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Long-Term Mortality and Early Valve Dysfunction According to Anticoagulation Use: The FRANCE-TAVI registry

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ABSTRACT
Background: The optimal anti-thrombotic treatment after transcatheter aortic valve replacement (TAVR) remains a matter of debate. Dual antiplatelet therapy (DAPT) is recommended but single antiplatelet therapy or oral anticoagulation (OAC) are frequently used according to the patient profile. Whether this may impact clinical outcome is unknown.
Method and objectives: FRANCE-TAVI is a prospective multicenter nation-wide French registry. Our objectives were to identify independent correlates of long-term all-cause mortality and early bioprosthetic valve dysfunction (BVD, defined as increased prosthetic gradient ≥10 mmHg or new gradient ≥20 mmHg).
Results: Of 12,804 patients included between January 1, 2013 and December 31, 2015, 11,469 (age 82.8±0.07 years old [mean±SE], logistic Euroscore 17.8±0.1%, mean duration follow-up was 495±3.5 days) were alive at discharge with known antithrombotic treatment and were analyzed for mortality. 2555 had at least 2 echocardiographic evaluations and were eligible of BVD assessment. One third of patients had a history of atrial fibrillation and the same proportion had OAC at discharge (n=3836). Neither aspirin nor clopidogrel were independently associated with mortality. Male gender (adj HR 1.63 [1.44-1.84], p<0.001), history of atrial fibrillation (adj. HR 1.41 [1.23-1.62], p<0.001) and chronic renal failure (adj. HR 1.37 [1.23-1.53], p<0.001) were the strongest independent correlates of mortality. Anticoagulation at discharge (adj. OR 0.54 [0.35-0.82], p=0.005) and a non-femoral approach (adj. OR 0.53 [0.28-1.02], p=0.049) were independently associated with lower rates of BVD, while chronic renal failure (adj. OR 1.46 [1.03-2.08], p=0.034) and prosthesis size ≤23mm (adj. OR 3.43 [2.41-4.89], p<0.001) yielded higher risk of BVD.
Conclusions: Gender, renal failure and atrial fibrillation, impacted the most mortality at 3-year follow-up. In contrast anticoagulation (mostly given for atrial fibrillation) decreased the risk of BVD after TAVR.

Keywords: TAVR, anticoagulation therapy, structural valve deterioration

Classification: Transcatheter aortic valve replacement; structural valve deterioration; oral anticoagulation therapy.

Condensed abstract: We evaluated whether oral anticoagulation therapy was an independent correlate of long-term survival and early bioprosthetic valve dysfunction (BVD) in 11,469 patients who underwent successful Transcatheter Valve Implantation. One third was on oral anticoagulation at discharge mainly for the prevention of cardioembolic stroke. Anticoagulation at discharge (adj. OR 0.54 [0.35-0.82], p=0.005) and prosthesis size ≤23mm (adj. OR 3.43 [2.41-4.89], p<0.001) were the strongest independent correlates of BVD. Gender, renal failure and atrial fibrillation, impacted the most mortality at 3-year follow-up. However, anticoagulation at discharge remained a correlate of mortality, independently of atrial fibrillation, despite the strong correlation between the two factors.

Abbreviations:
BMI: body mass index
CABG: coronary arterial bypass graft
COBP: chronic obstructive broncho-pulmonary disease
DAPT: dual antiplatelet therapy
LVEF: left ventricle ejection fraction
MG: mean gradient
SAPT: single antiplatelet therapy
OAC: oral anticoagulation

TAVR: transcatheter aortic valve replacement
BVD: bioprosthetic valve dysfunction

