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ORIGINAL ARTICLE

Incidence, predictors and impact of bleeding after transcatheter aortic valve implantation using the balloon-expandable Edwards prosthesis

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ABSTRACT

Objectives To evaluate the incidence, predictors and impact of bleeding after transcatheter aortic valve implantation (TAVI).

Design Single-centre prospective observational study.

Setting Charles Nicolle University Hospital, Rouen, France.

Interventions We included 250 consecutive patients who underwent TAVI between May 2006 and October 2011. All procedures were performed using Edwards SAPIEN and SAPIEN XT valves via transfemoral (TF) and transapical (TA) routes. Surgical cutdown was used for TF access when implanting the SAPIEN valve, while percutaneous access was used for SAPIEN XT implantation. Life-threatening bleeding (LTB), major and minor bleeding and other complications were defined using Valve Academic Research Consortium criteria.

Results TAVI was performed via TF access in 190 cases (76%) and the SAPIEN XT valve was used in 123 cases (49.2%). Bleeding after TAVI was noted in 68 patients (27.2%): LTB in 33 (13.2%), major bleeding in 23 (9.2%) and minor bleeding in 12 (4.8%). By multivariate analysis, only TA access was an independent predictor of LTB (OR 3.7, 95% CI 1.73 to 7.9, p=0.001). Patients presenting with LTB after TAVI had a higher 30-day mortality (33.3% vs 3.7%, p<0.001) and 1-year mortality (54% vs 18%, p<0.001). LTB was an independent predictive factor of 1-year mortality (HR 2.54, 95% CI 1.3 to 4.9, p=0.002).

Conclusions Bleeding is a frequent complication of TAVI, occurring in 27% of cases. LTB is associated with higher 30-day and 1-year mortality.

INTRODUCTION

In patients with severe symptomatic aortic stenosis (AS), transcatheter aortic valve implantation (TAVI) is considered an alternative to medical treatment in non-operable patients[1] and appears to be comparable to surgery in the high-risk subgroup.[2] While procedural complications like pacemaker implantation, aortic regurgitation and vascular complications have been the subject of multiple reports,[3–9] specific analyses of bleeding after TAVI are limited.[10 11] The negative impact of bleeding[12] and blood transfusions[13] after percutaneous coronary intervention has led to a paradigm shift in recent years and haemorrhage was included in the composite endpoint of cardiovascular events.[14 15] Bleeding and transfusions are frequent complications after TAVI,[16] and life-threatening bleeding (LTB) is associated with higher 30-day[10 17 18] and 1-year mortality.[19] This suggests that bleeding after TAVI could have the same clinical importance as after percutaneous coronary intervention.

This study aimed to evaluate the incidence, predictors and impact of bleeding after TAVI.

METHODS

Study population

We included consecutive patients with severe symptomatic AS implanted in our centre between May 2006 and October 2011. A team of cardiologists and cardiac surgeons established the indication for TAVI, when patients were considered inoperable, at high-surgical risk (logistic EuroSCORE≥20%) or had other risk factors (eg, porcelain aorta, previous thoracic radiotherapy or frailty). A CT scan for femoral access evaluation was performed systematically. Clinical and echocardiographic follow-up was planned at 1, 3, 6 and 12 months and then yearly. All patients provided signed informed consent.

Procedure

Procedures were performed using the Edwards SAPIEN and SAPIEN XT valves (Edwards Lifesciences, Irvine, California, USA), as previously described.[20] All procedures were carried out using transfemoral (TF) or transapical (TA) access. For TF implantation of 23 mm and 26 mm valves, 22 F and 24 F sheaths were used with the SAPIEN valve and 18 F and 19 F sheaths were used with the SAPIEN XT valve. For TA access, the 28 F Ascendra 1 or 26 F Ascendra 2 introducer (Edwards Lifesciences) was used in all cases. Femoral closure was surgical when using the SAPIEN valve or percutaneous with the Prostar system (Abbott Vascular, Abbott Park, Illinois, USA) when using the SAPIEN XT valve. Surgical closure of the ventricular apex was achieved with circular pledgets. TF procedures were performed using local anaesthesia and conscious sedation. All patients had their blood typed and two units of blood were placed in reserve before the procedure. The levels of haemoglobin (Hb), platelets and prothrombin time were measured before the procedure. Loading doses of aspirin (250 mg intravenously) and clopidogrel (300 mg) were administered before TF procedures if the patients were not previously treated, while only aspirin was administered before TA procedures. Aspirin was continued indefinitely and clopidogrel was continued for 1 month.

