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PH.D. THESIS

LATE BLEEDING EVENTS IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION IN THE WORKUP PRE-TAVR

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List of Abbreviations

AF, atrial fibrillation

AS, aortic stenosis

CAD, coronary artery disease

DAPT, dual antiplatelet therapy

GI, gastrointestinal

LBE, late bleeding event

OAC, oral anticoagulant

PCI, percutaneous coronary intervention

SAPT, single antiplatelet therapy

TAVR, transcatheter aortic valve replacement

INTRODUCTION

Coronary artery disease (CAD) is a frequent finding in transcatheter aortic valve replacement (TAVR) candidates, although its prevalence has progressively decreased along with the reduction in patients' mean age and surgical risk.(1) In the TAVR field, the pre-procedural evaluation and the indications for treatment of significant CAD remain a matter of debate, due to the inconstancy of available evidence.(2) Given the expansion of TAVR indications to younger and lower-risk patients, handling CAD in this population has gained paramount importance.

CAD may impact the procedural TAVR risk and the long-term prognosis.(3) Patients affected by severe aortic stenosis (AS) and concomitant CAD constitute a complex subset with a high risk of bleeding complications due to advanced age and comorbidity burden.(4) Likewise, the need for antiplatelet and/or anticoagulation therapy (in patients with an established indication) after percutaneous coronary intervention (PCI) enhances such bleeding risk.(5)

PCI in the workup pre-TAVR has been associated with a higher occurrence of bleeding events within the first 30 days after TAVR, primarily driven by the intensive antithrombotic treatment required in this setting.(6) However, to date, the clinical impact of late bleeding (after 30 days) in this population remains unknown. Thus, the aim of the present study was to comprehensively evaluate the incidence, predictors, and clinical impact of late bleeding events (LBEs) in a real-world cohort of patients undergoing PCI during the workup pre-TAVR.

METHODS

Study population and procedure

This multicenter study included 1,457 patients from 15 centers from Canada and Europe who underwent a PCI as part of pre-TAVR work-up (defined as PCI performed within the three months prior to the TAVR procedure) and survived the periprocedural (30-day) period after TAVR. Data were collected in accordance with the ethics committee of each participating center, and all patients provided signed informed consent for the procedures.

The indication for PCI was stable CAD for the vast majority of patients, with less than 2% undergoing PCI in the context of chest pain and troponin elevation (type-1 or AS-related type-2 myocardial infarction). The management of CAD, including PCI strategy, the procedural use of functional invasive tests for myocardial ischemia and intravascular ultrasound, and duration of antiplatelet therapy were left to the discretion of each local heart team and physician responsible for the procedure. Significant CAD was assessed either by angiographic assessment (≥70% stenosis in an epicardial coronary vessel or ≥50% left main artery stenosis) or fractional flow reserve (FFR) (≤0.80). Revascularization was considered complete when all significant lesions in vessels >2 mm diameter had been successfully treated. The indications for TAVR, device type and procedural approach were assessed by each heart team based on an extensive clinical and anatomical pre-operative assessment. The transfemoral approach was the default choice, and alternative access was reserved for patients with unfavorable peripheral anatomy.

Data collection and study definitions

Baseline, procedural, and follow-up data were prospectively collected in a dedicated database. Clinical follow-up was performed in each participating center at 1, 12 months post-TAVR and yearly thereafter, either by medical visit or by telephone. The patient's vital status was updated after every medical contact, recording the date of the last contact for every patient. Records from referring cardiologists, general practitioners, and other hospitals were consulted whenever necessary for further

information. The information regarding the PCI procedure was obtained for procedural reports which were revised by an interventional cardiologist.

All adverse events were prospectively collected and adjudicated based on the Valve Academic Research Consortium-2 (VARC-2) criteria.(7) Accordingly, bleeding events were classified as life-threatening or disabling, major, or minor. Life-threatening or disabling bleeding was defined as fatal bleeding; or bleeding occurring in a critical organ (e.g., intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome); or bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery; or overt bleeding with a drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units. Major bleeding was defined as overt bleeding associated with a drop in the hemoglobin level of at least 3.0 g/dL; or bleeding requiring transfusion of two or three units of whole blood/RBC; or bleeding causing hospitalization or permanent injury or requiring surgery. Minor bleeding was defined as any bleeding worthy of clinical mention that does not qualify as life-threatening, disabling, or major events.

LBEs were defined as those occurring more than 30 days after the TAVR procedure. When a LBE was identified, bleeding source and antithrombotic treatment at the time of the event were recorded.

Statistical analysis

Qualitative variables were reported as percentages and continuous data as mean ± SD or median (interquartile range [IQR]), depending on their distribution. Continuous variables were compared using Student's t-test (2-tailed) or Mann-Whitney U rank sum tests as appropriate. Qualitative variables were compared with chi-square or Fisher exact tests. Survival curves were summarized using Kaplan-Meier estimates, and log-rank tests were used to compare groups. Cox multivariable regression analysis was performed to identify independent predictors of bleeding events and the predictors of mortality in the whole PCI-TAVR cohort. Variables with clinical interest and with $p<0.10$ on univariable analysis were entered in a multivariable analysis. The multivariable analysis

was performed using backward stepwise Cox regression. All analyses were performed using a hierarchical method to account for between-center variability. A 2- sided alpha level of 0.05 was used for all statistical testing. Data of patients were censored after the first LBE. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Baseline and procedural characteristics (for PCI and TAVR), and in-hospital outcomes of the study population are shown in **Table 1** and **Table 2**. Mean age of the patients was 81.1±7.4 years, 41.5% were women, and the mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 5.7% (IQR: 3.1% to 6.8%).

Most (94.2%) PCI procedures were staged before TAVR. The median delay between PCI and TAVR was 31 (IQR: 8 to 68) days. In TAVR procedures, transfemoral access was the approach of choice for most patients (79.0%). Balloon- and self-expanding transcatheter valves were used in 66.5% and 33.5% of cases, respectively. In-hospital bleeding occurred in 185 (12.7%) patients. At hospital discharge, 59.6% of study population received dual antiplatelet therapy (DAPT), 34.3% was on an oral anticoagulant (OAC) (monotherapy: 3.0%; in combination with antiplatelet therapy: 31.4%), and 5.5% received single antiplatelet therapy (SAPT). **Supplemental Tables 1** and **2** provide details about antithrombotic treatment at discharge (according to the occurrence of LBEs) and at time of LBE, respectively.

Incidence, Type and Factors Associated with LBE

A total of 116 (7.9%) patients experienced a LBE. The median time of occurrence was 11.1 months (IQR: 3.2 to 28.6 months) after TAVR, and the annual incidence (up to 7-year follow-up) ranged from 2.9% to 4.2% (3.47 per 100 person-years). Frequency of bleeding events according to severity are highlighted in **Figure 1**. LBEs consisted of a minor, major, and life-threatening or disabling in 21 (18.1%), 63 (54.3%), and 32 (27.6%) patients, respectively. Major and life-threatening bleeding occurred at a median of 10.2 months (IQR: 2.9 to 26.8 months) and 6.3 months (IQR: 2.7 to 24.2 months), respectively. The gastrointestinal (GI) tract (n=53, [45.7%]) was the most frequently identified source of LBE. Intracranial bleeding occurred in 19 patients (16.4%) (**Figure 2**).