Introduction

Transcatheter aortic valve replacement (TAVR) to treat symptomatic aortic stenosis has expanded exponentially becoming a therapeutic option for intermediate and high-risk patients (1). The one year risk of stroke after discharge can be estimated to be as high as 2-3% (2) and silent valve thrombosis has been reported in up to 20% of patient (3,4). Dual anti-platelet therapy (DAPT) is recommended by international guidelines (5) although high on-clopidogrel platelet reactivity is frequent in senior patients (6,7). Furthermore, nearly one-third of TAVR patients display stabilized coronary artery disease or undergo stent implantation prior to TAVR and a similar proportion has atrial fibrillation (8,9) requiring chronic oral anticoagulation therapy (OAC) with or without antiplatelet therapy. There has been no large randomized trial assessing different anti-thrombotic strategies after TAVR. In addition, OAC is a potential approach to prevent early bioprosthetic valve dysfunction (BVD) vs. antiplatelet therapy alone (10). Our aim was to investigate if the type of anti-thrombotic treatment influences long-term mortality and early BVD in the FRANCE-TAVI registry and to explore independent correlates of long-term mortality and early BVD after TAVR.

Methods

Patient selection and study design

FRANCE-TAVI is a national multicenter prospective French registry that included 12804 patients who underwent TAVR in 1 of the 48 participating centers between January 1, 2013 and December 31, 2015 (11). It was designed to provide procedural characteristics and outcomes over time on a nationwide scale given scarce data. Patients provided written consent before inclusion. In this analysis we included patients alive at hospital discharge with known antithrombotic treatment status at the time of discharge.

Clinical and echocardiographic data was extracted from the FRANCE-TAVI registry. Outcomes of interest were all-cause death and valvular hemodynamic deterioration defined as

the rate of increased prosthetic gradient ≥10 mmHg between baseline and follow-up, or a new prosthetic gradient ≥20 mmHg on follow-up in patients without baseline trans-prosthetic gradient≥20 mmHg(12). Mortality data was acquired from an INSEE query on April 12, 2016, with dates of death available. Echocardiographic data was extracted from the FRANCE TAVR ancillary declarative registry of echocardiographic follow-up up to May 9th, 2016. The follow-up mean gradient of interest was the latest reported with a mandatory minimum duration of three months from TAVR to the follow-up echocardiography.

Objectives and outcomes

The primary objective was to identify the independent correlates of all-cause mortality at three years. The secondary objective was to identify the independent correlates of BVD at three years.

Statistical analysis

Variables are presented as mean (standard error=standard deviation/$\sqrt{n}$) or median (inter-quartile range) or number (%). Baseline characteristics were compared between the groups by means χ^2 or Fisher's exact test when appropriate for categorical variables, and Mann-Whitney U test or Student t test according to variable distribution (normality tested with Shapiro Wilk test) for quantitative variables.

To account for missing values, multiple imputations were performed using 5, 10 and 20 iterations to assure convergence (13–15). The frequency of missing values ranged from 0 to 24% and was assumed to be missing at random. Variables were considered for multivariable analysis when they were related to all-cause mortality or BVD on univariate analysis with p-value<0.2. The selected variables were included in the stepwise multivariable Cox regression for all-cause mortality and logistic regression for BVD (exit p-value=0.1) to identify independent correlates of the outcomes of interest. This operation was reiterated until conversion of the variables retained across multiple imputation databases in a stable model.

Then results were pooled according to Rubin's rule (13). Survival rates were studied with the Kaplan Meier method while censuring data at the latest follow-up available. We also performed a sensitivity analysis retaining only patients with complete data (complete cases analysis) to explore compatibility with the model obtained after multiple imputation. Results are reported as adjusted hazard ratio (adj. HR) or odds ratio (adj. OR) with their 95% confidence interval (95%CI).

A P-value <0.05 was considered significant unless otherwise specified. SPSS 23 (IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp) software was used to perform the statistical analysis.