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Oral anticoagulants were stopped before TAVI. A 70 IU/kg bolus of unfractionated heparin was injected after sheath placement and was reversed with intravenous protamine in all TA procedures before apical closure, or in case of bleeding during TF procedures. A final iliofemoral arteriography was performed at the end of the TF procedure. Transfusions were started if bleeding led to hemodynamic instability or if the level of Hb decreased below 7 g/dl. In all other situations the decision to transfuse was left to the discretion of the treating physician.

Definitions

Bleeding and other complications were adjudicated according to the Valve Academic Research Consortium (VARC).[21] Anaemia was defined as a Hb level <13 g/dl in men and <12 g/dl in women according to the WHO definition. The sheath to artery ratio (SAR) was defined as the ratio between the sheath outer diameter and the minimal iliofemoral artery diameter.[7]

Statistical analysis

Continuous variables are presented as mean (SD) or median (IQR), according to the distribution. Categorical variables are presented as frequencies and percentages. We used the Student t test or the Mann–Whitney test to compare differences between the continuous variables and the χ^2 or Fisher exact test to compare differences between categorical variables, as appropriate. Survival curves were constructed using Kaplan–Meier analysis and compared with the log-rank test. Predictive factors of LTB were assessed by forward logistic regression. All baseline variables with a p value < 0.05 in the univariate analysis were introduced in the model, which was confirmed by backward analysis. Independent predictors of 1-year mortality were analysed using forward Cox multivariate regression and confirmed by backward analysis. Variables with p<0.05 in the univariate analysis were entered in the multivariate Cox regression. Differences were considered statistically significant at p values <0.05. All statistical analysis was performed using SPSS Statistics software V.17.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Baseline characteristics

A total of 250 patients underwent TAVI in our centre between May 2006 and October 2011. Baseline characteristics are shown in table 1. TA access was used in 60 patients (24%), while 190 procedures (76%) were performed using TF access. The SAPIEN XT valve was used in 123 interventions (49.2%), via TA in 11 cases (18.3%) and via TF access in 112 (91.1%). The Ascendra 2 system was used in 17 patients (28.3%). The median age was 85 years (IQR 80–88) and the mean logistic EuroSCORE was 23.2±13%. Baseline anaemia was present in 113 patients (55.1%) and mean Hb before the procedure was 11.7±1.5 g/dl. Minimal arterial diameter was smaller in the SAPIEN XT group (6.75±1.17 mm vs 8.5±1.3 mm, p<0.001) while the SAR was similar (0.92±1.6 vs 0.97±1.3, p=0.107).

Bleeding complications and transfusions

Bleeding complications were observed in 69 patients (27.6%); LTB was present in 33 patients (13.2%), major bleeding in 24 patients (9.6%) and minor bleeding in 12 (4.8%). SAPIEN and SAPIEN XT TAVI were associated with a similar incidence of LTB (15.7% vs 10.6%, p=0.23), major bleeding (8.7% vs 10.6%, p=0.61) and minor bleeding (2.4% vs 7.3%, p=0.067). LTB frequency was higher with TA access (26.7% vs 8.9%, p<0.001). The incidence of bleeding was similar with the TA Ascendra and Ascendra 2 systems (4 vs 16 patients, p=0.33). Bleeding was related to access in 69% of cases (figure 1). Femoral access bleeding necessitated a stent graft implantation in 12 patients (35.3%) and urgent vascular surgery in 6 (17.6%). At least one red blood cell (RBC) unit was administered in 88 patients (35.2%), and 35 patients (14%) were transfused without an identified source of bleeding. The mean number of transfused RBC units was 1.4±3.2 per patient.

