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Analysis of Length of Stay after Transfemoral Transcatheter Aortic Valve Replacement: Results from the FRANCE TAVI Registry

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Short title: Length of stay after TAVR

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ABSTRACT

Background: Currently, there are no recommendations regarding the minimum duration of in-hospital monitoring after transfemoral (TF) transcatheter aortic valve replacement (TAVR) and practices are extremely heterogeneous. We therefore aimed to evaluate length of stay (LOS) and predictive factors for late discharge after TF TAVR using data from the FRANCE TAVI registry.

Methods: TAVR was performed in 12,804 patients in 48 French centers between 2013 and 2015. LOS was evaluated in 5,857 TF patients discharged home. LOS was calculated from TAVR procedure (day 0) to discharge. The study population was divided into 3 groups based on LOS values. Patients discharged within 3 days constituted the "very early" discharge group, patients with a LOS between 3 and 6 days constituted the "early" discharge group, and patients with a length of stay >6 days constituted the "late" discharge group.

Results: The median LOS was 7 (5-9) days and was extremely variable among centers. The proportion of patients discharged very early, early, and late was 4.4% (n=256), 33.7% (n=1997), and 61.9% (n=3624) respectively. Variables associated with late discharge were female sex, co-morbidities, major complications, self expandable valve, general anesthesia, and a significant center effect. In contrast, history of previous pacemaker was a protective factor. The composite of death and re-admission in the very early and early versus late discharge groups were similar at 30 days (3.3% vs. 3.5%, p=0.66).

Conclusions: LOS is extremely variable after TF TAVR in France. Co-morbidities and complications were predictive factors of late discharge after TAVI. Interestingly, the use of self-expandable prosthesis and general anesthesia may also contribute to late discharge. Our results confirm that early discharge is safe.

Key words: aortic stenosis, TAVR, length of stay

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is increasingly involved in the management of aortic stenosis. Initially limited to inoperable and high-risk patients, indications for TAVR have now extended to intermediate-risk patients, especially when a femoral approach is feasible [1, 2]. After the procedure, patients remain hospitalized to check for complications before being discharged home (or to a rehabilitation center). Currently, there is no recommendation concerning the minimum duration of in-hospital monitoring and practices are extremely heterogeneous [3]. We and others previously demonstrated that early discharge home (i.e., within 3 days after the procedure) was feasible and safe [4-11]. Prolonged unjustified hospitalization can expose patients to potential complications and may not be cost effective.

FRANCE TAVI is an all-comers prospective registry of the French Society of Cardiology since 2013 and includes all consecutive patients who have TAVR [12]. We aimed to evaluate the length of stay (LOS) after transfemoral (TF) TAVR in patients discharged directly home and predictive factors for prolonged hospitalization.

METHODS

Launched in January 2013, FRANCE TAVI is an initiative of GACI, the French Society of Cardiology's working group of interventional cardiology, with the participation of the French Society of Thoracic and Cardiovascular Surgery [12]. Device manufacturers partly funded the registry but had no role in data collection or analysis or in manuscript preparation. Designed as an all-comers registry, it prospectively includes data on all patients who have TAVR for severe aortic stenosis in 48 of 50 active centers in France and who volunteer to participate. FRANCE TAVI was designed in continuity with the FRANCE 2 registry to provide further data on baseline characteristics of patients as well as procedural aspects and clinical outcomes of TAVR recipients on a national scale [13]. The decision to perform TAVR and the choices of approach and device used were made on the basis of assessment by a multidisciplinary heart team at each participating center, as previously described [12]. Procedures and post procedural management were performed in accordance with each site's routine protocol. Follow-up was performed either on site or by telephone contact with the patient or the patient's physician depending on each site's protocol at 30 days and then every year. Patients included in the registry provided written informed consent for the procedure and for anonymous processing of their data. The registry was approved by the Institutional Review Board of the French Ministry of Higher Education and Research and by the National Commission for Data Protection and Liberties. The FRANCE TAVI dataset was collected using a dedicated web-based interface from the French Society of Cardiology. All data, including in-hospital complications and follow-up, were site reported according to the definitions within the national dataset. The database was managed by the French Society of Cardiology, which implemented regular data quality checks, including range checks and assessments of internal consistency. In cases of missing, extreme, or inconsistent values, centers were contacted and asked to verify and modify records as appropriate. For the purposes of this analysis, a FRANCE TAVI database encompassing all patients included from January 2, 2013, to December 31, 2015, was locked. Complications were classified using Valve Academic Research Consortium 2 criteria [3]. The safety endpoint was a composite of all-cause mortality or repeat hospitalization 7 within 30 days.

Statistical analysis

LOS was calculated from TAVR procedure (day 0) to discharge. The study population was divided into 3 groups based on LOS values. Patients discharged within 3 days constituted the very early discharge group,

patients with a LOS between 3 and 6 days constituted the early discharge group, and patients with a length of stay >6 days constituted the "late discharge group".

We created a variable to evaluate a potential center effect on LOS. This variable categorized centers according to median LOS. Centers with a median LOS less than 7 days (n=13) were called "centers with short LOS" whereas centers with a median LOS more than 7 days (n=35) were called "centers with prolonged LOS". The volume of the centers was estimated based on tertile values and expressed as low (<75), medium (75-140), and high (>140) volume groups.

Qualitative variables were expressed as percentage, and quantitative variables as mean ± SD or median (25th to 75th interquartile range). Comparison of numerical variables was performed with the Student t test or Wilcoxon rank-sum test, depending on variable distribution. When there were more than 2 groups to compare, and according to the distribution of the variable, an Anova test or a kruskall-Wallis test were used. The chi-square test or Fisher's exact test was used to compare qualitative variables. A logistic regression multivariable analysis was used to assess independent correlates of late discharge (LOS > 6 days). The model was built on the basis of the univariate association between the variable and late discharge with a $p<0.10$. The correlation between LOS and volume of activity was assessed using Spearman's rank correlation coefficient. The survival free from rehospitalization was compared between patients with very early/early and late discharge with a log-rank test. Then, adjustment for confounders was performed by a matched analysis. First, a general linear model was fitte with LOS by age, sex, EuroSCORE, respiratory failure, history of mitral valve prosthesis, atrial fibrillation, any complication, post-TAVI pacemaker, post-TAVI acute kidney injury, local anesthesia, valve type, center and year of intervention as covariates. This model was used to predict the LOS with the center effect subtracted from the prediction, in order to calculate an excess of LOS compared to the average of the center. Patients with very early/early discharge in centers belonging to the lowest tertile of LOS, were randomly paired 1:1 with patients with late discharge in centers belonging to the upper tertile. Then, a matched Cox model was used to compare the survival free from rehospitalization between patients with early and late discharge. In order to avoid sampling fluctuations due to the random seed used for matching, 512 random matches were performed and the model having the median Hazard Ratio was selected.

