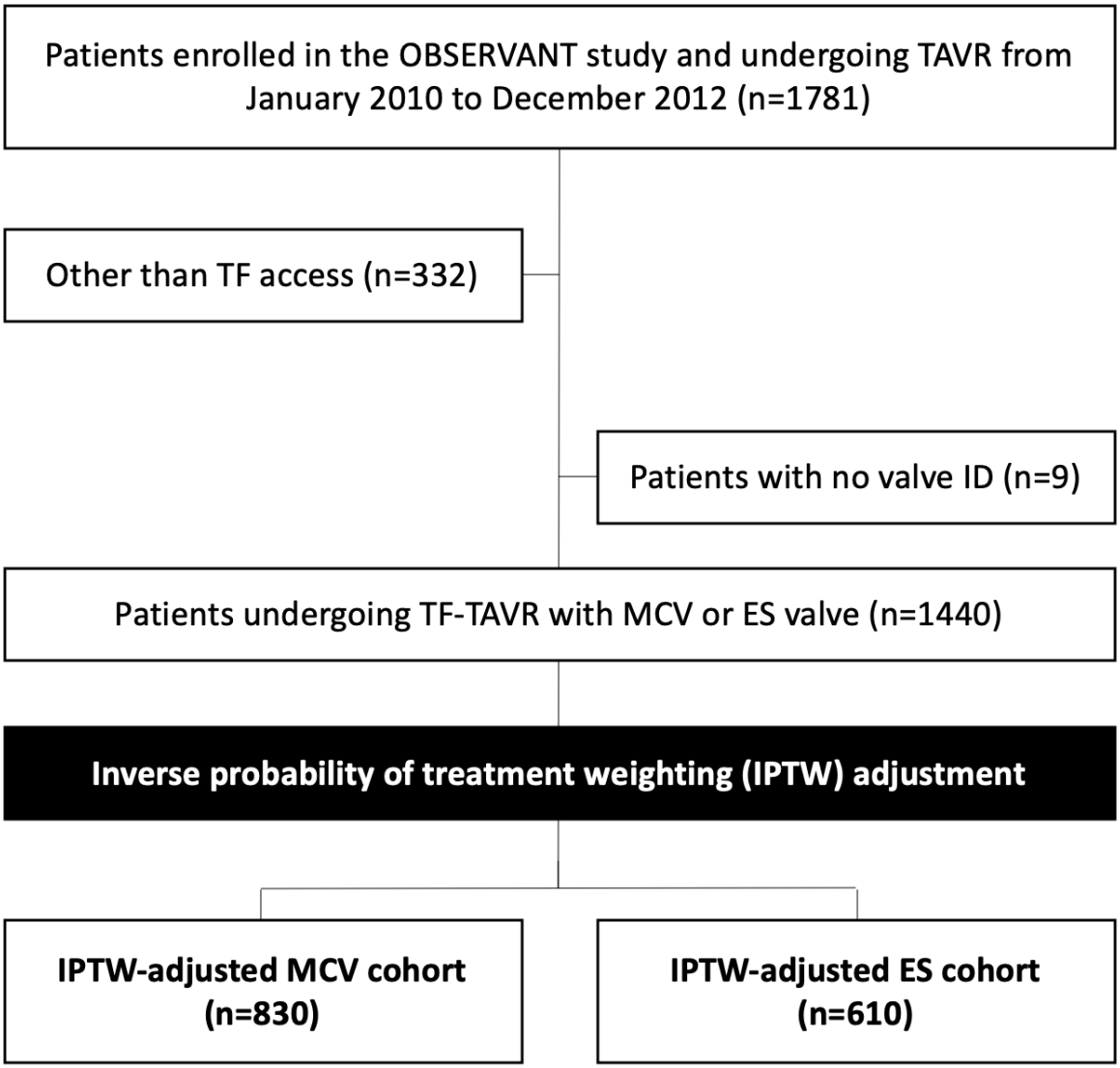

Figure 2. Time-to-event curves of IPTW-adjusted Kaplan-Meier estimates for 5-year all-cause mortality according transcatheter aortic valve (TAV) type. Curves are reported with 95% confidence interval box.

