

FREQUENCY, TIMING, AND IMPACT OF ACCESS-SITE AND NON-ACCESS SITE BLEEDING ON MORTALITY AMONG PATIENTS UNDERGOING TRANSCATHETER AORTIC VALVE REPLACEMENT

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ABSTRACT

Background. Bleeding is frequent and associated with impaired prognosis among patients undergoing transcatheter aortic valve replacement (TAVR). It is currently unknown whether the site of bleeding differentially influences the outcome of TAVR patients.

Objective. To examine the frequency, timing, and association of access and non-access site bleeding with mortality in the setting of TAVR during long-term follow-up.

Methods. We evaluated 926 consecutive patients undergoing TAVR from 2007 through 2014. Bleeding was assessed according to the Valve Academic Research Consortium (VARC-2) criteria. The primary outcome of interest was all-cause mortality up to 5 years of follow-up.

Results. A total of 285 (30.7%) patients experienced at least one (minor, major or life-threatening) bleeding event up to 5 years. Compared with patients not experiencing bleeding, the adjusted risk of all-cause mortality was significantly increased among patients with access site (hazard ratio, HR, 1.34, 95% confidence intervals, CI, 1.01-1.76, $p=0.04$) as well as non-access site bleeding (HR 2.08, 95%CI 1.60-2.71, $p<0.001$). However, non-access site bleeding conferred a significantly higher risk of mortality compared with access-site bleeding (HR 1.56, 95%CI 1.12-2.18, $p=0.009$). At multivariable analysis, female gender was a significant correlate of access site bleeding, whereas chronic kidney disease and the STS score were significantly associated with non-access site bleeding.

Conclusions. Among patients with severe aortic stenosis undergoing TAVR, access site and non-access site bleeding were independently associated with an increased risk of mortality, with the greatest risk related to non-access site bleeding during long-term follow-up.

Keywords: aortic stenosis; TAVR; bleeding; access site bleeding; non-access site bleeding.

Clinical Perspectives

What's known? Although transcatheter aortic valve replacement (TAVR) has been consistently associated with lower rates of bleeding events than conventional surgery, the differential prognostic impact of access site and non-access site bleeding in TAVR setting is unknown.

What's new? In this study, bleeding occurring at the access site as well as non-access site bleeding increased both the risk of mortality up to 5-year follow-up. However, non-access site bleeding conferred a greater prognostic impact than bleeding related to the access site. Female gender was associated with access site-related events, while the STS score and chronic renal failure were associated with non-access site bleeding.

What's next? Future studies should specifically investigate novel strategies to prevent both forms of bleeding and focus on the identification of clinical subsets at higher risk of bleeding.

Condensed Abstract

Few data are available on the prognostic impact of access site and non-access site bleeding in patients with aortic stenosis undergoing transcatheter aortic valve replacement (TAVR). We evaluated 926 patients who underwent TAVR between 2007 and 2014. During 5-year follow-up, a total of 285 (30.7%) patients presented at least one bleeding episode. Bleeding events related to the access site as well as those not related to the access site increased both the risk of subsequent mortality. However, non-access site bleeding was associated with a 56% relative increase in the risk of mortality compared with access site events.

78 Transcatheter aortic valve replacement (TAVR) is the treatment of choice for patients with
79 symptomatic, severe aortic stenosis deemed inoperable or at high-to-intermediate risk for
80 conventional, surgical aortic valve replacement (SAVR).(1,2) Due to its less invasive nature, TAVR
81 affords a substantial reduction in the risk of bleeding compared with SAVR, resulting in a 50-60%
82 relative risk reduction of major bleeding in systematic reviews of randomized trials.(3,4) Despite
83 this, clinically-relevant bleeding still occurs in approximately every fourth patient undergoing
84 TAVR and confers an impaired prognosis by increasing the risk of morbidity and mortality.(5,6)
85 However, significant heterogeneity exists as it relates to the origin of bleeding in the setting of
86 TAVR. Indeed, hemorrhagic events can arise from either the site of vascular access and its
87 neighboring tissues (access site bleeding) or from locations remote to the vascular access (non-
88 access site bleeding). These two entities entail distinct temporal patterns as access site bleeding
89 is confined to the peri-procedural period, while non-access site bleeding may additionally develop
90 during longer term follow-up. As of yet, it remains unknown whether the site of bleeding
91 differentially influences the prognosis of patients undergoing TAVR. Therefore, the aim of the
92 present study was to comprehensively evaluate the frequency, timing, and association of access
93 and non-access site bleeding with long-term mortality among patients undergoing TAVR in a large
94 prospective registry.