All statistical tests were 2 sided. Differences were considered statistically significant at a p value <0.05. All data were analyzed using SPSS software (version 23.0; IBM, Armonk, New York).

RESULTS

Study flowchart

The flowchart of the studied population is presented in Figure 1.

From January 2013 to December 2015, 48 out of 50 French centers participated in the FRANCE TAVI registry. A total of 12,804 patients had TAVR during this period [12]. Among them 12,700 (99.2%) patients were implanted using either a balloon-expandable valve (SAPIEN XT or SAPIEN 3, Edwards LifeSciences, Irvine, California, USA; n=8,230) or a self-expandable valve (Medtronic COREVALVE, Minneapolis, Minnesota, USA; n=4,470) via a transfemoral approach in 10,505 (82.7%) patients. After TF TAVR, 404 (3.8%) patients died during the index hospitalization, 11 3,938 (37.5%) patients were transferred to another institution or to a rehabilitation center, and the discharge destination was unknown in 306 patients (2.91%). Thus, 5,857 (55.7%) TF TAVR patients were discharged directly home and were the studied population.

LOS and predictive factors of late discharge

LOS was highly variable among centers (Figure 2, p<0.001). The median LOS was 7 days (IQR 5-9). Based on LOS values, the study population was divided into 3 groups. The proportion of patients discharged very early within 3 days was very low (4.4%, n=256). The proportion of patients discharged early and late was 33.7% (n=1997) and 61.9% (n=3624), respectively. The median LOS was 3 (3-3) days in the very early discharge group, 5 (5-6) days in the early discharge group, and 8 (7-11) days in the late discharge group (p<0.001). Baseline characteristics are shown in Table 1. Patients in the very and early discharge groups had lower logistic EuroSCORE (p<0.001) and had a higher rate of previous pacemaker implantation (p=0.02). Furthermore, patients in the late discharge group had more frequent COPD, atrial fibrillation, history of surgical mitral valve replacement, and severe pulmonary hypertension (defined by systolic pulmonary artery pressure >60 mmHg).

Procedural characteristics differed also among groups (Table 2). Patients in the very early discharge group had TF TAVR more frequently using local anesthesia (p=0.002). A self-expandable valve was also more frequently used in the late discharge group (p<0.001). Moreover, intra-procedural trans oesophageal echography was more frequently used in the early and late discharge groups (p<0.001). As expected, both groups had a high rate of procedural success and a low rate of complications since we only selected patients discharged directly home. Complications of any kind, except annulus rupture, were more frequent in the late discharge group and

particularly the rate of new pacemaker implantation (p<0.001), stroke (p<0.001), vascular complications (p<0.001), infectious complications (p<0.001), and acute kidney injury (p <0.001) (Table 2).

The results of the multivariable analysis are shown in Table 3. Variables independently associated with late discharge were female sex, co-morbidities (history of mitral valve prosthesis, respiratory failure, atrial fibrillation, severe pulmonary hypertension) and complications (pacemaker, tamponade, stroke, vascular complications, and acute kidney injury). A history of previous pacemaker implantation was a protective factor (HR 0.83, 95% CI: 0.69-0.98, p=0.031). Interestingly, the use of a self-expandable prosthesis and general anesthesia were also independently associated with late discharge.

We also incorporated into the multivariate model, the center effect which was significantly associated with late discharge (adjusted HR: 5.56, 95% CI: 4.81-6.42, p<0.001). Interestingly, centers with a shorter LOS more frequently used local anesthesia (73.1% vs. 52.0%, p<0.001) and less frequently used self-expandable prosthesis (24.6% vs. 33.2%, p<0.001) as compared to those with prolonged LOS.

We also evaluated the impact of the volume of the centers on LOS. The median LOS was not significantly different among low [8 (6-10)], medium [7 (6-9)], and high [7 (5-9)] volume centers (p=0.39). Self-expandable prosthesis and intra-procedural trans oesophageal echography were more frequently used in low volume centers (p<0.001). The volume of the centers was not predictive of late discharge when integrated in the model (adjusted HR: 1.05, 95% CI 0.92-1.19, p=0.46). Furthermore, there was no significant correlation between the volume of centers and median LOS (Figure 3).

Safety analysis

The composite endpoint of all-causes death or repeat hospitalizations within 30 days occurred in 73 (3.3%) patients in the very early and early discharge groups and in 127 (3.5%) patients in the late discharge group without any significant difference (p=0.66). Death occurred in 6 (0.3%) patients in the very early early and early discharge groups and in 14 (0.4%) patients in the late discharge group at 30 days (p=0.50). Repeat hospitalization occurred in 67 (3.0) patients in the very early and early discharge groups and in 113 (3.1%) patients in the late discharge group at 30 days (p=0.82). Furthermore, 30-day death or repeat hospitalizations were not significantly different between groups of centers with short or prolonged LOS (4.0 vs. 3.2%, p=0.16).

We also evaluated the influence of very early and early discharge on long-term outcomes. Very early and early discharge patients had better outcomes since survival, free from repeat hospitalization, was

significantly higher (log rank P<0.001, Figure 4A). After propensity score matching, the difference remained significant (Figure 4B).

DISCUSSION

The main findings of this evaluation of LOS after TF TAVR in patients discharged home are summarized as follows: 1) the median length of stay in our population was highly variable between centers and long (i.e., 6 days) for patients treated by TAVR via a femoral approach; 2) the main determinants of late discharge were female sex, co-morbidities, complications, the use of a self-expandable prosthesis, general anesthesia, and center effect; 3) early discharge was safe.