LBEs occurred more frequently in patients with atrial fibrillation (AF) or flutter (38.1% vs 26.2%, p=0.007), and the occurrence of a periprocedural (within 30 days) bleeding event was also associated with a higher rate of LBEs (18.9% vs 12.7%, p=0.035). The combination of oral

anticoagulant with antiplatelet agents was more commonly prescribed at discharge in patients with a LBE (43.1% vs 30.4%, p=0.005). (**Table 1**).

The variables associated with the occurrence of LBEs are shown in **Table 3**. In the multivariable model, periprocedural major bleeding (hazard ratio [HR]: 2.00, 95% confidence interval [CI]: 1.10 to 3.62, p=0.020) and the combination of antiplatelet and anticoagulation therapy at discharge (HR: 1.72, 95%CI: 1.19 to 2.49, p=0.004) were independently associated with an increased risk of LBEs. Antithrombotic treatment at time of LBE stratified according to bleeding severity is shown in **Figure 3**. Whereas most patients with minor bleeding were on OAC, DAPT regimen was more frequent in patients with a major and life-threatening LBE. Moreover, around 20% of patients were on association therapy (SAPT or DAPT + OAC) at the time of LBE, irrespective of bleeding severity.

LBE and Clinical Outcomes

The median length of follow-up of the study population was 22 (interquartile range [IQR]: 12 to 40) months. The follow-up was complete in all, but 80 patients (5.4%) lost to follow-up. A total of 440 patients (30.2%) died during the study period. Late bleeding was associated with a mortality rate of 11.2% at the time of index hospitalization. After a median follow-up of 15 months (IQR: 1 to 34 months) following the LBE, a total of 65 patients (56%) had died. The rate of occurrence of LBEs during the study period, overall and for major and life-threatening bleeding is shown in **Figure 4**.

Long-term outcomes after TAVR stratified according to the occurrence of LBE are summarized in **Table 4**. Compared with those not having any LBE, patients experienced LBEs had significantly higher rates of death (56.0% vs 27.9%, p<0.001), cardiovascular death (11.2% vs 8.7%, p=0.001), acute coronary syndrome (16.4% vs 7.5%, p<0.001), major stroke (15.5% vs 5.2%, p<0.001), cardiovascular rehospitalization (50.9% vs 23.3%, p<0.001), and major adverse cardiovascular and cerebrovascular events (MACCE) (all-cause death, myocardial infarction, stroke) (60.0% vs 31.3%, p<0.001). The univariable and multivariable analyses of the factors associated with increased all-cause late (>30 days) mortality following TAVR are reported in **Table 5**. LBE was

identified as an independent predictor of all-cause mortality after TAVR (HR: 1.39; 95% CI: 1.05 to 1.83; p=0.020). The Kaplan-Meier curves for all-cause mortality following TAVR according to the occurrence of LBEs are shown in **Figure 5**. LBE significantly increased the risk for mortality at 4-year follow-up compared with no bleeding. **Supplementary Figure 1** reports the rate of all-cause death, cardiac and non-cardiac death, stratified according to bleeding severity. While minor and major bleeding events had no impact on mortality, life-threatening bleeding occurrence was associated with an increased mortality risk (HR: 3.25, 95%CI: 2.03 to 4.91, p<0.001).

DISCUSSION

To the best of our knowledge, the present study is the first to evaluate the incidence, predictors, and clinical impact of LBEs after TAVR in patients with significant CAD diagnosed during the pre-procedural workup. The main findings can be summarized as follows: 1) among patients undergoing PCI in the workup pre-TAVR, LBEs (>30 days) occurred in about 1 out of 10 patients after a median follow-up of 2 years; 2) GI and neurological were the most frequently identifiable sources of bleeding; 3) early (<30 days) major bleeding events and the combination of antiplatelet and anticoagulation therapy were independent predictors of LBEs; and 4) LBEs determined an increased risk of mortality and morbidity during the long-term follow-up (**Figure 6**).

Incidence and Location of LBE

During the first years of TAVR experience, efforts have been mainly focused on improving acute results, assuming that these would guarantee the best long-term outcomes. Nonetheless, besides the periprocedural frame, late-onset events, both hemorrhagic and ischemic, remain frequent and adversely affect prognosis.(8, 9) As of yet, late bleeding prevention represents an overriding and less investigated domain. Evidence on the incidence and predictors of LBE are scarce, especially in feeble TAVR subsets, such as patients affected by significant CAD. In this setting, the technical and pharmacological management of coronary revascularization could increase the TAVR-related procedural risk and impact the long-term results.

In our study, a relatively high proportion of TAVR recipients treated with PCI experienced a LBE (8%). This incidence is higher than reported in previous analyses in octogenarian TAVR cohorts (5.9% LBE at a median time of 132 days) as well as in patients with CAD undergoing PCI (6.2% at a median time of 300 days).(9, 10) The higher late bleeding risk in our cohort, suggests a complex and multifactorial interplay between AS and CAD. Patients affected by concomitant CAD represent a challenging subset of TAVR recipients. The advanced age, the high prevalence of comorbidities, and the need for a more intensive antithrombotic regimen, usually define the enhanced bleeding risk in this population.

GI bleeding was the most frequently identifiable source of late bleeding, which is in accordance with previous studies.(9, 11–13) Heyde's syndrome is a prevalent condition associated with severe AS, accountable for a significant proportion of GI bleeding in this population.(14) Thus, the interaction between a more intensive antithrombotic regimen and AS vulnerability for GI bleeding may play an important role in the observed higher risk for LBEs in our population. Appropriate screening (i.e., gastroscopy, colonoscopy), and the use of gastroprotection, should probably be considered in patients with an increased bleeding propensity.

Intracranial bleeding accounted for 16.4% of LBEs, being the second most common site of bleeding. The global incidence of intracranial bleeding was 1.3%. In previous studies including either PCI or TAVR population, the rate of late intracranial bleeding (2 years median follow-up) was 0.66% and 0.77%, respectively. (8, 15) This highlights the pronounced bleeding susceptibility of the TAVR population requiring PCI. Given the recognized harmful clinical impact of intracranial bleeding, further efforts should be made to reduce their occurrence, evaluating the risk/benefit ratio of an intended PCI, and implementing a less aggressive and shorter antithrombotic therapy.

Predictors of LBEs

Early major bleeding events (within 30 days after TAVR) and the combination of antiplatelet and anticoagulation therapy at discharge were independently associated with an increased risk of LBEs in the multivariable model.

The role of early bleeding in predicting LBE deserves special interest. Since we did not find significant differences regarding the procedural features in patients having a LBE, neither in PCI nor in TAVR procedures, it could point to intrinsic patient bleeding susceptibility.