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Methods

96 Study population and procedure

97 The Bern TAVR Registry is part of the Swiss TAVR Registry (NCT01368250) and prospectively
98 collects clinical and procedural data of all consecutive patients undergoing TAVR at Bern
99 University Hospital (Bern, Switzerland). The registry was approved by the local ethics committee
100 and patients provided written informed consent to participate. The study complies with the
101 declaration of Helsinki.

102 The decision to perform TAVR was based on the evaluation of the Heart Team. Patients in the
103 TAVR cohort received either the Medtronic CoreValve bioprosthesis (Medtronic, Minneapolis,
104 MN, USA), the Edwards Sapien XT or Sapien 3 transcatheter heart valve (Edwards LifeSciences,
105 Irvine, CA, USA), the Symetis Acurate TA aortic bioprosthesis (Symetis, Ecublens, Switzerland), the
106 Portico valve (St. Jude Medical, Minneapolis, MN, USA), or the Lotus heart valve (Boston Scientific,
107 Natick, MA, USA) through the femoral, transapical, or subclavian access, as previously
108 described.⁽⁷⁾ Post-procedural care consisted of heart rhythm monitoring for at least 48 hours
109 after intervention, laboratory tests and 12-lead electrocardiogram on daily basis, and
110 echocardiography before discharge.

111

112 Data collection and study definitions

113 In-hospital complications were closely monitored until discharge. Active follow-up was scheduled
114 at 30 days, 12 months and yearly thereafter at clinic visits and through standardized telephone
115 interviews. Patients were questioned about their health status, symptoms, medication and the
116 occurrence of adverse events. A dedicated, independent clinical event committee, involving

cardiologists and cardiac surgeons, evaluated and adjudicated all adverse events including bleeding events, according to the Valve Academic Research Consortium (VARC-2) criteria (SwissTAVI CEC).(8) Accordingly, bleeding events were classified as life-threatening or disabling bleeding, major bleeding, or minor bleeding.

Access site bleeding was defined as any bleeding related to access site or access-related vascular injury and hence included bleeding events originating from the puncture site as well as those arising from adjacent areas. All other events not fulfilling the criteria for access site bleeding were classified as non-access site bleeding. In case of multiple bleeding events (>1 episode), the first occurring bleeding event contributed to the analyses. The site of bleeding was independently adjudicated by 2 investigators (RP and AF), and, in case of disagreement, consensus was resolved by a third investigator (SS). All data were entered into a dedicated web-based database managed and monitored by the Clinical Trials Unit Bern (University of Bern, Switzerland).

Statistical analysis

Continuous variables are expressed as mean±standard deviation or median with interquartile range (IQR). Categorical variables are reported as counts and percentages. To test the association between baseline variables and the time to the occurrence of bleeding, we used a uni- and multivariable parametric Weibull survival models.

The association between access and non-access site bleeding and mortality was examined using parametric Weibull survival models in which bleeding was considered as a time-varying covariate. The time in days between the index TAVR procedure and the first bleeding event triggered the status change from the non-bleeding to the bleeding group. Risk estimates are expressed as

hazard ratios (HRs) and 95% confidence intervals (CIs). Furthermore, the adjusted risk of death associated with no bleeding, access, and non-access site bleeding was calculated by including covariates with a univariable effect on all-cause mortality at level of significance less than 0.20 (gender, diabetes, and Society of Thoracic Surgeons [STS] score). A subgroup analysis was conducted to evaluate the association between bleeding and mortality among patients who underwent transfemoral or transapical TAVR. Kaplan-Meier time-to-event curves (with the horizontal axis representing the time since either the index TAVR procedure or bleeding) were constructed to show the rate of mortality up to 5 years across the three study groups. Weibull survival models were finally used to examine the correlates of access and non-access site bleeding up to 5 years follow-up in the overall cohort. Variables whose p-values were less than 0.05 in univariable models were retained in the multivariable model. Statistical significance was determined by a 2-sided $p < 0.05$. All analyses were performed with Stata statistical software (version 14.1; StataCorp LP, College Station, TX).