Results

Univariate analysis of all-cause mortality

In total, 11469 out of 12804 patients were alive with known status for anticoagulation at discharge (**Figure 1**). Patient age was 82.8±0.07 year old, logistic Euroscore 17.8±0.11% and half of patients were females. The median duration of follow-up was 428 (239-718) days. Survival rate with 95% confidence interval was 90.4% [89.7- 91.0] at one year, 80.1% [79.0%- 81.2%] at two years and 69.9% [67.9 – 71.9] at three years. One third (33.4%) of patients were discharged on OAC of whom 71% had an indication for known atrial fibrillation. Systolic pulmonary arterial pressure was the most frequent missing data while atrial fibrillation and aortic regurgitation status were the most important ones but reaching less than 10% (Online Table 1).

Variables associated with all-cause mortality at 3 years on univariate analysis were gender, NYHA III-IV>2, Acute Pulmonary Oedema <1 year, logistic Euroscore I, prior TAVR, prior CABG, prior non-CABG cardiac surgery, prior peripheral artery disease, chronic respiratory insufficiency, severe reduction of mobility, history of cardiac stimulator, diabetes, moderate to severe renal failure (eGFR≤60 ml/min), atrial fibrillation, coronary

stenosis >50% prior to TAVR, LVEF, moderate to severe mitral regurgitation, pulmonary hypertension (systolic pulmonary artery pressure >30mmHg on echocardiography), non-femoral TAVR access, prosthesis diameter ≤23 mm, moderate to severe prosthetic regurgitation, auto-expandable (vs balloon expandable) valve, aspirin at discharge, clopidogrel at discharge, anticoagulation at discharge (**Central illustration**). Results were consistent in the multiple imputation and complete cases models.

Multivariable Cox regression analysis of all-cause mortality

Neither aspirin nor clopidogrel exposure was independently associated with all-cause mortality in the multivariable model. Male gender, history of atrial fibrillation and moderate to severe chronic renal failure were the strongest independent correlates of mortality. Other independent correlates were anticoagulation exposure at discharge, diabetes, non-femoral access, gender, NYHA III or IV, Euroscore I, prior CABG (protective), prior non-CABG cardiac surgery (protective), moderate to severe prosthetic regurgitation, auto-expandable valve type, and prosthesis diameter ≤23 mm (**Table 2**). Kaplan Meier curves according to the use of anticoagulation at discharge are shown in Online Figure 1 ($_{unadjusted}$HR 1.50; 95% CI 1.35-1.66). The results of the complete cases analyses were consistent except for moderate to severe prosthetic regurgitation, auto-expandable valve type, and prosthesis diameter ≤23 mm (**Table 1**).

Univariate analysis of valvular hemodynamic deterioration

Mean prosthetic gradient was reported in 2555 patients (22.3%) at baseline and follow-up of whom one third had anticoagulation at discharge. Median time to follow-up echocardiography was 12 (11-15) months without difference according to treatment groups (p=0.26). A total of 140 patients (5.5%, IC95% 4.6-6.4%) were diagnosed with BVD. "One third and one fourth of patients displayed an increase of valve mean gradient of ≥10mmHg from baseline to follow-up or a new mean gradient ≥20mmHg at follow-up, respectively, and

half (45%) displayed both ". The proportion of missing variables is similar as for mortality (Online Table 2). Variables associated with BVD on univariate analysis ($p<0.2$) were age, gender, BMI, prior TAVR, moderate to severe chronic renal failure, atrial fibrillation, LVEF, non-femoral TAVR access, auto-expandable (vs balloon-expandable valve type), prosthesis diameter ≤23 mm, aspirin at discharge, clopidogrel at discharge and anticoagulation at discharge.

Multivariable logistic regressions analysis of BVD

Multivariable stepwise logistic regression identified high BMI, prior TAVR, prosthesis size ≤23 mm, moderate to severe chronic renal failure to be predictive of BVD while anticoagulation at discharge and non-femoral TAVR access were protective (**Table 3**). These results were consistent with the complete cases analyses.

Discussion

The major finding of the present study is that gender, renal failure and atrial fibrillation were the most potent predictors of mortality after successful TAVR (Central Illustration). Anticoagulation, given in 70.8% of cases for atrial fibrillation, remained a correlate of mortality, independently of AF, despite the strong correlation between the two factors. However, post-TAVR anticoagulation decreased the risk of BVD as opposed to anti-platelet treatment.