LOS after TAVR

Currently, there is no recommendation concerning the minimum duration of in hospital monitoring after TAVR and practices are extremely heterogeneous worldwide with considerable differences in LOS in contemporary TAVR registries. The objective of post-TAVR hospital surveillance is to verify the absence of complications (serious complications with TAVR mostly occur within the first 24 to 48 h of the procedure), the delayed need for pace maker implantation, and to assess the hemodynamic performance of the aortic bioprosthesis by echocardiography before being discharged home or to a rehabilitation center. In France, the LOS remains high although a slight decrease in median LOS has been observed between FRANCE 2 (2010-2011) and FRANCE TAVI (2013-2015) registries [9 (7-13) vs. 8 (6-11), $p<0.001$] probably related to lower rates of co-morbidities and complications [12, 13]. The FRANCE TAVI database has been frozen for analysis only for the period 2013-2015. During 2016-2018, 14 071 TF TAVR patients discharged home have been included in the FRANCE TAVI registry. The median LOS slightly decreased [6 (IQR: 5-7) vs. 7 (IQR: 5-9) days]. In the United States, shorter LOS have recently been reported, with a significant reduction in average LOS between 2012 and 2015 (6.3 vs. 4.6 days, $p<0.0001$) [14]. In some centers, an early discharge (i.e., < 3days) program has been implemented particularly for transfemoral procedures using a minimalist approach showing that early discharge was feasible and safe [4-11]. There is therefore a considerable heterogeneity of practices concerning the LOS after a TAVR.

Predictive factors of late discharge

Our study confirmed that co-morbidities and severe complications (tamponade, stroke, vascular complications, and acute kidney injury) were predictive of late discharge [5-11, 15]. Furthermore, as expected, conduction abnormalities (the most frequent complication of TAVI nowadays) requiring the need of a

pacemaker were also associated with prolonged hospitalization while the presence of a pacemaker before TAVR was associated with early discharge. It seems logical that the occurrence of conductive abnormalities after TAVR, requiring or not pacemaker implantation, certainly prolongs in hospital monitoring and delays discharge. Indeed, although most new conduction disturbances occur intraprocedurally, they may occur up to 3 days after intervention. Early discharge in these patients is probably feasible with protocols for arrhythmia monitoring, or early pacemaker indications such as rapid implantation in patients presenting with persistent complete atrioventricular block or severe conduction disorders [15]. Very recently, Rodés-Cabau et al. provide an algorithm strategy for managing conduction disturbances post-TAVR which may reduce unjustified and prolonged monitoring [16]. According to ECG changes/arrhythmias during the procedure and the analysis of the ECG before and after the procedure, the patients are categorized in 5 groups: 1) no ECG changes in patients without right bundle branch block (BBB) pre-procedure; 2) no ECG changes in patients with right BBB pre-procedure; 3) ECG changes (increase > 20 ms in PR or QRS intervals duration) in patients with conduction disturbances (right or left BBB, intraventricular conduction delay with QRS > 120 ms, or first-degree atrioventricular block) preprocedure; 4) new-onset left BBB that persists at the end of the procedure; or 5) transient or persistent high degree atrioventricular block during the procedural period. Interestingly, in the absence of other complications, early discharge is proposed in group 1 at day 1, in group 2 in the absence of arythmia or ECG changes at day 2, in groups 3 and 4, in case of regression of ECG changes or if no further changes occurred (QRS duration < 150 ms and/or PR < 240 ms) at day 2. Finally, in group 5, patients with persistent high degree atrioventricular block should have early pacemaker. In contrast, patients without recurrence and without conduction abnormalities at day 2 could be discharged early [16].

Interestingly, we also observed that general anaesthesia was significantly and independently associated with prolonged hospitalization. In France, the majority of procedures were still performed using general anaesthesia even though there has been a gradual increase in procedures using local anaesthesia and conscious sedation, from 31.3% in 2010 to 48.3% in 2015, according to FRANCE 2 and FRANCE TAVI registries [12, 13]. The impact of the mode of anesthesia on LOS was previously reported with conflicting results. In the UK and STS/ACC US TVT registries, LOS was significantly longer with general anesthesia than local anesthesia (8.0 ± 13.5 vs. 5.7 ± 5.5 days, $p<0.0001$ and 6.5 vs. 6.0 days, $p<0.001$; respectively) whereas LOS was not significantly different using general or local anesthesia in the GARY registry [9 (7-13) vs. 9 (7-12) days, $p=0.11$] [17-19]. On the other hand, a recent meta-analysis comparing local and general anesthesia during TAVR procedures has shown that general anesthesia increased hemodynamic instability requiring intra and post

procedural catecholamine treatment, red blood cells transfusion, and pneumoniae resulting in longer hospital and intensive care unit stays [20]. It should be noted that centers that have developed early discharge programs mainly perform TAVR procedures using a minimalist approach with local anesthesia [4-11]. On the other hand, we also observed prolonged LOS using self-expandable as compared to balloon expandable bioprosthesis. We believe that this can be partly explained by the more frequent occurrence of conductive disorders with this type of prosthesis. A retrospective propensity-matched analysis of patients treated with balloon and self-expandable prosthesis also reported increased LOS in intensive care units using self-expandable prosthesis compared to balloon-expandable prosthesis (3.4 ± 4.5 vs. 2.8 ± 3.9 days, p=0.016) although total LOS was not reported [21]. Only two randomized studies have compared outcomes between self and balloon-expandable transcatheter heart valves. In the CHOICE study, LOS was not reported [22]. More recently, the results of the SOLVE trial (a 2x2 randomized trial of self-expandable vs. balloon-expandable valves and general vs. local anesthesia in patients undergoing TAVR) have been reported. LOS was very high and not significantly different between balloon (Sapien 3) and self-expandable (Evolut R) prosthesis (9 ± 7 vs. 9 ± 7 days, p=0.97) [23]. Moreover, these authors also evaluated the impact of anesthesia strategy on LOS without significant difference between general and local anesthesia (9 ± 7 vs. 9 ± 7 days, p=0.74). Finally, we observed an important center effect on LOS without significant influence of the volume of the center. We believe that this essentially reflects different organizational habits between French centers. It is possible that LOS is also linked to late programming of the next patient (e.g. 7 days later) when the bed is dedicated and reserved for TAVR patients. LOS can also be influenced by prolonged delays to obtain a post-TAVR echocardiography in the absence of anticipation. It is also possible that an unanticipated discharge to a rehabilitation center may prolong the duration of hospitalization although in our analysis we only included patients discharged home.