Predictors of bleeding

By univariate analysis, prior coronary aortic bypass graft, peripheral arterial disease and TA access were significantly associated with LTB after TAVI. By multivariate analysis, TA access was the only independent predictor of LTB (OR 3.7, 95% CI 1.73 to 7.9, p=0.001; see online supplemental table 1). Independent predictors of major bleeding were the presence of carotid stenosis (OR 7.86, 95% CI 1.2 to 51.55, p=0.032) and TA route (OR 5.2, 95% CI 1.02 to 26.53, p=0.047).

Thirty-day mortality and bleeding

Overall mortality at 30 days was 7.6%. The causes of 30-day mortality were pulmonary bleeding (n=1), septic shock (n=3), sudden death (n=2), valve embolisation (n=2), multiorgan failure (n=1), aortic dissection (n=1), ventricular fibrillation during TAVI (n=1), myocardial infarction (n=2), limb ischaemia (n=2), respiratory failure (n=1) and tamponade (n=3). Compared with survivors, non-survivors at 30 days had a higher incidence of LTB (57.9% vs 9.5%, p<0.001) and a similar incidence of major bleeding (0% vs 10.4%, p=0.231) and minor bleeding (5.3% vs 4.8%, p=1.0). Non-survivors had a higher rate of baseline anaemia (78.9% vs 53.2%, p=0.03), a higher logistic EuroSCORE (29.7±10.5% vs 22.6±12.9% p=0.023), an increased incidence of acute kidney injury (AKI) (57.9% vs 26%, p=0.003), device failure (37.6% vs 7.4%, p=0.004) and severe left ventricular systolic dysfunction (LVSD) (66.7% vs 7.5%, p<0.001) after TAVI.

One-year mortality and bleeding

One-year Kaplan–Meier survival curves stratified by the presence of LTB after TAVI are shown in figure 2. The survival rate was similar in patients with major bleeding (78.5% vs 77%, log rank p=0.72) or minor bleeding (91.7% vs 76.5%, log rank p=0.49). By multivariate analysis, LTB was an independent predictor of 1-year mortality as were baseline anaemia, discharge aortic regurgitation >1, device failure and severe LVSD after TAVI (table 2). Post-procedural transfusion during the hospital stay was also associated with increased 1-year mortality (figure 2).

DISCUSSION

Main findings

The main results of the present study are: (1) bleeding after TAVI was frequent, half being life-threatening; (2) the only independent predictor of LTB after TAVI was TA access; (3) LTB was an independent predictor of 1-year mortality.

Incidence of bleeding complications

A recent meta-analysis of VARC clinical outcomes including 3519 patients found a pooled estimated rate of bleeding of 41.4% (95% CI 35.5% to 47.6%).[16] The pooled estimate rate of LTB was 15.6% (95% CI 11.7% to 47.6%), which was similar to the LTB frequency of 13.2% reported in our study. Gurvitch *et al*[22] reported a total incidence of bleeding of 26.8% with the Edwards valve, while another study with the CoreValve reported an incidence of 32%.[23] In a series evaluating both the Edwards valve and CoreValve and various accesses, the overall