Post-TAVR DAPT remains the default strategy according to the international guidelines but without appropriate randomized trials to support strongly this recommendation (5,16,17). The ARTE study even suggested that the DAPT strategy was increased the risk of major bleeding without any clinical benefit (18). Conversely, multiple antithrombotic therapies combining oral anticoagulation with antiplatelet therapy versus oral anticoagulation alone led to a lower net clinical benefit without reduction in ischemic events (19).

The risk of cerebral embolism after TAVR remains high (20) and anticoagulation within the first 3 to 6 months post-TAVR may prevent the thromboembolic risk as for surgical bioprosthesis especially during the early phase of healing (10,21,22). This has been recently implemented in the ACC/AHA valvular disease update where anticoagulation may be used in the post-TAVR setting when the bleeding risk is low in patients without any other indication for chronic oral anticoagulant (5,23). In the present study post-TAVR OAC exposure, a factor strongly related to AF, remains however significantly related with increased long-term mortality, despite adjustment for atrial fibrillation which is a stronger predictor of mortality than anticoagulation. There are both limitations as well as potential explanations for this finding. First, patients on OAC at discharge have more comorbidities (in addition to AF) than non-OAC treated patients with a substantial difference in age. Some of these differences may have been underestimated given that adjustments were performed on known collected variables. Other potential high risk profile features such as intra-cardiac thrombus, suspected cardio-embolic stroke, pulmonary embolism, and mitral valve disease were not considered and may have been key determinants of outcomes. Second, the detrimental impact of bleeding not captured here, must also have been of paramount importance in our OAC-treated population(19, 24). Finally, VKA was the most commonly used OAC therapy during the 2013-2015 recruitment period of the FRANCE-TAVI registry. It is likely that the established better safety of non-VKA oral anticoagulants in non-valvular AF may also apply to the post-TAVR setting (25–27). The observed mortality excess among post-TAVR OAC-treated patients further supports the need for randomized evaluations of anticoagulation with NOAC versus antiplatelet therapy. These trials are ongoing. ATLANTIS (NCT02664649) evaluates apixaban versus standard of care in all comers irrespective of the need for OAC (28). GALILEO (NCT02556203) compares rivaroxaban versus DAPT after

successful TAVR in patients without other compelling indication for OAC such as atrial fibrillation (29).

The interaction between sub-clinical prosthesis thrombosis, cerebrovascular events and anticoagulation (4,10,21) supports bioprosthesis valve dysfunction as a potential risk factor of stroke/TIA. Del Trigo et al. previously reported a reduction in BVD occurrence with anticoagulation, but not with aspirin or clopidogrel (30, 31). Similarly, we found that neither aspirin nor clopidogrel were able to prevent BVD. However, observational data cannot allow accurate inference on the efficacy of anticoagulant treatment to prevent BVD because of its close association with atrial fibrillation. Indeed, mean gradient as evaluated by transthoracic echocardiography is highly variable in patients with atrial fibrillation and reduced in patients with tachycardia which artificially induces a pseudo-protective effect of atrial fibrillation regarding BVD. In addition, atrial fibrillation and anticoagulation are correlated (r=0.59 in our study) and both could reduce echocardiographic mean gradient. We believe that only a randomized trial can appropriately evaluate the potential benefit of anticoagulation in preventing BVD after TAVR.

Our analyses are robust demonstrating consistent findings with previous studies on the detrimental impact of the non-femoral access for TAVR (8), atrial fibrillation, well established comorbidities and gender (**Central Illustration**) (25). The effect of some procedure-related features on survival is also consistent with previous reports when considering moderate to severe prosthetic regurgitation and prostheses diameter ≤23 mm. However, there are also discrepancies between both models especially when considering procedure-related feature ks. A lack of power of the multiple imputation models that was performed in 11469 out of 12804 patients is a likely explanation. The increased mortality with the use of auto-expandable transcatheter heart valves should be considered with caution and may be related to technological gaps. Most of the balloon expandable valves were of the

last generation with less para-valvular leak whereas auto-expandable valves were mostly non-recapturable first generation valves with more frequent low implantation depth. This finding deserves obviously additional confirmatory or invalidating studies.