Safety of early discharge

As previously reported, we show that early discharge is safe without significant difference in the occurrence of 30-day death or re-admission [4-11]. We also evaluated long-term impact of early and late discharge. We first observed that early discharge was associated with better long-term outcome compared to those discharged late. However, it may also reflect that the better outcomes are related to the fact that patients with shorter LOS had fewer pre-procedure co- morbid conditions and fewer procedural related complications. Interestingly, after propensity score matching, the difference remained significant. While the strategy of early discharge is important from administrative and financial view points; such a practice, may also come with

additional clinical benefits in terms of improved short- and long-term outcomes. However, this result should be analyzed with caution, as it is possible that the difference observed is linked to the persistence of residual confounding factors.

Limitations

Our study presents some limitations. As a retrospective analysis from a prospective registry, our results should be considered hypothesis generating. Data were site reported and not subject to external validation or adjudication. Furthermore, the reasons for prolonged LOS are not documented in the FRANCE TAVI database. It is therefore possible that other factors contribute to LOS after TAVR. We could not evaluate the influence of ECG changes on LOS since we only had the proportion of patients requiring a pacemaker in the database. Similarly, we could not also evaluate the impact of frailty on LOS. Finally, we did not evaluate the impact of early ambulation (4 to 6 hours after the procedure) on LOS. Early ambulation is usually part of fast track protocols to favour early discharge [10, 11]. Interestingly, the results of the Early Mobilisation after TF-TAVI (MobiTAVI) trial have been recently reported showing that early mobilization was feasible, safe and associated with less infections and urinary catheter use [24].

The amount reimbursed for TAVR procedures in France was based on the level of severity of patients (Levels 1 to 4) and LOS with lower reimbursement when patient are discharged early. It is therefore possible that this may also have an impact on LOS in certain centers. Of note, this has been modified since March 2019 and LOS is no longer linked to reimbursement in France.

On the other hand, we included in this study only patients discharged at home and our results do not apply to patients transferred to another facility or a rehabilitation center.

Conclusions

Our study reports the high variability of LOS after TF TAVR in France. Determinants of prolonged hospitalization included not only co-morbidities and complications but also the type of transcatheter heart valve and the mode of anesthesia. Early discharge is safe and is potentially associated with better long-term outcomes. Quality of care including prevention and early detection of complication (such as vascular injury, conduction disturbances), early mobilization and early discharge program clearly influence LOS and may outcomes after TF TAVR.

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DISCLOSURES

The authors have no conflict of interest regarding the manuscript.

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FIGURE LEGENDS

Figure 1. *Title*: Flowchart. *Legend*: Description of the studied population.

Figure 2. *Title*: Boxplot analysis of length of stay according to centers. *Legend*: length of stay was extremely variable among centers.

Figure 3. *Title:* Correlation between length of stay and volume of activity. *Legend:* There was no significant correlation between length of stay and volume of centers.

Figure 4. *Title*: Survival free from rehospitalization in the overall population (A) and after propensity score matching (B). *Legend*: Plot of survival free from hospitalization in early versus late discharge groups. The difference remained significant after propensity score matching.

Table 1. Baseline characteristics

Variables	Very early discharge group (N=256)	Early discharge group (N=1977)	Late discharge group (N=3624)	P
Age (years)	83.0 ± 7.3	82.7 ± 7.3	82.6 ± 7.3	0.58
Male, n (%)	126 (49.2)	894 (45.2)	1837 (50.7)	<0.001
BMI (Kg/m^2)	26.7 ± 6.1	26.6 ± 5.1	26.6 ± 4.9	0.99
Diabetes, n (%)	59 (23.0)	471 (23.8)	926 (25.6)	0.28
Previous CABG, n (%)	19 (7.4)	233 (11.8)	414 (11.4)	0.12
Previous PCI, n (%)	56 (21.9)	573 (29.0)	1033 (28.5)	0.06
Previous SAVR, n (%)	13 (5.1)	97 (4.9)	171 (4.7)	0.93
Previous SMVR, n (%)	3 (1.2)	10 (0.5)	52 (1.4)	0.03
PAD, n (%)	30 (11.7)	349 (17.7)	595 (16.4)	0.05
COPD, n (%)	41 (16.0)	341 (17.2)	720 (19.9)	0.03
Previous stroke, n (%)	26 (10.2)	176 (8.9)	380 (10.5)	0.16
Previous pacemaker, n (%)	42 (16.4)	310 (15.7)	476 (13.1)	0.02
Recent MI, n (%)	5 (2.0)	22 (1.1)	57 (1.6)	0.30
Severe renal insufficiency, n (%)	12 (4.7)	160 (8.1)	349 (9.6)	0.01
Creatinine clearance (ml/min)	54.5 ± 19.6	57.5 ± 23.8	56.9 ± 24.5	0.47
Atrial fibrillation, n (%)	66 (25.8)	521 (26.4)	1118 (30.9)	0.001
NYHA 3-4, n (%)	157 (61.3)	1185 (59.9)	2278 (62.9)	0.09
Log. EuroSCORE (%)	14.8 ± 8.4	17.7 ± 10.8	19.5 ± 11.3	<0.001
MR grade 3-4, n (%)	6 (2.3)	48 (2.4)	79 (2.2)	0.91
Severe PH, n (%)	19 (7.4)	159 (8.0)	417 (11.5)	<0.001
Mean aortic gradient (mmHg)	46.9 ± 16.7	48.0 ± 15.7	47.4 ± 15.6	0.30
Aortic area (cm^2)	0.71 ± 0.25	0.69 ± 0.18	0.69 ± 0.22	0.35
LVEF (%)	58.0 ± 14.2	56.2 ± 13.4	55.7 ± 13.1	0.03

Abbreviations: BMI: body mass index, CABG: coronary artery bypass graft, PCI: percutaneous coronary intervention, SAVR: surgical aortic valve replacement, SMVR: surgical mitral valve replacement, PAD: peripheral arterial disease, COPD: chronic obstructive pulmonary disease, MI: myocardial infarction, MR: mitral regurgitation, PH: pulmonary hypertension, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association.