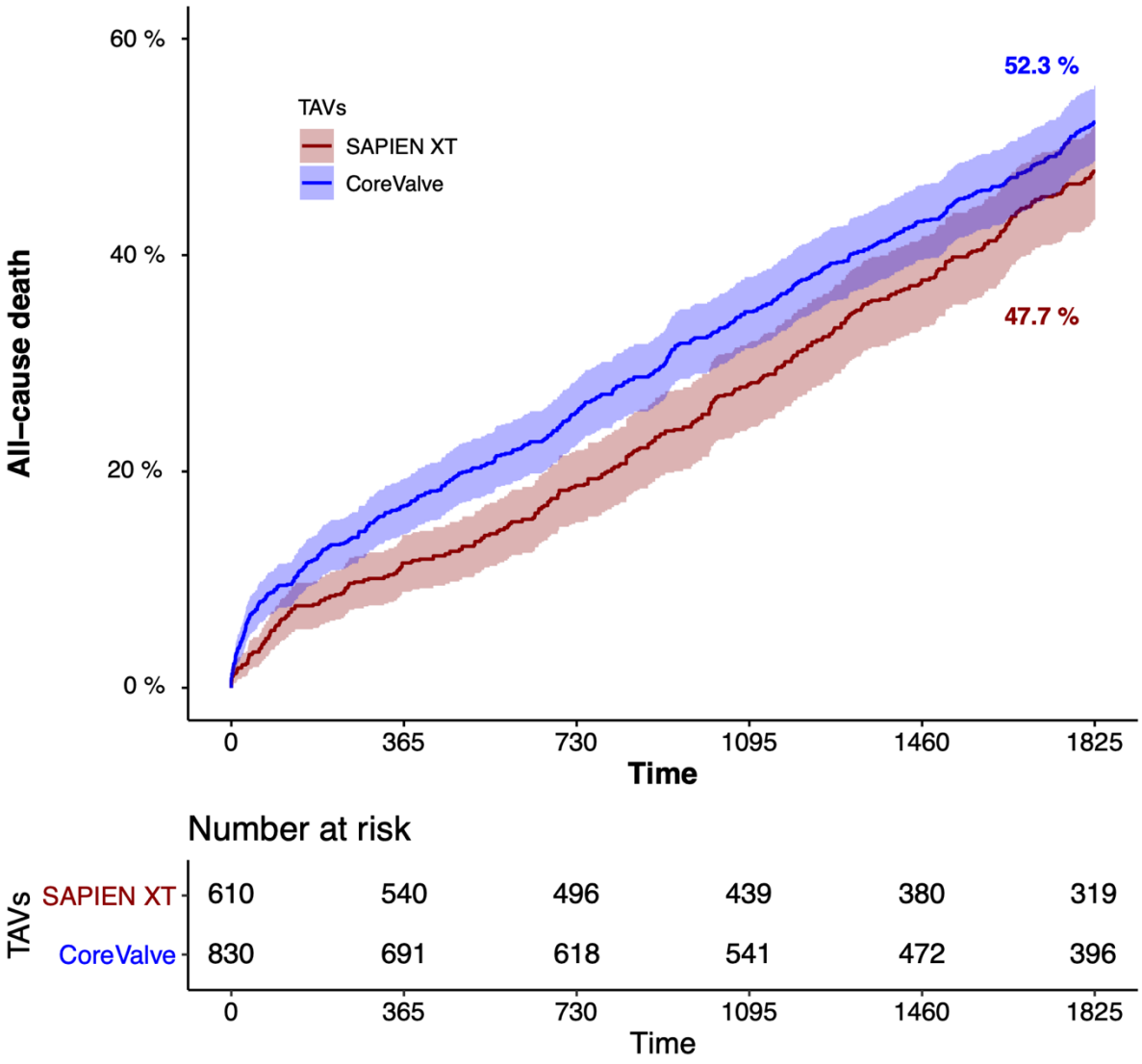

Figure 2. Time-to-event curves of IPTW-adjusted Fine-Gray cumulative incidence function of 5-year secondary endpoints according transcatheter aortic valve (TAV) type.