Body mass index, prior TAVR and small prothesis size (≤23 mm) have been previously reported to be associated with subsequent BVD. On top of these, we have identified non-femoral access to be associated with decreased risk of subsequent BVD while moderate to severe chronic renal failure with an increased risk of BVD. Trans-carotid, subclavian or direct aortic access might provide a better alignment during delivery with a more precise valve positioning and subsequent lower mean gradient and BVD. Chronic renal failure has been reported to be responsible for aortic valve calcification and increased mean gradient (32,33), and might even predispose to recurrence of stenosis on of the bioprosthetic valve.

There are several limitations to our study. First, analysis of observational registry data comes with the inherent risks of bias. Missing values can be a major drawback in large multicentre registries. We used multiple imputations followed by multivariable Cox regression and logistic regression to overcome these challenges. Multiple imputation has been reported to have the best performance to deal with sparse missing values in healthcare databases (13,14). Stepwise regression methods were chosen over other techniques given the large number of events in our database allowing a good prediction performance. Second, multicollinearity, especially between the use of OAC and atrial fibrillation, was explored by correlation matrix and was handled by a careful selection of variables according to the magnitude of association with the outcome of interest. Third, the declarative nature of the long-term clinical events in the FRANCE-TAVI registry yielded poor event recording. As a consequence, long-term bleeding and stroke were not considered and attention was focused

on mortality and BVD only. Finally, detection of valve thrombosis/deterioration by multidetector computed tomography might have resulted in different correlates.

Conclusions

Gender, renal failure and atrial fibrillation were the most potent predictors of mortality after successful TAVR. Anticoagulation was strongly linked to atrial fibrillation and other comorbidities, but remained a correlate of mortality. However, post-TAVR anticoagulation decreased the risk of BVD as opposed to anti-platelet treatment. The role of anticoagulation after TAVR is difficult to study in registries considering all the potential confounding variables and it should be used according to the current guidelines(1). Only the ogoing randomized trials will provide the best evidence for optimal antithrombotic management after TAVR.

Perspectives

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Post-TAVR antithrombotic treatment is mainly driven by the patient's characteristics. Post-TAVR anticoagulation is given in one third of patients after successful TAVR to prevent cardioembolic stroke. It decreases the risk of structural valve deterioration. It is also significantly associated with increased long-term mortality despite adjustment for atrial fibrillation, a stronger predictor of mortality than anticoagulation.

TRANSLATIONAL OUTLOOK: Ongoing randomized trials are awaited to clarify the clinical benefit of long-term anticoagulation after successful TAVR. The bleeding risk of this population is high, the need for antiplatelet therapy due to concomitant coronary artery disease is frequent and the determinants of valve thrombosis are partly known. These are the main challenges to be solved.

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Figure legends

Central Illustration: Post-TAVR Antithrombotic Strategy: Flow chart. Independent correlates of long-term survival and bioprosthesis valve dysfunction. These correlates are numerous with multiple and complex interactions. Plain and dotted arrows indicate known interactions and those preferentially highlighted by the FRANCE-TAVI registry (bold characters), respectively. Arrows width is proportional to the strength of the interaction. The red and blue colors outline factors associated with bleeding/anticoagulation or thrombosis/mortality, respectively. The "+" and "-" signs indicates positive and negative interactions. The use of oral anticoagulation varies co-linearly with atrial fibrillation and is associated with a reduced risk of bioprosthesis valve dysfunction. It also remains independently associated with mortality despite adjustment for atrial fibrillation which has a much stronger effect. Unknown confounders cannot be excluded. *indicates thrombus within the bioprosthesis.

Table 1: Baseline characteristics according to oral anticoagulation exposure at discharge.