Table 2. In-hospital outcomes

Variables	Very early discharge group (N=256)	Early discharge group (N=1977)	Late discharge group (N=3624)	P
Lenght of stay (days)	2.8 ± 0.4	5.1 ± 0.8	10.2 ± 5.4	<0.001
Local anesthesia, n (%)	219 (85.5)	1124 (56.9)	2030 (56.0)	<0.001
TEE, n (%)	16 (6.3)	421 (21.3)	958 (26.4)	<0.001
Balloon expandable valve, n (%)	229 (89.5)	1500 (75.9)	2315 (63.9)	<0.001
Procedural success, n (%)	255 (99.6)	1954 (98.8)	3547 (97.9)	0.01
Annulus rupture, n (%)	0 (0)	1 (0.1)	4 (0.1)	0.60
Coronary obstruction, n (%)	0 (0)	0 (0)	9 (0.2)	0.01
New MI, n (%)	0 (0)	0 (0)	7 (0.2)	0.11
New pacemaker, n (%)	12 (4.7)	106 (5.4)	719 (19.8)	<0.001
Tamponnade, n (%)	1 (0.4)	5 (0.3)	41 (1.1)	0.002
Cardiac surgery, n (%)	0 (0)	0 (0)	9 (0.2)	0.06
Stroke, n (%)	0 (0)	1 (0.1)	34 (0.9)	<0.001
Vascular complication, n (%)	8 (3.1)	68 (3.4)	282 (7.8)	<0.001
Infectious complication, n (%)	1 (0.4)	10 (0.5)	133 (3.7)	<0.001
Valve migration, ml/min	0 (0)	7 (0.4)	31 (0.9)	0.03
Two valves, n (%)	0 (0)	17 (0.9)	59 (1.6)	0.007
AKI, n (%)	0 (0)	15 (0.8)	117 (3.2)	<0.001
Any complication, n (%)	39 (15.2)	414 (20.9)	1784 (49.3)	<0.001

Abbreviations: TEE: trans oesophageal echocardiography, MI: myocardial infarction, AKI: acute kidney injury

Table 3. Multivariable analysis for risk factors of late discharge

	Hazard ratio	95% CI	P
Center effect	5.3	4.6 – 6.2	< 0.001
Gender (female)	1.3	1.1 – 1.4	< 0.001
BMI (per 1 Kg/m²)	1.0	0.9 – 1.0	0.76
LVEF (per 1% increase)	1.0	0.9 – 1.0	0.72
NYHA (3-4 vs. 1-2)	1.1	0.9 – 1.2	0.32
Previous SMVR	2.6	1.3 – 5.2	0.004
COPD	1.3	1.1 – 1.5	0.003
Severe renal insufficiency	1.2	0.9 – 1.4	0.18
Previous stroke	1.2	0.9 – 1.5	0.10
Previous pacemaker	0.8	0.7 – 0.9	0.04
Atrial fibrillation	1.4	1.2 – 1.6	< 0.001
Severe PH (> 60 mmHg)	1.3	1.1 – 1.6	0.01
General anesthesia	1.5	1.3 – 1.8	< 0.001
Intra-procedural TEE	1.3	1.1 – 1.6	0.002
Self-expandable vs balloon expandable valve	1.7	1.5 – 2.0	< 0.001
Procedural success	0.8	0.3 – 2.1	0.61
Valve migration	1.7	0.6 – 4.8	0.29
New pacemaker	4.4	3.5 – 5.5	< 0.001
Tamponade	10.1	2.9 – 35.1	< 0.001
Stroke	31.9	4.2 – 242.8	0.001
Vascular complication	2.8	2.1 – 3.8	< 0.001
AKI	4.7	2.6 – 8.4	< 0.001
Two valves	1.3	0.4 – 4.4	0.61

Abbreviations: BMI: body mass index, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, SMVR: surgical mitral valve replacement, COPD: chronic obstructive pulmonary disease, PH: pulmonary hypertension, TEE: trans oesophageal echocardiography, AKI: acute kidney injury.