Results

From August 2007 through June 2014, 926 consecutive patients with severe AS underwent TAVR. Baseline and procedural characteristics of the study population are summarized in **Table 1** and **2**. In the overall cohort, the mean age was 82.4 ± 5.8 years and 491 patients (53%) were women. The baseline standard predictor of risk was $6.6 \pm 4.4\%$ according to the STS score. Most patients underwent transfemoral TAVR (746 patients or 80.6%) and there was a similar implantation rate of self-expandable and balloon-expandable valve devices. Median follow-up was 2.75 years (IQR [1.17-4.40]).

Frequency, Time Course, and Mortality associated with Bleeding Events

As reported in **Table 3**, a total of 285 (30.7%) patients experienced at least one bleeding event up to 5 years, with a similar proportion between access site (145 patients or 51%) and non-access site bleeding (140 patients or 49%). Life threatening or major bleeding was observed in 224 (24.2%) patients, representing thus 78.6% of all bleeding events (122 or 84% of access site and 102 or 73% of non-access site bleeding events). As shown in **Figure 1**, the adjusted risk of mortality was significantly increased among patients who had life threatening (HR 2.30, 95%CI 1.71-3.08, $p < 0.001$) or major bleeding (HR 1.36, 95%CI 1.02-1.81, $p = 0.034$) compared those who did not experience a bleeding event.

The incidence of access and non-access site bleeding during follow-up is shown in **Figure 2**. Approximately 80% of all bleeding events occurred within the first 30 days after TAVR. However, while all access site bleeding events arose within the first 30 days after the index TAVR, late bleeding (>30 days) accounted for 40% of non-access site bleeding. The gastrointestinal tract was

the most frequent identifiable site of non-access site bleeding. In 53 patients (5.7%), more than 1 bleeding event was observed.

Clinical and Procedural Characteristics

In univariable analyses (**Table 1**), we found higher risk of bleeding in older patients, those with a lower body mass index, anemic patients, and those with chronic renal failure. As reported in **Table 2**, bleeding was associated with different prescription of antithrombotic therapy at discharge. **Table 4** describes antithrombotic therapy throughout follow-up. There was an increasing proportion of patients treated with either single antiplatelet therapy or oral anticoagulant starting from 1-year, while dual antiplatelet therapy and the combination of oral anticoagulant with single or dual antiplatelet therapy were less commonly prescribed during long-term follow-up.

Impact of Type of Bleeding on Mortality in the Overall Cohort

As shown in **Figure 3**, the rate of all-cause mortality up to 5 years follow-up associated with no bleeding, access site, and non-access site life-threatening or major bleeding amounted to 49%, 58.7%, and 72.6%, respectively.

Crude and adjusted analyses on mortality provided consistent results (**Figure 4 and 5**). As shown in **Figure 4**, the risk of mortality up to 5 years of follow-up was significantly increased in patients experiencing access site (adjusted HR 1.34, 95%CI 1.01-1.76, $p=0.04$) or non-access site bleeding (adjusted HR 2.08, 95%CI 1.60-2.71, $p<0.001$) compared with those not having any bleeding. However, non-access site bleeding conferred a significantly higher risk of mortality compared with access-site bleeding (adjusted HR 1.56, 95%CI 1.12-2.18, $p=0.009$) (**Figure 5**).