Characteristics	Total (n=11469)	No OAC (n=7633)	OAC (n=3836)	p-value
Age	82.8 (0.068)	82.7 (0.085)	82.9 (0.111)	0.60
BMI (kg/m²)	26.7 (0.056)	26.6 (0.070)	26.9 (0.094)	<0.001
Gender (male)	5683 (49.6)	3712 (48.6)	1971 (51.4)	0.005
NYHA class III-IV	7941 (68.9)	5214 (68.2)	2727 (71)	0.002
≥2 acute pulmonary edema in previous year	1536 (13.4)	938 (12.3)	598 (15.9)	<0.001
CCS Class IV angina	574 (4.9)	426 (5.6)	148 (3.8)	<0.001
Logistic Euroscore I	17.8 (0.114)	17.3 (0.139)	18.9 (0.198)	<0.001
Prior CABG	1327 (11.6)	906 (11.9)	421 (11)	0.17
Prior PCI	3441 (30.0)	2470 (32.4)	971 (25.3)	<0.001
Prior TAVR	114 (1.0)	71 (0.9)	43 (1.1)	0.34
Prior non-CABG surgery	798 (6.9)	457 (6.0)	341 (8.9)	<0.001
PAD	2558 (22.3)	1698 (22.2)	860 (22.4)	0.84
Chronic respiratory insufficiency	2269 (19.7)	1473 (19.1)	796 (20.9)	0.064
History of stroke/Transient Ischemic attack	1234 (10.9)	744 (9.7)	490 (12.8)	<0.001
Cardiac stimulator	1632 (14.2)	892 (11.7)	740 (19.4)	<0.001
Presence of stenosis>50% on pre-TAVR coronary angiography	4543 (39.6)	3119 (40.9)	1424 (37.1)	<0.001
Diabetes mellitus	2941 (26.0)	1946 (25.9)	995 (26.2)	0.74
Chronic renal failure	5069 (44.2)	3232 (42.3)	1837 (47.9)	<0.001

(eGFR<60mL/min)				
Atrial fibrillation	3789 (33.0)	1066 (14.0)	2723 (70.8)	<0.001
LVEF (%)	55.4 (0.128)	56.1 (0.150)	53.8 (0.217)	<0.001
Systolic pulmonary pressure pre-TAVR >30 mmHg	7918 (69)	4971 (65.1)	2947 (76.8)	<0.001
Non-femoral access	1895 (16.5)	1194 (15.6)	701 (18.3)	<0.001
Type of valve				0.37
- Balloon-expandable	7422 (64.7)	4918 (64.4)	2504 (65.3)	
- Self-expandable	4045 (35.3)	2714 (35.6)	1331 (34.7)	
Prosthesis diameter ≤23 mm	3215 (28.2)	2258 (29.6)	957 (24.9)	<0.001
AR moderate to severe post-TAVR	1151 (10.0)	758 (10)	393 (10.3)	0.69
Aspirin at discharge	9554 (83.3)	7123 (93.3)	2431 (63.4)	<0.001
Clopidogrel at discharge	6017 (52.5)	5379 (70.5)	638 (16.6)	<0.001
OAC and aspirin	2100 (18.3)	0	2100 (54.7)	<0.001
Triple therapy*	331 (2.9)	0	331 (8.6)	<0.001
DAPT (aspirin and clopidogrel)	5109 (44.5)	5109 (66.9)	0	<0.001

*OAC plus aspirin and clopidogrel

Table 2: Independent correlates of mortality using multiple imputation (m=20) and complete cases models ("-" indicates variables not significantly associated with mortality).