Figure 1

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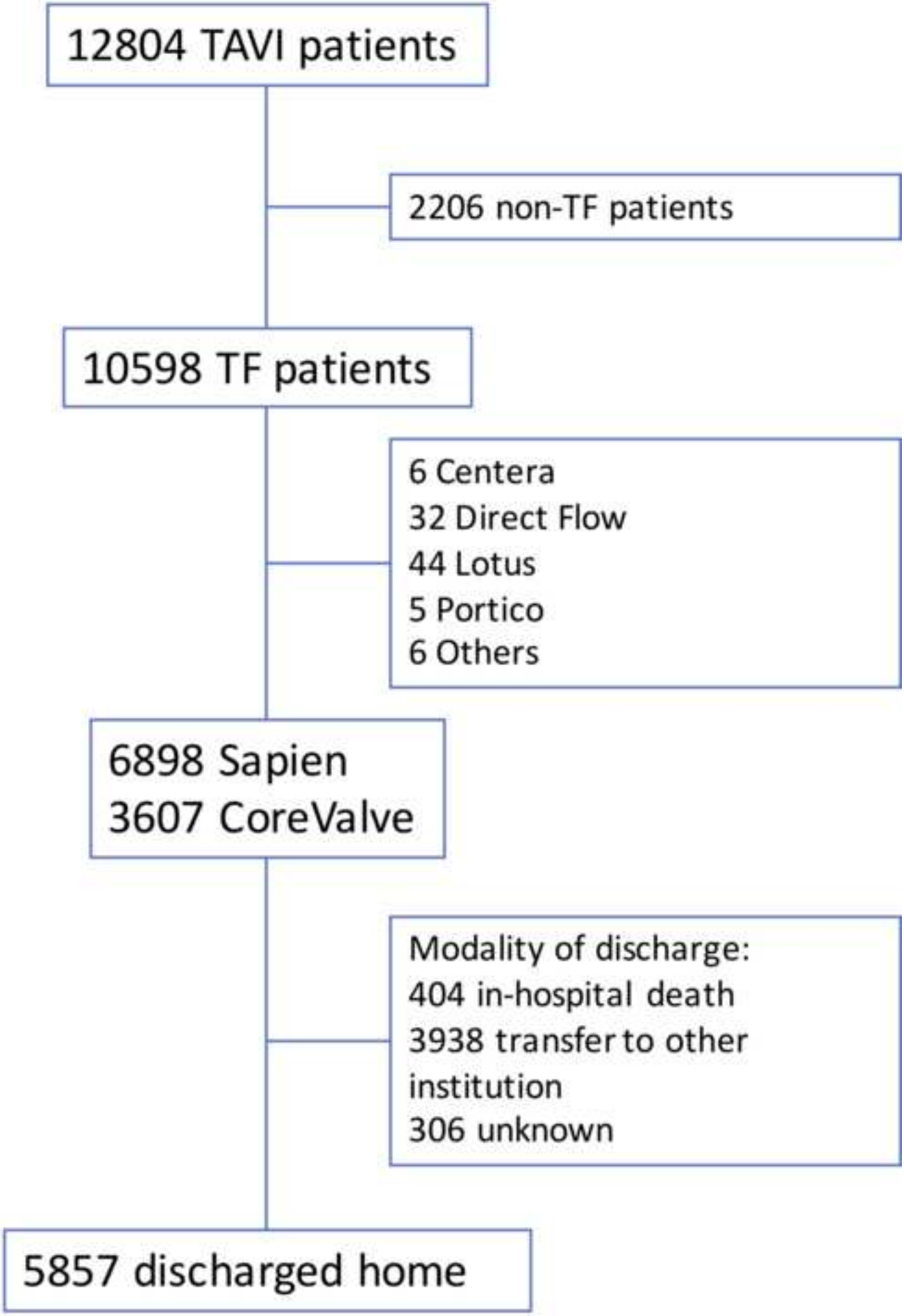

Figure 2

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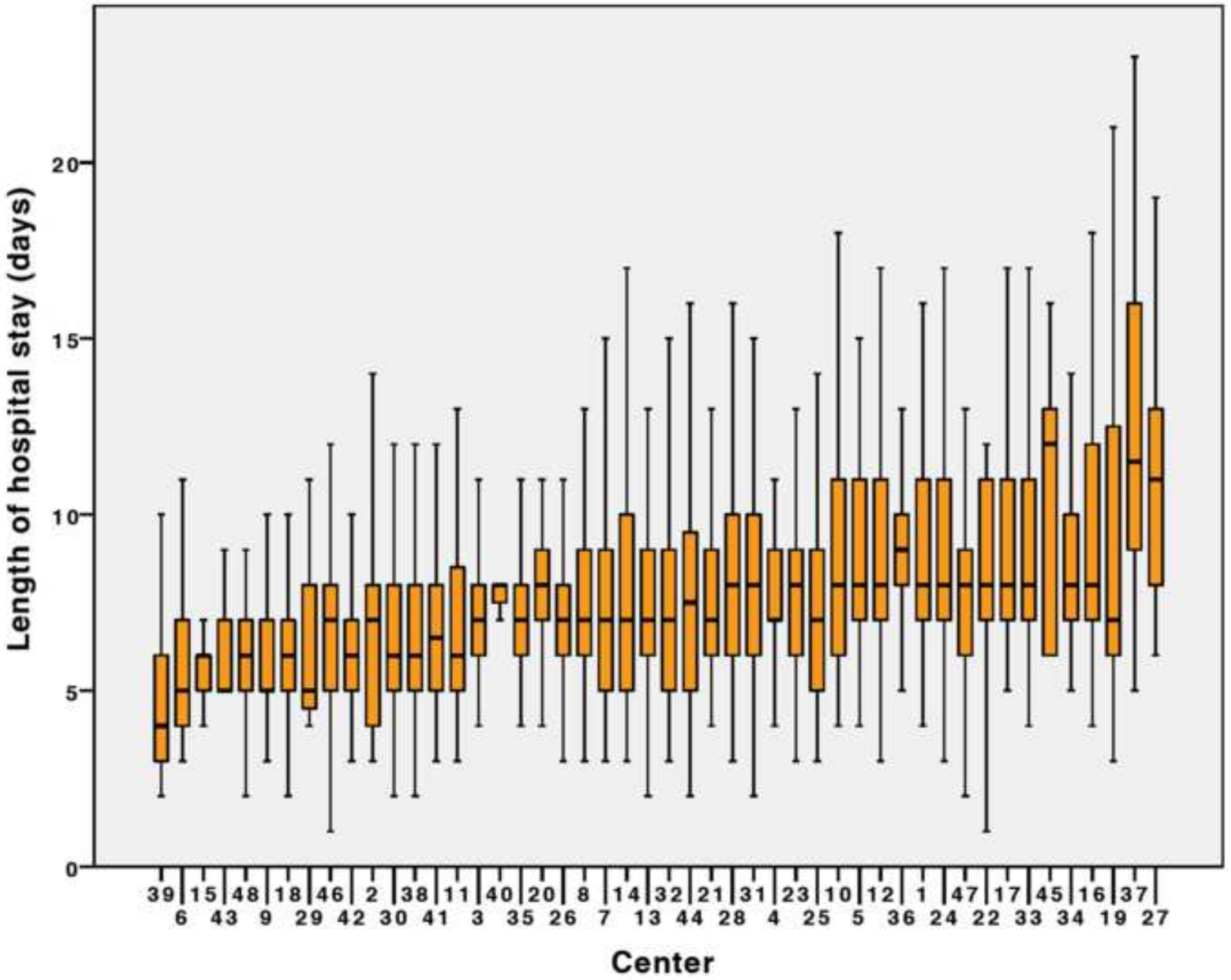