Table 1 Baseline and periprocedural characteristics

Variables	Overall (n=250)	No LTB (n=217)	LTB (n=33)	p Value
Age, years	83.3±6.5	83.5±6.4	81.9±7.4	0.207
Female	135 (54%)	122 (56.5%)	13 (39.4%)	0.067
Body mass index, kg/m^2	27.3±2.6	27.6±2.8	25.3±5.5	0.646
Hypertension	181 (72.7%)	159 (73.3%)	22 (68.8%)	0.592
Diabetes	64 (25.7%)	59 (27.2%)	5 (15.6%)	0.162
Coronary artery disease	87 (34.8%)	74 (34.1%)	13 (39.4%)	0.552
Previous CABG	49 (19.7%)	37 (7.1%)	12 (37.5%)	0.009
Peripheral arterial disease	55 (22.1%)	42 (19.4%)	13 (40.6%)	0.01
Carotid stenosis	8 (3.2%)	5 (2.3%)	3 (9.4%)	0.069
Creatinine, μmol/l	115.9±56.3	115.8±55.5	116.8±62	0.925
Porcelain aorta	20 (8%)	17 (7.8%)	3 (9.4%)	0.729
Logistic EuroSCORE, %	23.1±12.8	22.8±12.6	25.5±14.5	0.260
Sinus rhythm	182 (73.1%)	160 (74.1%)	22 (66.7%)	0.371
Haemoglobin, g/dl	11.7±1.5	11.7±1.5	11.6±1.5	0.663
Anaemia	138 (55.2%)	116 (53.5%)	22 (66.7%)	0.155
Platelets, 10^3/mm^3	220.6±69	221±71.6	219±51	0.883
Oral anticoagulant therapy	66 (26.7%)	62 (28.8%)	4 (12.5%)	0.051
Prothrombin time, %	76.1±18.2	75.7±18.6	79.9±15	0.201
Aortic valve area, cm^2	0.65±0.17	0.66±0.17	0.63±0.16	0.514
Mean gradient, mm Hg	44.6±16.7	44±17	46±17	0.459
LVEF<30%	26 (10.4%)	22 (10.1%)	4 (12.1%)	0.759
Aortic regurgitation >1	72 (28.8%)	24 (72.7%)	9 (27.3%)	0.835
Procedural				
Transapical	60 (24%)	44 (20.3%)	16 (48.5%)	<0.001
SAPIEN XT	123 (49.2%)	107 (49.3%)	20 (60.6%)	0.227
Duration of hospital stay, days	7 (5–10)	7 (5–9)	9 (5.5–27)	0.023
Duration of ICU stay, days	2 (1–3)	2 (1–2)	4 (2–7)	<0.001
Complications				
Device failure	23 (9.2%)	17 (7.8%)	6 (18.2%)	0.096
Myocardial infarction	5 (2%)	2 (0.9%)	3 (9.1%)	0.018
Major stroke	4 (1.6%)	4 (1.8%)	0 (0%)	1.00
Minor stroke	2 (0.8%)	2 (0.9%)	0 (0%)	1.00
AKI stage 1	64 (25.6%)	52 (24%)	12 (36.4%)	0.199
AKI stage 2	2 (0.8%)	1 (0.5%)	1 (3%)	0.247
AKI stage 3	5 (2%)	1 (0.5%)	4 (12.1%)	0.001
Infectious complications	37 (15.1%)	24 (11.3%)	13 (40.6%)	<0.001
Aortic regurgitation >1	72 (28.8%)	63 (29%)	9 (27.3%)	0.835
Major vascular complications	16 (6.4%)	6 (2.8%)	10 (30.3%)	<0.001
Minor vascular complications	29 (11.6%)	27 (12.5%)	2 (6.1%)	0.389
Death at 30 days	19 (7.6%)	8 (3.7%)	11 (33.3%)	<0.001
Pacemaker	15 (6.1%)	13 (6.1%)	2 (6.1%)	1.00
Transfusion ≥1 RBC	88 (35.2%)	58 (26.7%)	30 (90.9%)	<0.001
Discharge haemoglobin, g/dl	10 (9–11)	10 (9–11)	9.5 (9–10)	0.001

AKI, acute kidney injury; CABG, coronary aortic bypass graft; ICU, intensive care unit; LTB, life-threatening bleeding; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RBC, red blood cell unit.

incidence of bleeding was higher (63.3%).[24] The rate of LTB ranges from 4.9%[10] to 25.9%.[24] In the cited meta-analysis almost one out of two patients was transfused after TAVI. We reported a 14% rate of transfusions without an overt source, which is within the range of previously published data (7.7–35%).[22 23]

Predictors of bleeding

Predictors of LTB or major bleeding after TAVI were previously assessed only in a small observational study. Halliday *et al*[10] found diabetes, baseline Hb and coexisting vascular disease to be predictors of LTB or major bleeding complications. Access was not associated with an increased risk of LTB or major bleeding. In the PRAGMATIC multicentre registry, bleeding was significantly associated with TA access.[11] A surgical TF approach was independently associated with a lower tendency for transfusion compared with other approaches. Furthermore, the strongest predictor of transfusion of ≥4 RBC units was the presence of major vascular complications. Since transfusion of ≥4 RBC units is part of the definition of major vascular complications, the analysis seems circular, using a variable to predict itself. In the present analysis, TA access was the only independent predictor of LTB. Our findings are paralleled by the results from several large registries including patients implanted transapically. The German registry (13 860 patients) reported an increased rate of transfusion (>2 RBC) in the TA group