The association between each specific site of bleeding and mortality is reported in **Table 3**. Intracranial, pericardial and gastro-intestinal bleeding as well as bleeding in the setting of chronic anemia or trauma significantly increased the risk of mortality compared with no bleeding. Packed red blood cells (PRBC) transfusions were used in 130 (46%) patients in the overall cohort, in 64 (44%) patients with access site bleeding events, and in 66 (49%) patients with non-access site bleeding events. The effect of packed red blood cells (PRBC) transfusion on the association between type of bleeding and mortality is reported in **Online Table 1**. Among patients with access site bleeding, the risk of mortality remained low when PRBC transfusions were not required, whereas it was significantly increased in patients needing PRBC transfusions. Among patients with non-access site bleeding, the risk of mortality was significantly increased irrespective of the use of PRBC transfusion, but the magnitude of this association was more pronounced in case of transfusions. There was a strong association between bleeding severity and the use of PRBC transfusion (**Online Table 2**).

Impact of Bleeding on Mortality in the Transfemoral and the Transapical cohort

As shown in **Online Figure 1**, in the transfemoral cohort (n=746) access-site bleeding was associated with numerically increased risk of mortality (adjusted HR 1.33, 95%CI 0.99-1.79, p=0.056). However, non-access site bleeding significantly increased the risk of mortality compared with no bleeding (adjusted HR 2.51, 95%CI 1.84-3.43, p<0.001), yielding to a higher risk of mortality compared with access site bleeding (adjusted HR 1.87, 95%CI 1.28-2.72, p=0.001, **Online Figure 2**). Results were consistent in the analysis restricted to life-threatening or major bleeding events (**Online Figure 1 and 2**).

Among patients who underwent transapical TAVR (n=165), neither access-site bleeding (adjusted HR 1.58, 95%CI 0.69-3.61, p=0.27) nor non-access site bleeding (adjusted HR 1.52, 95%CI 0.69-3.61, p=0.27) were associated with a significantly higher risk of death compared with no bleeding (**Online Figure 3**). Consequently, there was no significant difference in the risk of mortality associated with non-access vs. access-site bleeding (adjusted HR 1.23, 95%CI 0.48-3.14, p=0.67) (**Online Figure 4**).

Correlates of Life-Threatening or Major Bleeding

Variables associated with access and non-access site bleeding are reported in **Table 5**. In the multivariable analysis, female gender was the only correlate of access site bleeding, whereas chronic kidney disease and the STS score were significant correlates of non-access site bleeding after TAVR. Antithrombotic therapy was not associated with bleeding events at univariable analysis. Moreover, antithrombotic therapy during follow-up was not associated with post-discharge, non-access site bleeding events (**Online Table 3**).

Discussion

The salient findings of this study, which evaluated the prognostic impact of bleeding in relation to its source among 926 patients undergoing TAVR, can be summarized as follows:

1. Bleeding after TAVR was observed in approximately 30% of patients up to 5 years, with a similar proportion between access site and non-access site events (51% and 49%). However, about 40% of non-access site bleeding events emerged more than 30 days after the index procedure;
2. Both access-site and non-access site bleeding conveyed an increased risk of all-cause mortality. Nevertheless, patients who experienced non-access site bleeding incurred a higher risk of mortality than those who experienced bleeding at the access site;
3. This pattern was consistently observed among patients undergoing transfemoral TAVR, but not in those undergoing transapical TAVR which, however, constituted less than 20% of the overall population;
4. Female gender was a correlate of access site bleeding, while chronic kidney disease and the STS score were correlates of non-access site bleeding.

Patients with severe aortic stenosis feature a heightened risk of spontaneous bleeding due to advanced age, numerous comorbidities, and impaired primary hemostasis with type IIA von Willebrand's disease.(9,10) Such predisposition, together with a greater invasiveness of the procedure and a frequent development of acquired coagulopathy during cardiopulmonary bypass, accounts for the high incidence of bleeding complications among patients undergoing SAVR.(11) Over the past years, TAVR emerged as a less invasive alternative to SAVR and has been associated with lower rates of life-threatening or major bleeding.(12-15) Indeed, a variety of

parameters of bleeding severity, including the magnitude of blood loss, hemoglobin decline, and number of transfused blood products, has been consistently improved by TAVR compared with SAVR across several studies.(16,17) As a result, the reduced risk of bleeding related to TAVR is considered one of the key mechanisms explaining the TAVR-related survival benefit proven in recent randomized trials.(12-15) Nevertheless, bleeding in TAVR continues to occur in a relatively high proportion – 30% in our study – and adversely affects prognosis as highlighted by several studies revealing that early as well as late bleeding events are linked with an increased risk of subsequent mortality.(17-21)