Figure 3

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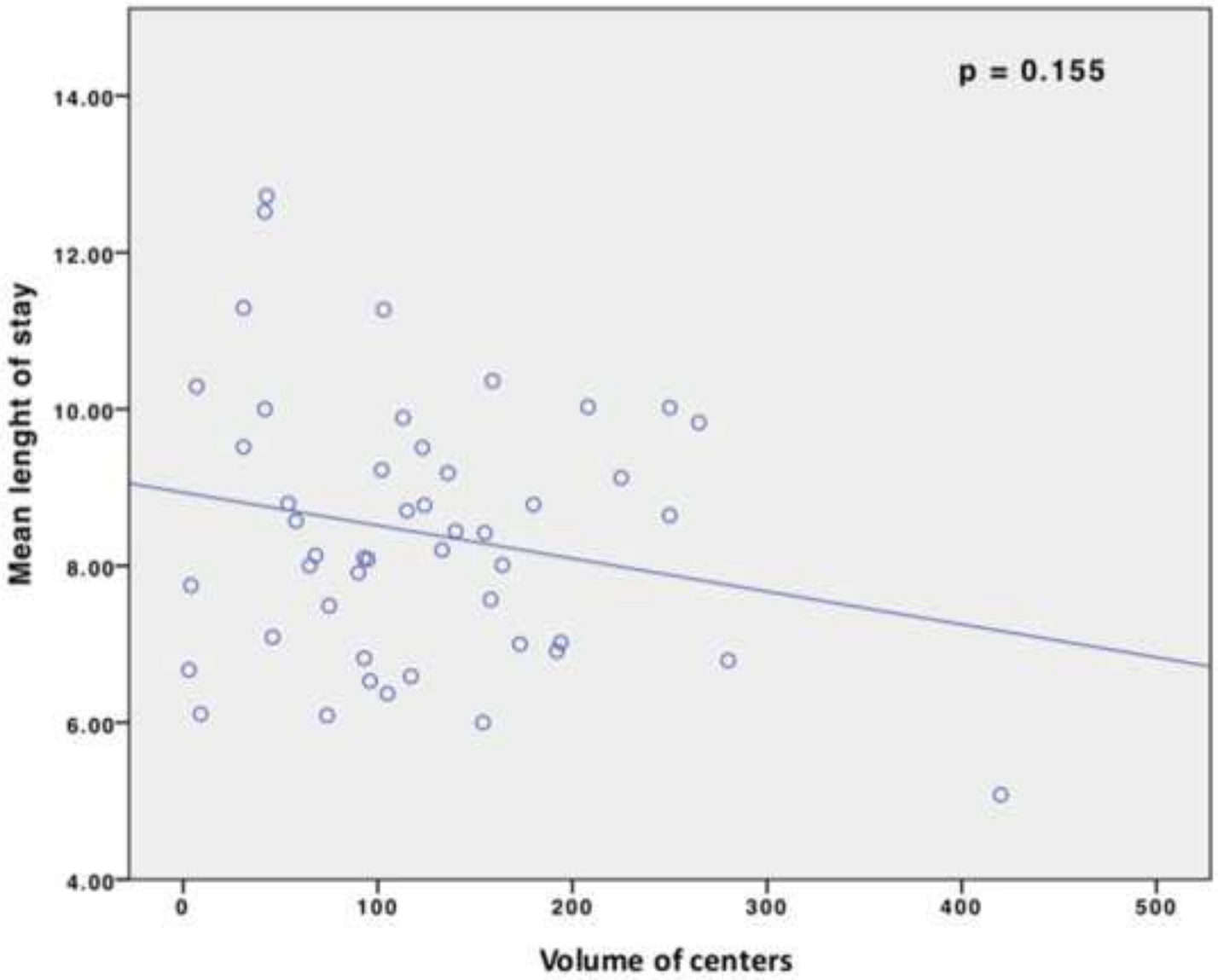

Figure 4

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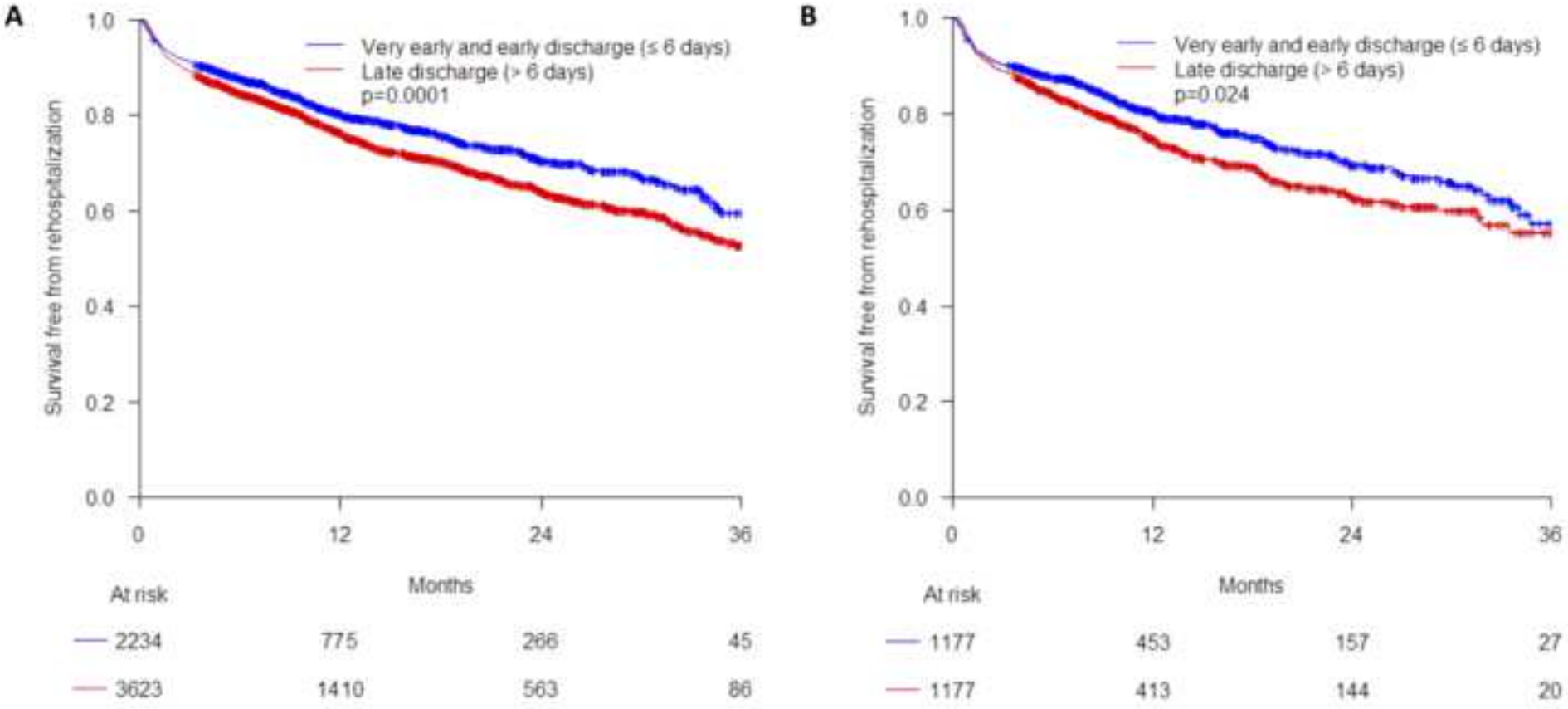