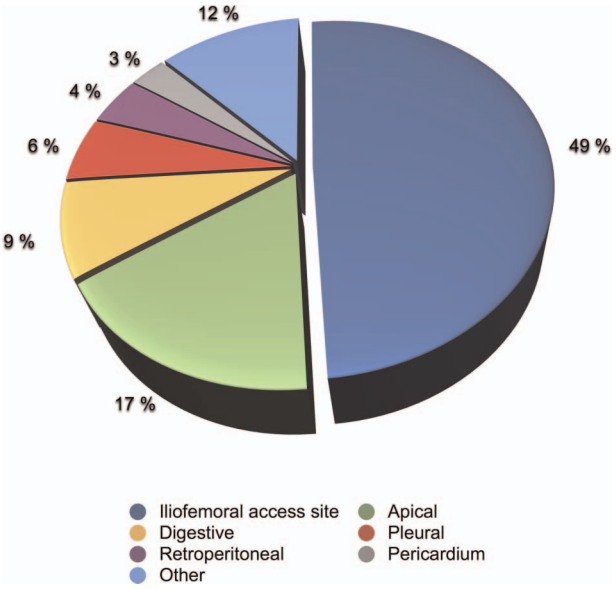

Figure 1 Causes of bleeding.

(25.4% vs 11.5%; Christian Hamm, German Aortic Valve RegistrY (GARY) in hospital outcome, ESC Congress, Munich 2012). Transfusions were also more frequent with the Edwards valve when using TA access in the FRANCE registry (27.4% vs 8.4%).[25] In the FRANCE 2 registry, VARC major or LTB was more frequent in patients undergoing TAVI using TA access.[26] Major bleeding incidence, according to the trial definition, was more than double when TA access was used in the SOURCE XT registry (11.4% vs 5%; Olaf Wendler, 30-day outcome from the SOURCE XT TAVI post-approval study, EuroPCR, Paris, 2012). Several explanatory hypotheses can be advanced for the propensity to bleeding associated with TA access. First, patients with TA access have a higher EuroSCORE and are more sick than patients undergoing TF interventions. Second, TA intervention is more invasive, requiring the insertion of larger sheaths in a beating ventricle, which has an intracavitary pressure higher than the systemic pressure. Various strategies can be employed during TF procedures to prevent or treat access site bleeding (eg, crossover techniques, balloon inflation, manual compression, covered stents), while apical bleeding can be more difficult to control and anticipate. We found major bleeding to be predicted by TA access and the presence of carotid stenosis. The presence of an associated vascular pathology could be a marker of more severe peripheral disease and imply a higher risk of vascular complications. Even if the femoral introducer size decreased with the SAPIEN XT model, we did not observe a significant decrease in the incidence of LTB. This could be due to the parallel decrease in iliofemoral diameter, the SAR being similar with the two models, and also to the shift from surgical to percutaneous closure.