To the best of knowledge, this is the first study evaluating the clinical impact of bleeding according to its source in the setting of TAVR and therefore extends prior observations in several ways. Our results showed a steadily increasing rate of mortality amounting to 49%, 59%, and 73% among TAVR patients experiencing no bleeding, access site, and non-access site bleeding, respectively. Although both access site and non-access site bleeding adversely impacted prognosis, non-access site resulted in a more than 1.5-fold higher risk of death compared with access-site bleeding in the transfemoral cohort. These findings parallel those observed in the field of percutaneous coronary intervention, where non-access related major bleeding complications have a significantly greater impact on mortality compared with access-site complications.(21-23) A possible reason for this analogy is that non-access site bleeding is a multifactorial event that encapsulates the patient risk profile as well as coexisting comorbidities, and whose risk is longitudinal and extends over time, which is not the case of access site events that typically occur in the aftermath of the index procedure. Accordingly, in our study, chronic kidney disease and the

STS score, which reflects the burden of age and comorbidities, resulted correlates of non-access site bleeding.

Because the risk of mortality was increased for both access site and non-access site bleeding, preventive strategies of either form of bleeding should be pursued to improve the safety profile of TAVR and patient prognosis. Importantly, as the association between bleeding source and mortality was consistently observed in the transfemoral cohort, the use of this route of access may not suffice to offset the detrimental effects of bleeding complications. In this context, procedural antithrombotic therapy and refinements in vascular access technique, closure of the access site, and the delivery sheath profile play a major role in the prevention of access site bleeding. Yet, the optimal antithrombotic regimen in TAVR remains to be well defined as recently highlighted by a randomized trial showing a similar risk of major bleeding with direct thrombin inhibition with bivalirudin against unfractionated heparin at 48 hours after TAVR.(24) Moreover, there is evidence that downsizing the introducer sheath profiles from 22 or 24 F to 18-19 F, and further to 14-18 F have resulted in a lower incidence of vascular complications, which are etiologically associated with access site bleeding.(25-29) Unsurprisingly, female gender was associated with access site bleeding, which is keeping with multiple studies showing a higher risk of early bleeding and vascular complications among women compared with men.(30) The mechanisms are likely multifactorial and include a lower body surface area, older age, and small femoral arteries in women undergoing TAVR.(31,32)

For the prevention of non-access site bleeding, strategies should be targeted to both short- and long-term follow-up, as 60% of bleeding events occurred within 30 days and the remaining 40% thereafter. During the mid- and long-term phase after TAVR, the selection of oral antithrombotic therapy appears of paramount importance.(5) Nevertheless, there is still limited evidence to

inform clinical decision in this regard, and currently at least three randomized trials are investigating different antithrombotic regimens after TAVR (NCT02247128, NCT02556203, and NCT02664649).(33,34) Obviously, the incidence of bleeding during the long-term follow-up points to the individual risk-profile of the patient and thus is less dependent from procedure-related factors, as also suggested by our multivariable analysis. In this respect, additional risk factors for late bleeding included low hemoglobin, atrial fibrillation, the presence of moderate or severe paravalvular leak in an analysis of 2,401 TAVR patients.(17)

The present study should be interpreted in light of the following limitations. First, the study population was based on the experience of a single, tertiary care center and therefore the results might not be extrapolated to other centers with different procedural experience as well as patient selection. Second, the lack of a greater prognostic impact of non-access site compared with access site bleeding among patients who underwent transapical TAVR should be carefully interpreted in view of the relatively small number of patients included in this cohort. The likely underpowered analysis should be therefore considered when potential different mechanisms underlying access-site bleeding are considered in the setting of transapical TAVR. Third, although the risk of mortality for access site and non-access site bleeding was adjusted for relevant covariates, there might have been residual confounders due to unmeasured factors. In this respect, data on sheath size were not available in the registry. Fourth, patients experiencing non-access site bleeding presented a higher risk profile and, therefore, bleeding events may represent in some cases a marker of disease rather than a true mediator of mortality. Fifth, although antithrombotic therapy did not influence the risk of post-discharge non-access site bleeding, results have to be carefully interpreted given the non-randomized nature of our study. Finally, the 5 years follow-up was not

324 available in all patients and, as a consequence, the long-term sequelae of non-access site bleeding
325 might have been partly underestimated.