The combination of antiplatelet therapy and anticoagulation at discharge independently predicted the occurrence of late bleeding. At the time of the bleeding event, more than 20% of patients received combined antithrombotic therapy. Of note, around one-third of patients having clinically relevant LBEs (major or life-threatening) were on DAPT, representing the most common regimen at this time point. In the PCI field, DAPT is the cornerstone of thrombotic and ischemic protection.(16)

Translating the same paradigm to TAVR poses unique challenges. Randomized studies suggested that, in TAVR patients, the empirical DAPT strategy portends an enhanced bleeding risk without clinical benefit in terms of ischemic prevention, when compared to SAPT.(17–19) Yet, the frequently encountered scenario involving patients who receive coronary stenting before TAVR lacks dedicated studies to inform clinical decision-making and warrants a case-by-case decision. Longstanding indication for anticoagulation (primarily AF) turns pharmacological management more challenging. OAC monotherapy has been associated with better clinical outcomes than combined antithrombotic therapy.(20) Based on this evidence, in TAVR patients undergoing recent PCI, current guidelines restricted the DAPT regimen from 1 up to 6 months. When OAC is indicated, triple therapy should be stopped after 1 week, followed by dual antithrombotic therapy (OAC+SAPT) from 1 up to 6 months.(21, 22) As TAVR patients frequently feature high-bleeding risk factors, a tailored antithrombotic therapy according to a careful weighing of individual bleeding and thrombotic risk should be pursued.(23) This represents an overworked focus in PCI setting, with recent evidence supporting a very short DAPT regimen (1-3 months) in patients at high bleeding risk.(24) Furthermore, P2Y12 inhibitor monotherapy after 1 to 3 month DAPT has emerged as a valuable treatment option in reducing the risk of both ischemic and bleeding events in comparison to DAPT, even in patients presenting complex coronary anatomy.(25) Given that most TAVR patients undergoing PCI have stable CAD, the tradeoff between safety/effectiveness could stretch out towards a safer approach, such as a short DAPT regimen. However, such interventions are still underused in TAVR and may stimulate future research in this field.

Unlike early bleeding, where anatomic and procedural factors prevailed, late bleeding is a multifactorial event that encompasses patients' risk profile, including frailty and comorbidities. In our analysis patients with LBE presented more frequently baseline AF.(9) Patients with AF have been shown to represent a high-risk population with increased mortality after TAVR, because of a higher occurrence of major bleeding or thromboembolic events.(26, 27) In patients with AF requiring PCI, the risk of bleeding events is enhanced by the need of associated anticoagulant and antiplatelet

therapy. Limiting the duration of antiplatelet therapy has been shown to provide a bleeding benefit in patients with recent coronary stenting.(28) In the PCI-TAVR setting, early discontinuation of antiplatelet therapy and maintaining OAC treatment alone may be considered in patients who are at increased risk of bleeding and/or at low ischemic risk. Also, the left atrial appendage occlusion could be an attractive option in patients with relative contraindications for OAC and bleeding diathesis. The ongoing WATCH-TAVR trial (NCT03173534) will shed light on the effectiveness of this approach in stroke and bleeding prevention in TAVR patients with AF.

Clinical Impact of LBE

Few studies investigated the impact of late-onset bleeding on long-term outcomes. Généreux et al reported a 4-fold increase in late mortality at 1-year follow-up in those patients with a LBE.(9) Consistently, we found that LBEs were an independent predictor of all-cause mortality after TAVR, and their occurrence resulted in a 1.5-fold higher risk for death compared with no bleeding up to a 4-year follow-up. The lower increase in LBE-related risk may be explained by the lower mean age (81years vs 84 years), and surgical risk (median STS score of 5.7% vs 11.7%) in our population. The bleeding impact reaches beyond heightened mortality, as proven by the higher rate of stroke, cardiac rehospitalization, acute coronary syndrome, and MACCE, which potentially undermines the TAVR clinical benefit.

Several randomized trials failed to show any prognostic benefit of PCI in stable CAD.(29) In TAVR, the only available evidence derives from the ACTIVATION (percutAneous Coronary inTervention prIor to transcatheter aortic VAlve implantaTION) trial. In this study, patients with significant CAD and Canadian Cardiovascular Society angina ≤2 were randomly assigned to undergo, or not, PCI before TAVR. Pre-TAVR PCI did not confer any benefit in terms of reduced rates of death and rehospitalization. However, a tendency towards an increased bleeding risk was found in the PCI group, predominantly driven by the increased use of DAPT.(6) These results reinforce the importance to better consider the indication of PCI in patients with CAD undergoing TAVR, especially on those with a higher risk of bleeding.

LBE should be considered as an indicator of the long-term prognosis and mortality of TAVR. The present study showed the detrimental impact of LBEs in the frail, high-risk subpopulation of patients undergoing PCI prior TAVR, highlighting the central role of antithrombotic therapy in enhancing such hemorrhagic risk. Even though an extreme challenge in treating this population, a better individualized and risk-adjusted antithrombotic therapy might help to prevent a proportion of LBEs. Further studies are awaited to provide a more solid evidence base regarding the safest and most effective pharmacological regimen post-TAVR in this subset.

Study Limitations

This study has some limitations. First, it was a retrospective non-prespecified analysis of data included in several prospective TAVR registries. Although the risk for mortality for LBEs was adjusted for relevant covariates, there might have been residual confounders due to unmeasured factors. In this respect, data on pharmacological gastroprotection (i.e., proton pump inhibition) were not available in our registry. Bleeding events were defined according to the former VARC-2 criteria, potentially affecting the contemporary application of the study results. However, most of the study population underwent TAVR before the VARC-3 consensus update. Therefore, we reported the bleeding severity as prospectively collected by applying the VARC-2 bleeding definition. Albeit details on bleeding complications have been prospectively collected, it is expectable an underestimation of minor bleeding due to the lack of clinical impact or need for intervention. Also, patients received different antithrombotic strategies, based on guideline recommendations that have changed during the study period. Finally, some of the variables defining a high-bleeding risk status were not collected in the database. However, our study included a very specific TAVR population whose baseline characteristics (mainly the advanced age) usually outline a high-bleeding risk in most patients.

CONCLUSIONS

In patients undergoing PCI in the workup pre-TAVR, LBEs occurred in about 8% of patients, with a rate of 3.47 per 100 person-years, higher than the incidence usually reported in octogenarian TAVR populations. The occurrence of periprocedural bleeding and combining antiplatelet and anticoagulation drugs at hospital discharge determined an increased risk, and late bleeding conferred an impaired prognosis including higher mortality and cardiac rehospitalization rates. These results should fuel further studies on potential preventive strategies of LBEs following TAVR. Likewise, a tailored pharmacological approach (such as a less invasive antithrombotic therapy and routine use of PPI in patients with high bleeding tendency) should be strengthened to reduce LBEs and improve TAVR outcomes.