Bleeding and outcome after TAVI

Various studies that analysed the predictors of early and late mortality after TAVI found bleeding to be associated with an increased risk of fatality. After 2 years of follow-up in the randomised PARTNER trial, major bleeding was associated with a twofold risk of mortality.[2] The definition used for major bleeding in this trial was similar to the VARC definition of LTB, including the transfusion of at least four RBC units. Halliday *et al*[10] studied the impact of bleeding on outcome and reported a higher in-hospital and 6-month mortality in patients with LTB. This was not observed with VARC major or minor bleeding, as in our series. Another multicentre study found LTB to be a predictor of 30-day mortality by multivariate analysis.[17] Tamburino *et al*[19] compared the 1-year outcomes of patients undergoing TAVI or surgical aortic valve replacement and found LTB to be a strong independent predictor of all-cause mortality at 1 year.[19] At 3-year follow-up in the CoreValve Italian Registry, LTB was associated with significantly higher mortality, the effect already being observed at 30 days.[18] Our study results are in line with these findings, showing a negative impact of LTB on 30-day and 1-year survival after TAVI. Bleeding after TAVI was mostly caused by access complications that can lead to haemodynamic instability, increasing the risk of AKI and ischaemia. Bleeding is generally associated with transfusions, which have deleterious effects by paradoxical impairment in oxygen delivery and transfusion-related immunomodulation associated with a higher risk of infection.[13] They also increase the incidence of AKI, which raises mortality.[27] Transfusions, especially ≥4 RBC units, have an adverse impact on outcome at 1 year.[11] This could be an effect of transfusion itself or transfusion could be a marker of a higher risk status, like baseline anaemia. Anaemia before TAVI was an independent predictor of 1-year mortality in a cohort of 118 consecutive patients.[28] In our analysis, transfusions and baseline anaemia had a negative impact on 1-year mortality. Anaemic patients were not more likely to bleed, but they had a higher rate of transfusion. Similar falls in Hb lead to lower final Hb levels in anaemic patients, which probably trigger transfusion.

Strategies to reduce bleeding after TAVI

Bleeding after TAVI could be decreased by careful selection of patients, use of smaller devices, performing TAVI without administration of clopidogrel or using bivalirudin instead of heparin.[29] It is important to limit the negative consequences of bleeding by having a more restrictive transfusional policy.

Limitations of the present study

This study reports the results of a highly experienced single centre using a single type of transcatheter heart valve. We included different models and techniques of vascular access and closure due to rapid technological improvement. This was necessary for assessing the differences in bleeding according to changes in devices used for TAVI. Even if most of the data were gathered prospectively, the recent publication of the VARC definitions required re-adjudication of some events. In order to avoid overfitting the logistic model for predicting LTB given the low number of events, we used a strict threshold of variable inclusion at 0.05. However, the rule of thumb of 10 events/variable appears to be too conservative and 5–10 events/variable provide an acceptable rate of type I error.[30] Death is one of the VARC criteria which define a bleed as LTB, which could render trivial and circular an analysis of LTB as a predictor of mortality. However, a fatal bleed generally occurs due to massive haemorrhage leading to haemodynamic instability or to localisation in a critical space (eg, intracranial, pericardium), which will already classify it as LTB. This was the case for all the patients in our study who presented with LTB (see online supplemental table 2).

Our observational findings should be considered hypothesis-generating and require further confirmation.

CONCLUSION

Bleeding after TAVI was a frequent complication, occurring in over 25% of patients, and was life-threatening in 13%. It was