	MI m=20 p-value	Adj. HR	95% CI lower	95% CI upper	Complete cases p-value	Adj. HR	95% CI lower	95% CI upper
Gender (male)	<0.001	1.63	1.44	1.84	<0.001	1.52	1.35	1.72
NYHA III or IV	<0.001	1.28	1.14	1.46	0,001	1.25	1.10	1.43
Euroscore I (per 1% increment)	<0.001	1.01	1.01	1.02	<0.001	1.01	1.01	1.02
Prior CABG	<0.001	0.64	0.54	0.77	<0.001	0.67	0.53	0.82
Prior non-CABG cardiac surgery	<0.001	0.59	0.46	0.76	<0.001	0.64	0.50	0.84
Diabetes mellitus	<0.001	1.25	1.12	1.41	0.002	1.22	1.08	1.38
Moderate/severe renal failure	<0.001	1.37	1.23	1.53	<0.001	1.33	1.18	1.50
Atrial fibrillation	<0.001	1.41	1.23	1.62	<0.001	1.39	1.20	1.61
Non-femoral access for TAVR	0.011	1.18	1.04	1.35	0.048	1.15	1.01	1.34
Moderate to severe prosthetic regurgitation	0.001	1.28	1.11	1.50	-	-	-	-
OAC at discharge	0.013	1.18	1.04	1.35	0.002	1.25	1.08	1.44

Auto-expandable (vs balloon expandable) valve	0.014	1.15	1.03	1.29	-	-	-	-
Prosthesis diameter 23 or less	0.042	1.17	1.01	1.36	-	-	-	-

n=11469 for multiple imputation analysis; n=9185 for complete cases analysis. MI = Multiple Imputation.

Table 3: Independent correlates of bioprosthetic valve dysfunction using multiple imputation (m=20) and complete cases models

	m=20 P-value	Adj. OR	95% CI upper	95% CI lower	Complete cases P-value	Adj. OR	95% CI upper	95% CI lower
BMI (per 1 kg/m² increment)	0.002	1.05	1.02	1.09	0.002	1.05	1.02	1.09
Prior TAVR	0.025	2.96	1.15	7.64	0.019	3.15	1.21	8.21
Moderate/severe renal failure	0.034	1.46	1.03	2.08	0.042	1.44	1.01	2.05
Non-femoral access	0.049	0.53	0.28	1.02	0.032	0.48	0.25	0.94
Prosthesis ≤23 mm	<0.001	3.43	2.41	4.89	<0.001	3.50	2.45	4.99
OAC at discharge	0.005	0.54	0.35	0.82	0.003	0.51	0.33	0.79

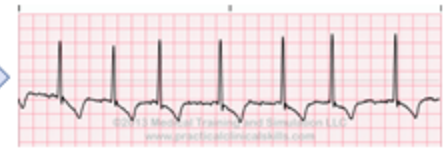
n=2555 for multiple imputation analysis; n=2516 for complete cases analysis.

PATIENT CHARACTERISTICS

- Gender
- NYHA III or IV
- Euroscore I
- Diabetes mellitus
- Chronic renal failure
- Prior surgery

Anticoagulation at discharge

Atrial Fibrillation

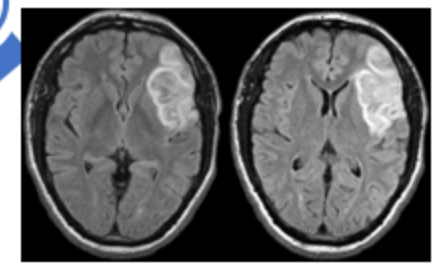


PROCEDURE CHARACTERISTICS

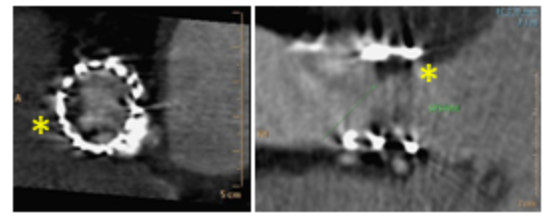
- Non-femoral approach
- Implant depth
- Type of bioprosthesis
- Size of the bioprosthesis
- Prior TAVI
- Prosthetic regurgitation

Long-term Mortality

Bleedings



Cardioembolic Stroke



Bioprosthetic Valve Dysfunction