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Figure Legends

Figure 1. Incidence and Type of LBEs following TAVR.
Cumulative incidence and severity of LBEs.
LBEs= late bleeding events.

Figure 2. Frequency and Location of LBEs.
Among 116 patients with bleeding and specified source, gastrointestinal bleeding was the most predominant cause of LBEs after TAVR.
LBEs= late bleeding events.

Figure 3. Antithrombotic therapy at time of LBEs stratified according to bleeding severity.
Antithrombotic treatment at time of LBE stratified according to bleeding severity.
DAPT= dual antiplatelet therapy; OAC= oral anticoagulant; SAPT= single antiplatelet therapy.

Figure 4. Incidence rate of LBEs during the follow-up.
Cumulative incidence of overall, major, and life-threatening bleeding over 4 years of follow-up.

Figure 5. Kaplan-Meier curves for all-cause mortality according to the occurrence of LBEs.
Kaplan-Meier estimate demonstrate higher rates of all-cause mortality according to the occurrence of late bleeding event (red line) compared to no late bleeding events (blue line) over 4 years of follow-up.

Figure 6. Late Bleeding Events after TAVR: Frequency, Predictors, and Outcomes.
Annual incidence of LBEs in the first 4 years after the TAVR procedure (top). Predictors of LBEs (middle). Bleeding location of LBEs (bottom, left), and Kaplan-Meier curve for all-cause mortality up to 4 years following LBEs (bottom, right).
CAD= coronary artery disease; HR= hazard ratio; LBEs= late bleeding events; PCI= percutaneous coronary intervention; TAVR= transcatheter aortic valve replacement.

Tables

Table 1. Baseline, Procedural Characteristics, and In-Hospital Outcomes According to the Occurrence of LBEs.

	Overall (N=1,457)	LBEs (n=116)	No LBEs (n=1,341)	p Value
Baseline characteristics				
Age, yrs	81.1±7.4	80.7±6.9	81.1±7.4	0.515
Female	605 (41.5)	45 (38.8)	560 (41.8)	0.534
BMI, kg/m^2	27.3±5.1	27.6±4.8	27.2±5.1	0.465
Dyslipidemia	983 (71.4)	82 (71.9)	901 (71.3)	0.904
Hypertension	1222 (83.9)	98 (84.5)	1124 (83.8)	0.852
Diabetes Mellitus	535 (36.7)	43 (37.1)	492 (36.7)	0.935
History of smoking	134 (9.8)	13 (11.4)	121 (9.7)	0.548
Coronary artery disease	1190 (76.9)	93 (80.2)	1034 (77.1)	0.449
Previous MI	339 (23.3)	34 (29.3)	305 (22.8)	0.112
Previous PCI	995 (68.4)	77 (66.4)	918 (68.6)	0.620
Previous CABG	204 (14.0)	17 (14.7)	187 (13.9)	0.842
Peripheral artery disease	344 (23.6)	30 (25.9)	314 (23.5)	0.776
COPD	299 (20.6)	26 (22.4)	273 (20.4)	0.607
Atrial fibrillation or flutter	381 (27.1)	43 (38.1)	338 (26.2)	**0.007**
Chronic renal disease (eGFR (<60 mL/min)	844 (57.9)	69 (59.5)	775 (57.8)	0.724
NYHA class III/IV	1014 (69.6)	78 (67.2)	936 (69.8)	0.566
Previous pacemaker	171 (11.8)	11 (9.5)	160 (11.9)	0.427
STS-PROM	5.7±4.5	6.1±5.4	5.7±4.4	0.517
Echocardiography findings				
LVEF, %	54.2±13.2	53.5±14.6	54.2±12.7	0.592
Mean aortic gradient, mmHg	44.2±14.7	43.1±12.0	44.3±14.9	0.320
Aortic valve area, cm^2	0.69±0.21	0.70±0.17	0.69±0.21	0.516
MR>2	3 (0.2)	1 (0.9)	2 (0.2)	0.221
Procedural characteristics				
Primary access				
Transfemoral	1149 (78.9)	85 (73.3)	1064 (79.3)	0.125
Non-transfemoral	308 (21.1)	31 (26.7)	277 (20.7)	
Valve type				
Balloon-expandable	969 (66.5)	78 (67.2)	891 (66.4)	0.862
Self-expandable	488 (33.5)	38 (32.8)	450 (33.6)	
Valve-in-valve	64 (4.4)	3 (2.6)	61 (4.6)	0.322
Echocardiography post-procedure				
LVEF, %	55.7±1.6	55.2±11.9	55.8±11.5	0.650

Mean aortic gradient, mmHg	10.3±5.1	10.4±4.6	10.3±5.1	0.886
AR>2	121 (8.4)	10 (8.7)	111 (8.4)	0.912
30-day complications				
Bleeding	185 (12.7)	22 (18.9)	1963 (12.2)	**0.035**
Life-threatening bleeding	43 (2.9)	5 (4.3)	38 (2.8)	0.383
Major bleeding	81 (5.6)	12 (10.3)	69 (5.2)	**0.019**
Minor bleeding	62 (4.3)	5 (4.3)	57 (4.3)	0.999
Major vascular complication	113 (7.8)	11 (9.6)	102 (7.6)	0.451
Stroke	43 (2.9)	3 (2.6)	40 (2.9)	0.820
Acute kidney injury	126 (8.3)	15 (13.0)	111 (8.3)	0.081
Myocardial infarction	1 (0.1)	0 (0)	1 (0.1)	0.999
Antithrombotic treatment at discharge				
None	2 (0.1)	0 (0)	2 (0.2)	0.999
Single antiplatelet therapy	80 (5.5)	4 (3.5)	76 (5.7)	0.314
Dual antiplatelet therapy	869 (59.6)	61 (52.6)	808 (60.3)	0.106
Anticoagulation therapy	44 (3.0)	1 (0.9)	43 (3.2)	0.252
Antiplatelet + Anticoagulation	458 (31.4)	50 (43.1)	408 (30.4)	**0.005**

Values are mean±SD, n (%), or median (interquartile range).

AR= aortic regurgitation; BMI= body mass index; CABG= coronary artery bypass grafting; COPD= chronic obstructive pulmonary disease; eGFR= estimated glomerular filtration rate; LBEs= late bleeding events; LVEF= left ventricular ejection fraction; MI= myocardial infarction; MR= mitral regurgitation; PCI= percutaneous coronary intervention; STS-PROM= Society of Thoracic Surgeons Predicted Risk of Mortality.