326

327 In conclusion, bleeding complications after TAVR were frequent by occurring in nearly 1 out of 3
328 patients up to 5 years follow-up. Access site and non-access site bleeding were associated with
329 an increased risk of mortality, but non-access site bleeding conferred a significantly greater
330 magnitude of risk than access site-related events. Female gender was a correlate of access site
331 bleeding, while chronic kidney disease and the STS score were correlates of non-access site
332 bleeding. Futures studies focused on preventive strategies for either form of bleeding are
333 warranted and might have an important clinical implications in the care of patients with severe
334 aortic stenosis undergoing transcatheter aortic valve implantation.

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434

Figure Legends

Figure 1. Effect of bleeding on mortality up to 5-year follow-up.

Figure 2. Incidence of bleeding over time as proportion of the entire population.

Figure 3. Cumulative time-to-event curves showing the rate of mortality up to 5 years among patients without bleeding events, patients with access site bleeding, and patients with non-access site bleeding. Bleeding is defined as life-threatening or major bleeding.

Figure 4. Unadjusted and adjusted risk estimates for access site and non-access site bleeding versus no bleeding in the overall cohort. Among patients without any bleeding, there were 227 deaths with 1764.9 person-years, corresponding to an annual mortality rate of 12.9%.

Figure 5. Unadjusted and adjusted risk estimates for access site vs. non-access site bleeding in the overall cohort.

451 **TABLE 1.** Baseline clinical characteristics

	Overall	Patients with Bleeding Events	Patients without Bleeding Events	p-value	Patients with access site bleeding	Patients with non-access site bleeding
	N = 926	N = 285	N = 641		N = 145	N = 140
Age (years)	82.4 ± 5.8	83.0 ± 5.3	82.1 ± 6.0	0.027	83.4 ± 4.8	82.5 ± 5.8
Female gender, n (%)	491 (53)	161 (56)	330 (51)	0.45	90 (62%)	71 (51%)
BMI, (kg/cm ²)	26.3 ± 5.1	25.6 ± 4.6	26.6 ± 5.2	0.004	25.7 ± 4.9	25.5 ± 4.4
Diabetes mellitus, n (%)	244 (26%)	84 (29%)	160 (25%)	0.13	41 (28%)	43 (31%)
Dyslipidemia, n (%)	588 (63%)	170 (60%)	418 (65%)	0.21	87 (60%)	83 (59%)
Hypertension, n (%)	788 (85%)	237 (83%)	551 (86%)	0.66	119 (82%)	118 (84%)
Previous MI, n (%)	150 (16%)	45 (16%)	105 (16%)	0.90	22 (15%)	23 (16%)
Previous CABG, n (%)	97 (11%)	21 (8%)	76 (13%)	0.71	9 (7%)	12 (9%)
Previous PCI, n (%)	255 (28%)	75 (26%)	180 (28%)	0.52	39 (27%)	36 (26%)
Previous stroke, n (%)	40 (4%)	5 (2%)	35 (6%)	0.52	3 (2%)	2 (2%)
Peripheral vascular disease, n (%)	164 (18%)	56 (20%)	108 (17%)	0.82	23 (16%)	33 (24%)
COPD, n (%)	144 (16%)	48 (17%)	96 (15%)	0.47	20 (14%)	28 (20%)
Anemia, n (%)	539 (58%)	170 (60%)	369 (58%)	0.04	78 (54%)	92 (66%)
Hemoglobin (g/l)	120.5 ± 16.6	119.2 ± 16.9	121.1 ± 16.4	0.005	120.6 ± 17.4	117.7 ± 16.4
Chronic kidney disease, n (%)	648 (70%)	219 (77%)	429 (67%)	0.017	110 (76%)	109 (78%)
Atrial fibrillation, n (%)	301 (33%)	92 (32%)	209 (33%)	0.18	47 (32%)	45 (32%)
LVEF, (%)	53.4 ± 15.1	53.7 ± 14.6	53.2 ± 15.3	0.58	53.6 ± 15.2	53.8 ± 14.0
Aortic valve area, (cm ²)	0.6 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.54	0.6 ± 0.3	0.6 ± 0.2
Mean transvalvular gradient, (mmHg)	42.3 ± 17.3	43.3 ± 17.4	41.9 ± 17.3	0.72	43.5 ± 17.4	43.0 ± 17.6
Logistic EuroSCORE, (%)	21.8 ± 13.3	23.2 ± 13.6	21.2 ± 13.1	0.06	23.3 ± 14.4	23.0 ± 12.9
STS score, (%)	6.6 ± 4.4	7.1 ± 4.8	6.4 ± 4.1	0.004	7.2 ± 4.5	7.1 ± 5.2
Antithrombotic therapy before TAVR				0.88		