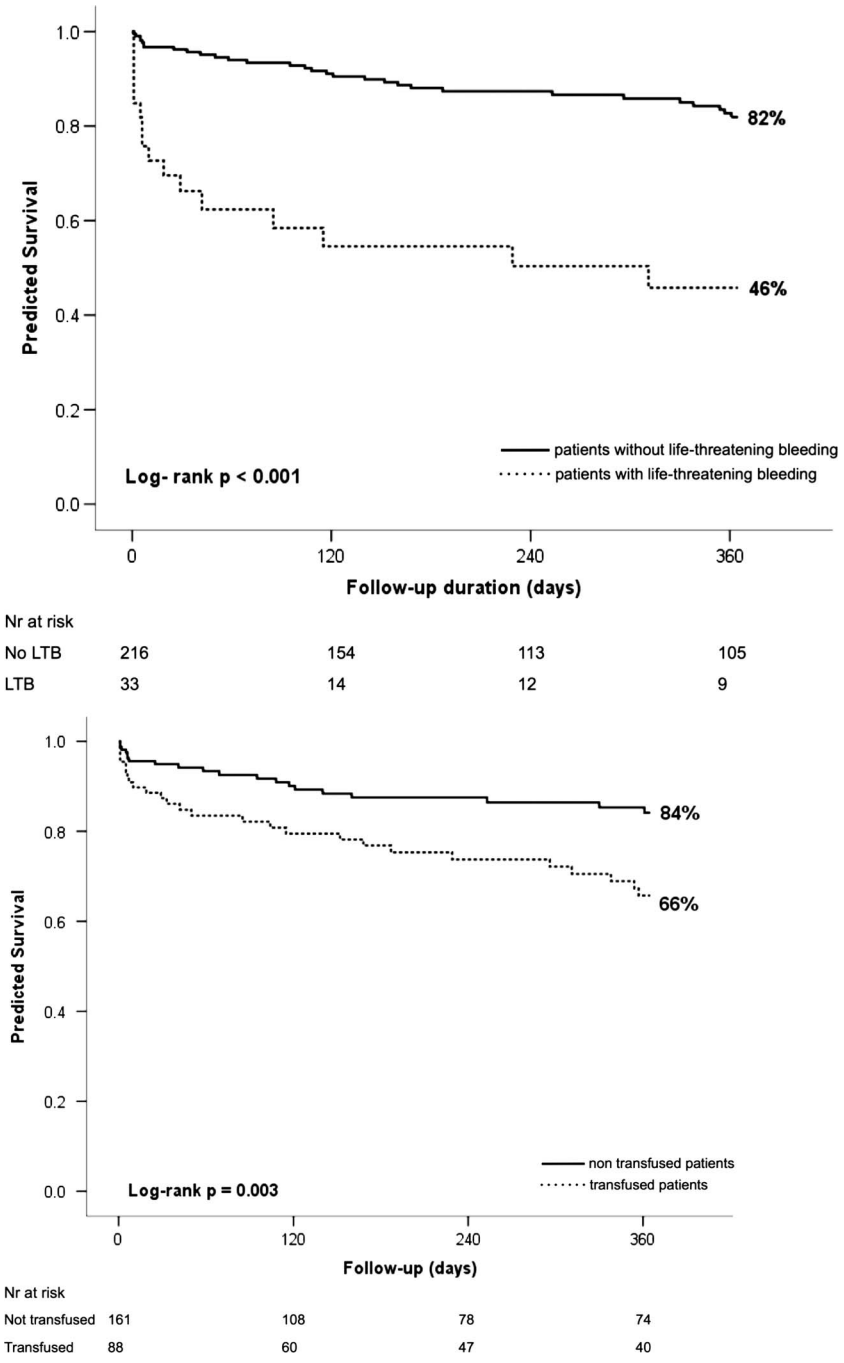

Figure 2 Survival analysis at 1 year stratified by occurrence of life-threatening bleeding (top) and occurrence of transfusion (bottom). LTB, life-threatening bleeding.

Table 2 Predictors of 1-year mortality

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
Device failure	3.3 (1.6 to 6.9)	0.001	2.78 (1.25 to 6.2)	0.013
AKI stage 3	7.78 (2.77 to 21.94)	<0.001		
Life-threatening bleeding	4.82 (2.62 to 8.87)	<0.001	2.54 (1.3 to 4.9)	0.006
Peripheral arterial disease	2.6 (1.44 to 4.7)	0.002		
Baseline anaemia	2.92 (1.48 to 5.76)	0.002	2.3 (1.16 to 4.7)	0.017
Carotid stenosis	4.2 (1.5 to 11.8)	0.007		
AR>1 after TAVI	2.21 (1.23 to 3.97)	0.008	2.18 (1.14 to 4.2)	0.018
Previous CABG	1.89 (1.005 to 3.55)	0.048		
LVEF<30% after TAVI	8.2 (4.5 to 15)	<0.001	6.67 (3.5 to 12.76)	<0.001

AKI, acute kidney injury; AR, aortic regurgitation; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation.

mostly related to access, and the TA approach was an independent predictor of LTB. LTB after TAVI was associated with increased 30-day and 1-year mortality.

Contributors BB, MG, CT and P-YL designed the study. BB, ED, MG and AC collected the data and performed the analysis. BB and ED drafted the manuscript. J-PB, AC and HE reviewed and modified the paper. All authors read and agreed with the final form of the manuscript.

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Competing interests HE and P-YL are proctors for Edwards Lifesciences; AC is a consultant for Edwards Lifesciences.

Ethics approval All patients were included in international registries approved by individual ethics committees or in the national registry approved by the institutional review board of the French Ministry of Health.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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