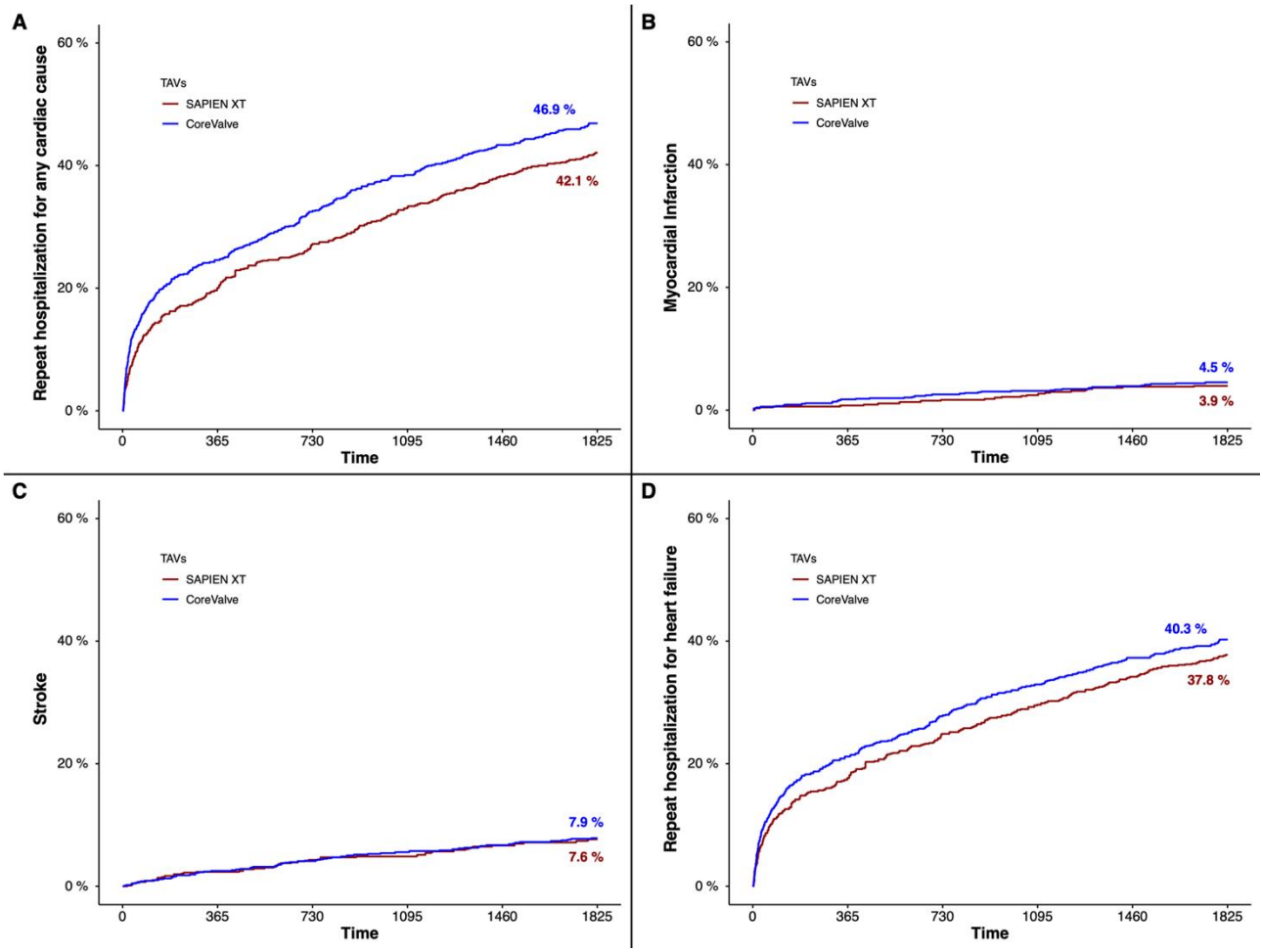

Figure 3. Kaplan-Meier time-to-event estimates of 5-year all-cause mortality according the grade of paravalvular regurgitation after TAVR.