Single antiplatelet therapy, n (%)	390 (49%)	125 (52%)	265 (48%)	67 (53%)	58 (50%)
Dual antiplatelet therapy, n (%)	156 (20%)	43 (18%)	113 (20%)	22 (17%)	21 (18%)
Oral anticoagulant, n (%)	172 (22%)	53 (22%)	119 (21%)	24 (19%)	29 (25%)
Oral anticoagulant plus single or dual antiplatelet therapy, n (%)	80 (10%)	21 (9%)	59 (11%)	14 (11%)	7 (6%)
None, n (%)	125 (14%)	41 (14%)	84 (13%)	18 (12%)	23 (17%)

452 Depicted are means ± SD or counts (%). P-values are derived from Weibull survival models. Chronic kidney disease was defined a glomerular filtration
453 rate <60 ml/min/1.73 m².BMI: body mass index. COPD: chronic obstructive pulmonary disease. EuroSCORE: European System for Cardiac Operative
454 Risk Evaluation. LVEF: left ventricular ejection fraction. SAPT: single antiplatelet therapy. STS: Society of Thoracic Surgeons.

455 **TABLE 2.** Procedural characteristics and antithrombotic therapy at discharge

	Overall	Patients with Bleeding Events	Patients without Bleeding Events	p-value	Patients with access site bleeding	Patients with non-access site bleeding
	N = 926	N = 285	N = 641		N = 145	N = 140
General anesthesia, n (%)	319 (34.4%)	113 (39.6%)	206 (32.1%)	0.065	44 (30.3%)	69 (49.3%)
Residual moderate/severe aortic regurgitation, n (%)	105 (11.3%)	40 (14.0%)	65 (10.1%)	0.087	19 (13.1%)	21 (15.0%)
Concomitant PCI, n (%)	143 (15.4%)	51 (17.9%)	92 (14.4%)	0.188	26 (17.9%)	25 (17.9%)
Permanent Pacemaker Implantation, n (%)	129 (20.4%)	35 (21.2%)	94 (20.2%)	0.231	15 (18.1%)	20 (24.4%)
In-hospital stay after TAVR, (days)	9.36 ± 4.86	10.52 ± 6.38	8.95 ± 4.12	<0.001	9.64 ± 5.28	11.41 ± 7.24
Access				0.575		
Transfemoral, n (%)	746 (80.6%)	224 (78.6%)	522 (81.4%)		130 (89.7%)	94 (67.1%)
Transapical, n (%)	165 (17.8%)	55 (19.3%)	110 (17.2%)		12 (8.3%)	43 (30.7%)
Transsubclavian, n (%)	12 (1.3%)	6 (2.1%)	6 (0.9%)		3 (2.1%)	3 (2.1%)
Other, n (%)	3 (0.3%)	0 (0.0%)	3 (0.5%)		0 (0.0%)	0 (0.0%)
Device				0.404		
Medtronic CoreValve, n (%)	429 (47.1%)	131 (47.1%)	298 (47.1%)		79 (56.0%)	52 (38.0%)
Edwards Sapien XT, n (%)	380 (41.7%)	129 (46.4%)	251 (39.7%)		55 (39.0%)	74 (54.0%)
Edwards Sapien 3, n (%)	51 (5.6%)	6 (2.2%)	45 (7.1%)		3 (2.1%)	3 (2.2%)
Symetis Acurate, n (%)	39 (4.3%)	10 (3.6%)	29 (4.6%)		2 (1.4%)	8 (5.8%)
SJM Portico, n (%)	3 (0.3%)	1 (0.4%)	2 (0.3%)		1 (0.7%)	0 (0.0%)
BSC Lotus, n (%)	9 (1.0%)	1 (0.4%)	8 (1.3%)		1 (0.7%)	0 (0.0%)
Anti-thrombotic therapy at discharge				0.003		
Single antiplatelet therapy, n (%)	43 (4.8%)	18 (6.7%)	25 (4.0%)		10 (7.3%)	8 (6.1%)
Dual antiplatelet therapy, n (%)	576 (64.6%)	164 (61.2%)	412 (66.1%)		88 (64.2%)	76 (58.0%)