Table 2. Angiographic Characteristics of Coronary Angiogram and PCI Performed Before TAVR According to the Occurrence of LBEs

	Overall (N=1,457)	LBEs (n=116)	No LBEs (n=1,341)	p Value
Vessel disease				
1	717 (49.2)	63 (54.3)	654 (48.8)	
2	460 (31.6)	33 (28.5)	427 (31.8)	0.519
3	280 (19.2)	20 (17.2)	260 (19.4)	
SYNTAX score	12.0±9.0	10.9±8.9	12.1±9.1	0.289
Number of vessels treated				
1	1020 (70.0)	88 (75.9)	932 (69.5)	
2	355 (24.4)	22 (19.9)	333 (24.8)	0.338
3	82 (5.6)	6 (5.2)	76 (5.7)	
PCI distribution				
LM	156 (10.7)	11 (9.5)	145 (10.8)	
LAD	579 (39.7)	35 (10.2)	544 (40.6)	
LCx	267 (18.3)	28 (24.1)	239 (17.8)	0.282
RCA	412 (28.3)	38 (32.8)	374 (27.9)	
SVG	32 (2.2)	3 (2.6)	29 (2.2)	
LIMA	6 (0.4)	1 (0.9)	5 (0.4)	
Number of lesions treated	1.5±0.8	1.4±0.7	1.5±0.8	0.197
Complete revascularization	1094 (75.1)	80 (68.9)	1014 (75.6)	0.112
Residual SYNTAX score	2.5±5.4	2.8±6.2	2.5±5.3	0.706
PCI timing				
Before TAVR	1373 (94.2)	111 (95.7)	1262 (94.1)	0.484
Concomitant to TAVR	84 (5.8)	5 (4.3)	79 (5.9)	
Peri-procedural complications				
Major/Life-threatening bleeding	49 (3.4)	6 (5.2)	43 (3.2)	0.276
Stroke	3 (0.2)	0 (0)	3 (0.2)	0.999
Heart failure	43 (3.1)	4 (3.5)	39 93.1)	0.809
Acute kidney injury	61 (4.2)	5 (4.3)	56 (4.2)	0.812

Values are mean±SD, n (%), or median (interquartile range).

LAD= left anterior descending artery; LBEs= late bleeding events; LCx= left circumflex artery; LIMA= left internal mammary artery; LM= left main artery; RCA= right coronary artery; SVG= saphenous vein graft; PCI= percutaneous coronary intervention; SYNTAX= SYNergy between PCI with TAXUS and Cardiac Surgery.

Table 3. Factors associated with LBEs after TAVR

	Univariable model		Multivariable model	
	HR (95%CI)	**p value**	**HR (95%CI)**	**p value**
Periprocedural major bleeding	2.03 (1.09-3.79)	0.026	2.00 (1.10-3.62)	0.020
Antiplatelet + Anticoagulation therapy at discharge	1.74 (1.20-2.51)	0.003	1.72 (1.19-2.49)	0.004

CI= confidence interval; HR= Hazard Ratio; LBEs= late bleeding events.

Table 4. Long-Term Outcomes of the Study Population according to the presence of LBEs.

	Overall (N=1,457)	LBEs (n=116)	No LBEs (n=1,341)	p Value
Death	440 (30.2)	65 (56.0)	375 (27.9)	<0.001
Cardiovascular death	130 (8.9)	13 (11.2)	117 (8.7)	0.01
Acute coronary syndrome	120 (8.2)	19 (16.4)	101 (7.5)	<0.001
STEMI	16 (13.3)	0 (0)	16 (15.8)	
NSTEMI	76 (63.3)	15 (78.9)	61 (60.4)	0.148
Unstable angina	28 (23.3)	4 (21.1)	24 (23.8)	
Stable angina	17 (1.2)	3 (2.6)	14 (1.0)	0.148
Coronary revascularization	59 (4.1)	8 (6.9)	51 (3.8)	0.134
Stroke	88 (6.0)	18 (15.5)	70 (5.2)	<0.001
Rehospitalization for cardiac causes	371 (25.5)	59 (50.9)	312 (23.3)	<0.001
MACCE	486 (33.5)	69 (60.0)	417 (31.3)	<0.001

Values are n (%). *Median follow-up of 23 (interquartile range: 12 to 40) months post–transcatheter aortic valve replacement. ** MACCE was defined as a composite of all-cause death, myocardial infarction, and stroke.

MACCE= major adverse cardiovascular or cerebrovascular event; NSTEMI= non–ST-segment elevation myocardial infarction; STEMI= ST-segment elevation myocardial infarction.

Table 5. Independent predictors of all cause death after TAVR

	Univariable model		Multivariable model	
	HR (95%CI)	**p value**	**HR (95%CI)**	**p value**
Age, yrs*	1.0 (1.02-1.04)	<0.001	1.03 (1.02-1.05)	<0.001
Diabetes mellitus	1.31 (1.08-1.59)	0.006	1.47 (1.20-1.79)	<0.001
COPD	1.61 (1.31-1.98)	<0.001	1.64 (1.32-2.05)	<0.001
Previous PAD	1.02 (1.01-1.04)	0.032	-	-
Atrial fibrillation	1.47 (1.21-1.79)	<0.001	1.36 (1.10-1.67)	0.004
Chronic renal disease	1.31 (1.08-1.59)	0.006	-	-
NYHA class III/IV	1.29 (1.05-1.59)	0.014	-	-
Previous pacemaker	1.35 (1.07-1.71)	0.012	-	-
Bleeding at 30 days	1.50 (1.17-1.92)	<0.001	-	-
Stroke at 30 days	1.77 (1.03-3.05)	0.038	-	-
Non transfemoral access	1.24 (1.01 1.53)	0.047	1.31 (1.05-1.64)	0.016
Major vascular complications at 30 days	1.38 (1.03-1.85)	0.031	-	-
Acute kidney injury	1.48 (1.12-1.96)	0.005	-	-
Late bleeding	1.49 (1.14-1.94)	0.003	1.39 (1.05-1.83)	0.020
Late Stroke	2.03 (1.52-2.72)	0.001	1.85 (1.28-2.68)	0.001
Late MI	0.90 (0.68-1.19)	0.444	-	-

*For each increase of 1 year.
Variables included in the analysis: age, diabetes mellitus, COPD, PAD, atrial fibrillation, chronic renal disease, NYHA class III/IV, previous pacemaker, early bleeding, early stroke, non-transfemoral access, major vascular complications, acute kidney injury, late bleeding events, late stroke, MI.
CI= confidence interval; HR= Hazard Ratio. Abbreviations as in Table 1.