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Durand et al., manuscript number CRCD-D-19-00933: response to Reviewers

Responses to the Reviewer 1

The following are numbered consecutively with the queries of Reviewer 1

1. The authors report interesting register data from France concerning the length of hospital stay according to TAVI.

We thank the reviewer for his/her laudatory comment.

2. The multivariate analysis identified among others a centre effect, atrial fibrillation, TEE, valve type, type of anaesthesia or pacemaker neediness as influencing factors. In the discussion, the influence of ECG changes or predictive ECG changes is correctly considered; unfortunately, no further information can be found. It would be helpful to describe the ECG before and after TAVI, separated by groups.

We agree with the Reviewer's concern. However, the description of ECG before and after TAVR was not available in the database of the FRANCE TAVI registry. We only have the proportion of patients with an history of pacemaker before TAVI and the incidence of pacemaker after TAVI. This has been underlined in the limitation section of the revised manuscript page 12, lines 9-10.

3. Furthermore, it is noticeable that the topic of center and anesthesia is not considered more closely. Possibly the center effect is based on the fact that there are differences in the frequency of local anesthesia.

As required by the Reviewer, we evaluated the incidence of local anesthesia according to the center effect. As expected, centers with a shorter LOS more frequently used local anesthesia as compared to those with prolonged LOS (73.1% vs. 52.0%, $p<0.001$). Nevertheless, when these two variables were included in the multivariate model they remained independently associated with prolonged LOS suggesting that the center effect is not only related to the proportion of local anesthesia. This has been added in the revised manuscript page 7, lines 10-12.

Responses to the Reviewer 3

The following are numbered consecutively with the queries of Reviewer 3

Authors assessed the length of hospital stay in the French TAVR registry. As expected, longer hospital stay was associated with female sex, co-morbidities, major complications, self expandable valve, general anesthesia, and center.

1. I would strongly recommend to look into patients with very early discharge and grade into 3 groups (e.g. 1-3 days, >3-<7, and >7 days). This may provide interesting insights, particularly in times where low-risk patients are increasingly being treated.

As suggested by the Reviewer, we have added "a very early discharge "group in the revised manuscript. Data are shown in tables 1 and 2 in the revised manuscript pages 19 and 20. The proportion of patients with very early discharge (≤ 3 days) was low (4.4%). Given the small number of patients discharged very early, the multivariate analysis (table 3) has not been modified.

2. Center experience impacted the length of hospital stay. Please detail how low, medium and high volume was defined.

We agree with the Reviewer's concern. Using tertiles values of the number of patients treated by centers, we defined Low (< 75), medium (75-140) and high volume (> 140) centers. This has been added in the revised manuscript page 5, lines 6-7. We also added in the revised manuscript (page 7, lines 13-14) the median LOS in the 3 groups and the difference was not significant

3. Self-expandable valves and use of TEE were associated with longer hospital stay. This may be related to center experience as well. Please comment.

We agree with the Reviewer that self-expandable valves and use of TEE were associated with longer hospital stay. As suggested by the Reviewer, we evaluated the use of TEE and self-expandable valves according to the volume of center (Low, medium, and high volume). The results are summarized below:

	Low	Medium	High	P
Self-expandable valve, %	37.4	37.7	26.1	<0.001
TEE, %	37.6	9.9	29.1	<0.001

Self-expandable valves were less frequently used in high volume centers and TEE was less frequently used in medium and high-volume centers. This has been added in the revised manuscript page 7, lines 14-16.

4. I assume, figure 4 depicts non-matched patients. If so, I would suggest to perform a matched-pair analysis because the groups are very different.

We agree with the Reviewer's concern. We did a propensity score matching based on a logistic regression model including baseline age, gender, logistic EuroSCORE for predicted risk of surgical mortality, chronic obstructive pulmonary disorder, atrial fibrillation, history of surgical mitral valve replacement, local anesthesia, model of prosthesis, stroke, vascular complication, acute kidney injury, and pacemaker, as covariates. This has been added in the revised manuscript in the method section page 5, lines 15-26. Interestingly, after propensity score matching, very early and early discharge patients had improved outcomes as

compared to those discharge late. This has been added in the revised manuscript in Figure 4B. However, this result should be analyzed with caution, as it is possible that the difference observed is linked to the persistence of residual confounding factors. This has been added in the revised manuscript page 12, lines 1-3.

5. The SOLVE trial has been published, please cite accordingly (Thiele H, Eur Heart J. 2020 Feb 12. pii: ehaa036. doi: 10.1093/eurheartj/ehaa036). Same with the MobiTAVI study, Vendrik J, Neth Heart J. 2020 Feb 28. doi: 10.1007/s12471-020-01374-5.

When we submitted the manuscript, these two studies were not published. These two references (23, 24) have been therefore added in the revised manuscript page 17, lines 12-21.

Letter to the Editor

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