Figure 1

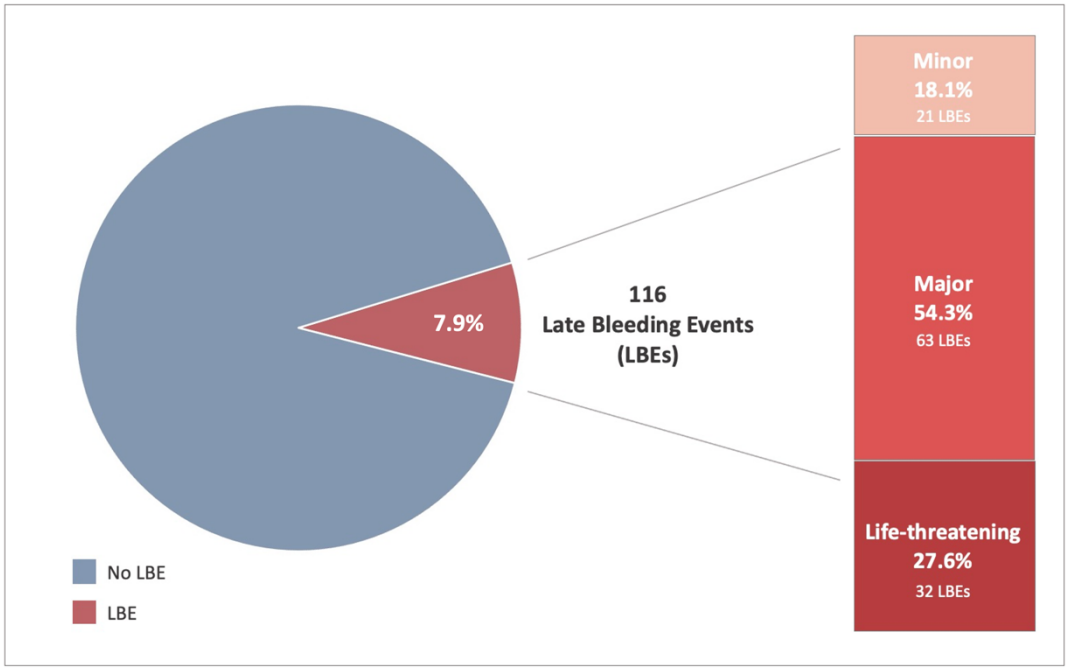

Minor
18.1%
21 LBEs
Major
54.3%
63 LBEs
Life-threatening
27.6%
32 LBEs
116
Late Bleeding Events
(LBEs)
7.9%
No LBE
LBE

Figure 2

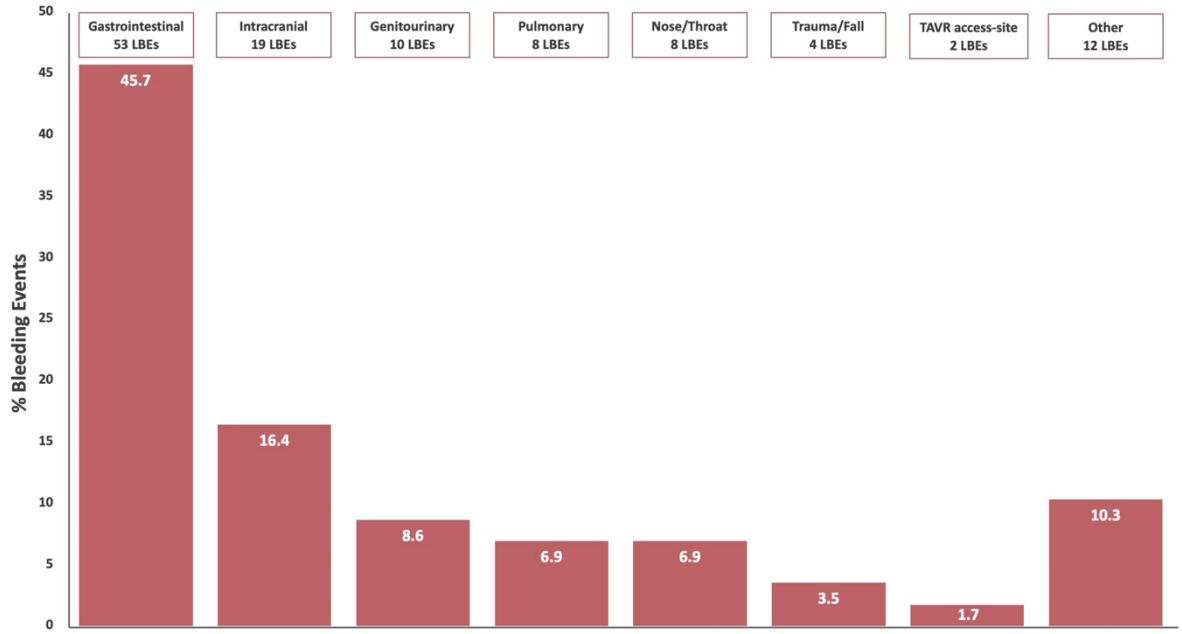

% Bleeding Events
50
45
40
35
30
25
20
15
10
5
0
Gastrointestinal
53 LBEs
45.7
Intracranial
19 LBEs
16.4
Genitourinary
10 LBEs
8.6
Pulmonary
8 LBEs
6.9
Nose/Throat
8 LBEs
6.9
Trauma/Fall
4 LBEs
3.5
TAVR access-site
2 LBEs
1.7
Other
12 LBEs
10.3

Figure 3

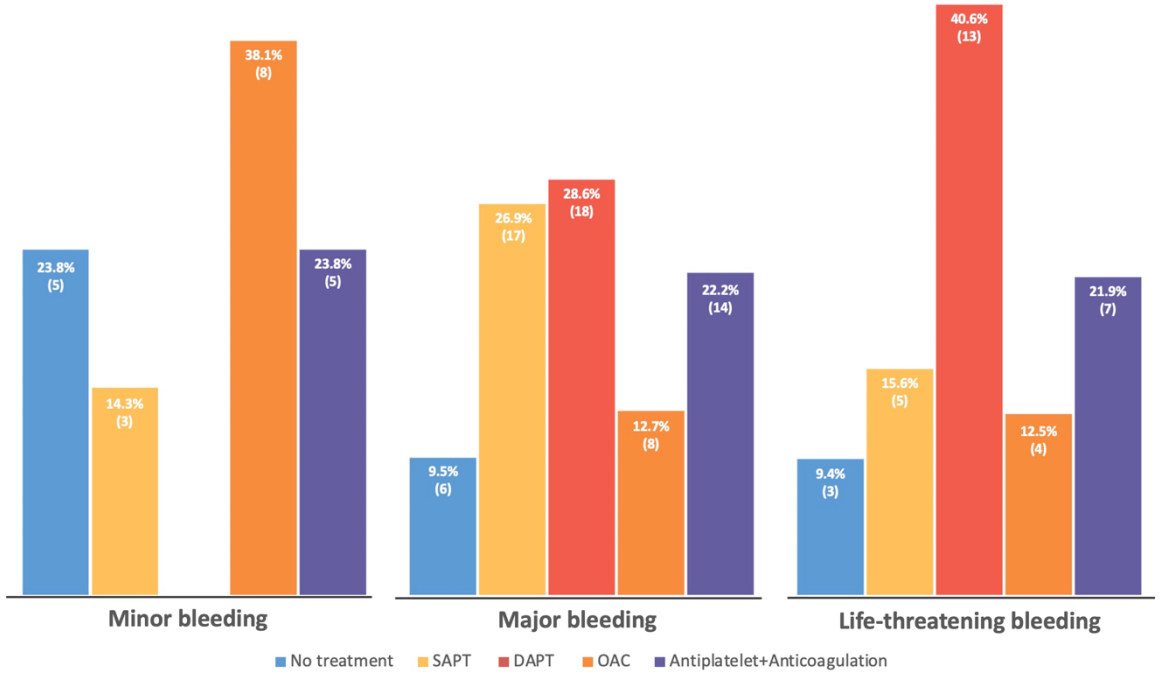

23.8% (5)
14.3% (3)
38.1% (8)
23.8% (5)
9.5% (6)
26.9% (17)
28.6% (18)
12.7% (8)
22.2% (14)
9.4% (3)
15.6% (5)
40.6% (13)
12.5% (4)
21.9% (7)
Minor bleeding
Major bleeding
Life-threatening bleeding
No treatment
SAPT
DAPT
OAC
Antiplatelet+Anticoagulation

Figure 4

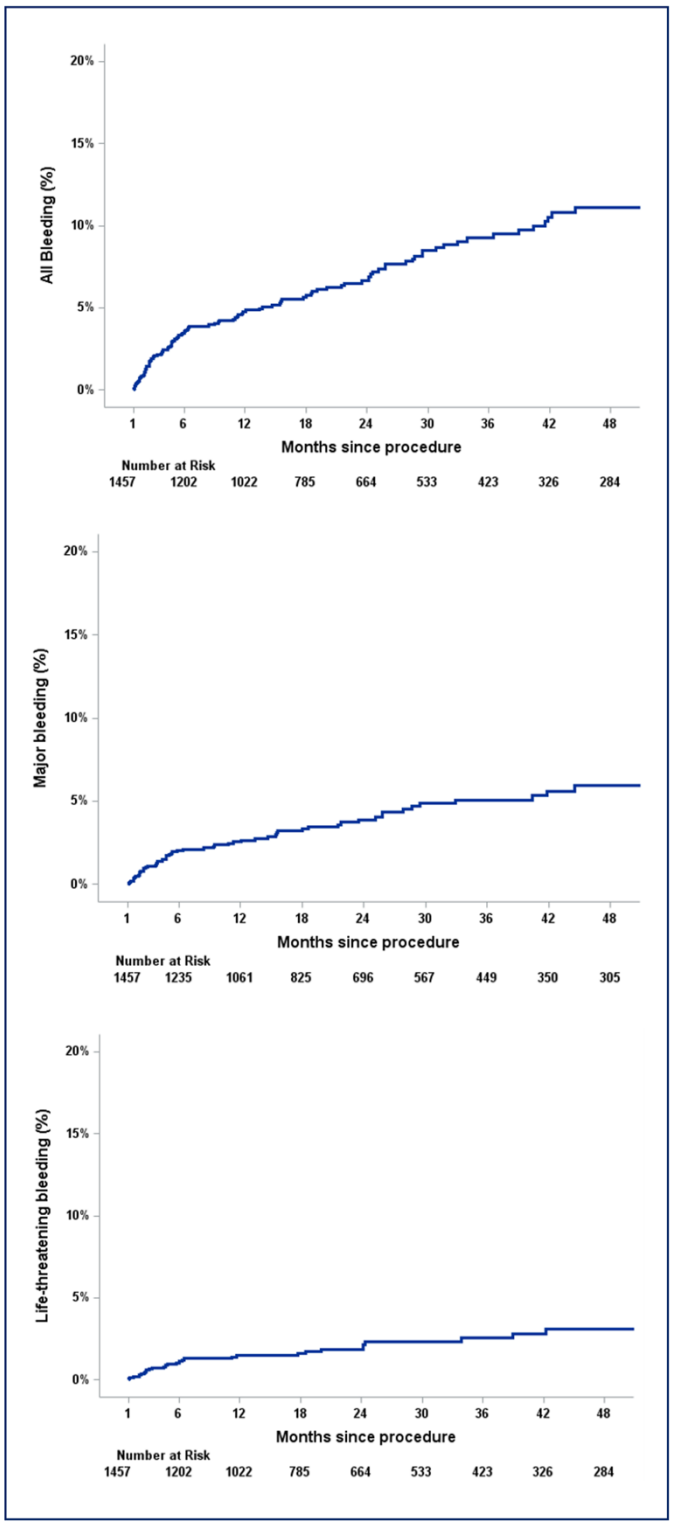

All Bleeding (%)
20%
15%
10%
5%
0%
1 6 12 18 24 30 36 42 48
Months since procedure
Number at Risk
1457 1202 1022 785 664 533 423 326 284
Major bleeding (%)
20%
15%
10%
5%
0%
1 6 12 18 24 30 36 42 48
Months since procedure
Number at Risk
1457 1235 1061 825 696 567 449 350 305
Life-threatening bleeding (%)
20%
15%
10%
5%
0%
1 6 12 18 24 30 36 42 48
Months since procedure
Number at Risk
1457 1202 1022 785 664 533 423 326 284

Figure 5

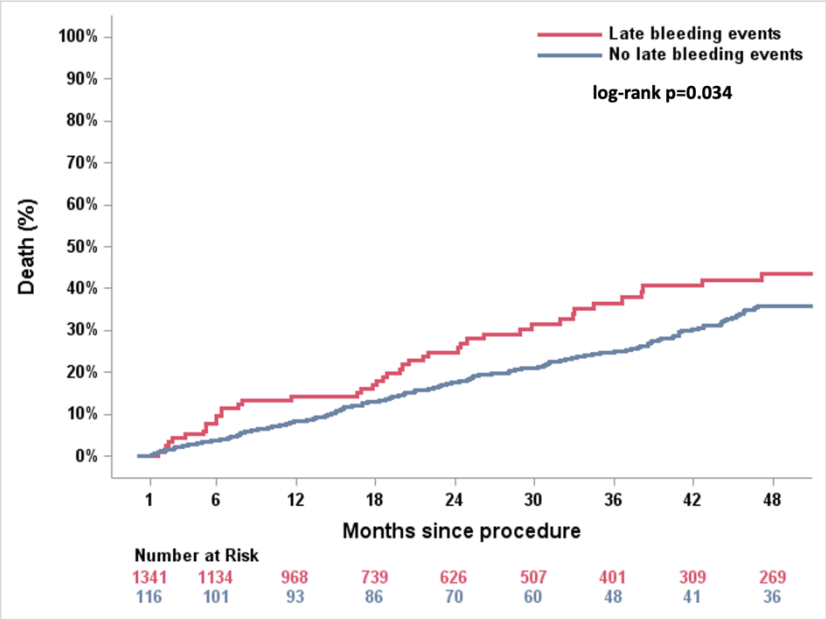
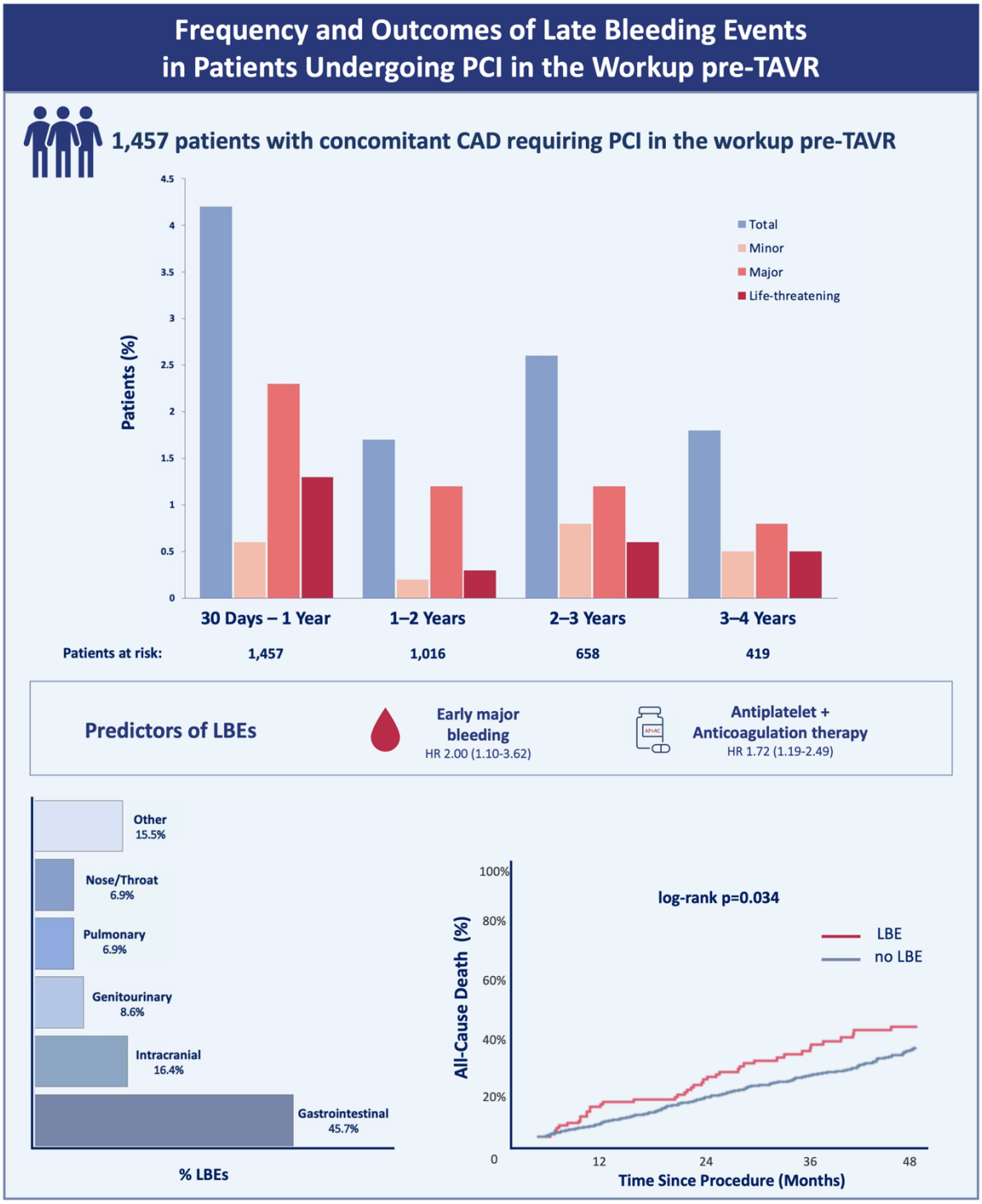

Late bleeding events
No late bleeding events
log-rank p=0.034
Death (%)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
1
6
12
18
24
30
36
42
48
Months since procedure
Number at Risk
1341 1134 968 739 626 507 401 309 269
116 101 93 86 70 60 48 41 36

Figure 6


Frequency and Outcomes of Late Bleeding Events in Patients Undergoing PCI in the Workup pre-TAVR
1,457 patients with concomitant CAD requiring PCI in the workup pre-TAVR
Patients (%)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Total
Minor
Major
Life-threatening
30 Days – 1 Year
1–2 Years
2–3 Years
3–4 Years
Patients at risk:
1,457
1,016
658
419
Predictors of LBEs
Early major bleeding
HR 2.00 (1.10-3.62)
Antiplatelet + Anticoagulation therapy
HR 1.72 (1.19-2.49)
Other 15.5%
Nose/Throat 6.9%
Pulmonary 6.9%
Genitourinary 8.6%
Intracranial 16.4%
Gastrointestinal 45.7%
% LBEs
log-rank p=0.034
LBE
no LBE
All-Cause Death (%)
100%
80%
60%
40%
20%
0
12
24
36
48
Time Since Procedure (Months)

Supplementary Table 1. Antithrombotic treatment at discharge according to the occurrence of LBEs.

		Overall (n=1,457)	LBEs (n=116)	No LBEs (n=1,341)	p value
SAPT	**ASA**	63 (4.3)	3 (2.6)	60 (4.5)	0.338
	Clopidogrel	13 (0.9)	1 (0.9)	12 (0.9)	0.971
	Other	4 (0.3)	0 (0)	4 (0.3)	0.555
DAPT	**ASA + Clopidogrel**	846 (58.1)	58 (50.0)	788 (58.8)	0.081
	ASA + Ticagrelor/Prasugrel	25 (1.7)	3 (2.6)	22 (1.6)	0.448
Anticoagulation	**VKA**	10 (0.7)	1 (0.9)	9 (0.7)	0.763
	NOACs	34 (2.3)	0 (0)	34 (2.5)	0.105
Anticoagulation + SAPT	**VKA + SAPT**	119 (8.2)	19 (16.4)	100 (7.5)	<0.001
	DOACs + SAPT	113 (7.8)	11 (9.5)	102 (7.6)	0.469
Triple therapy	**VKA + DAPT**	133 (9.1)	12 (10.3)	121 (9.0)	0.635
	DOACs + DAPT	93 (6.4)	8 (6.9)	85 (6.3)	0.814

ASA= acid acetylsalicylic; DAPT= dual antiplatelet therapy; DOACs= direct oral anticoagulant; SAPT= single antiplatelet therapy; VKA= vitamin K antagonist.

Supplementary Table 2. Antithrombotic treatment at time of bleeding events.

		LBEs (n=116)
No treatment	**-**	14 (12.1)
SAPT	**ASA**	21 (18.1)
	Clopidogrel	4 (3.4)
	Other	0 (0)
DAPT	**ASA + Clopidogrel**	28 (24.1)
	ASA + Ticagrelor/Prasugrel	3 (2.6)
Anticoagulation	**VKA**	9 (7.8)
	DOACs	11 (9.5)
Anticoagulation + SAPT	**VKA + SAPT**	13 (11.2)
	DOACs + SAPT	12 (10.3)
Triple therapy	**Anticoagulation + DAPT**	1 (0.9)

ASA= acid acetylsalicylic; DAPT= dual antiplatelet therapy; DOACs= direct oral anticoagulant; SAPT= single antiplatelet therapy; VKA= vitamin K antagonist.

Supplemental Figure 1