	Oral anticoagulant, n (%)	45 (5.1%)	14 (5.2%)	31 (5.0%)	8 (5.8%)	6 (4.6%)
	Oral anticoagulant plus single or dual antiplatelet therapy, n (%)	227 (25.5%)	72 (26.9%)	155 (24.9%)	31 (22.6%)	41 (31.3%)
	None, n (%)	5 (0.6%)	2 (0.7%)	3 (0.5%)	1 (0.7%)	1 (0.8%)
456	Depicted are means ± SD or counts (%). P-values are derived from Weibull survival models.					
457	PCI: percutaneous coronary intervention. TAVR: transcatheter aortic valve replacement.					

458 **TABLE 3.** Bleeding severity and location during follow-up

459

	Bleeding severity			All bleeding events		
	Minor bleeding	Major bleeding	Life threatening bleeding	No. events	Adjusted HR of bleeding vs. no bleeding (95%CI)	P-value
Access site bleeding	23 (38%)	80 (59%)	42 (47%)	145 (51%)	1.34 (1.01-1.76)	0.04
Non-access site bleeding	38 (62%)	55 (41%)	47 (53%)	140 (49%)	2.08 (1.60-2.71)	<0.001
Intracranial	0 (0%)	0 (0%)	8 (9%)	8 (3%)	3.34 (1.24 - 9.00)	0.017
Intraocular	0 (0%)	0 (0%)	1 (1%)	1 (0%)	2.98 (0.42 - 21.38)	0.28
Gastrointestinal	12 (20%)	25 (19%)	10 (11%)	47 (16%)	2.54 (1.68 - 3.85)	<0.001
Genito-urinary	4 (7%)	5 (4%)	1 (1%)	10 (4%)	0.70 (0.24 - 1.98)	0.50
Epistaxis	4 (7%)	1 (1%)	0 (0%)	5 (2%)	0.97 (0.24 - 3.94)	0.97
Chronic anemia	0 (0%)	3 (2%)	1 (1%)	4 (1%)	4.38 (1.63 - 11.78)	0.003
Pericardial	0 (0%)	2 (1%)	12 (13%)	14 (5%)	4.49 (2.44 - 8.27)	<0.001
Pulmonary	1 (2%)	1 (1%)	5 (6%)	7 (2%)	0.77 (0.19 - 3.11)	0.71
Trauma	4 (7%)	2 (1%)	0 (0%)	6 (2%)	4.38 (1.63 - 11.81)	0.003
Other surgery	1 (2%)	0 (0%)	4 (4%)	5 (2%)	2.29 (0.57 - 9.22)	0.24
Other	12 (20%)	16 (12%)	5 (6%)	33 (12%)	1.62 (0.99 - 2.66)	0.055

460 Analysis includes the first bleeding event at patient-level (each patient counted only once). Hazard ratios (HRs) with 95% confidence intervals (95%Cis)
 461 are derived by Weibull's survival models in which patients without bleeding events was considered the control group. HR are adjusted for gender,
 462 diabetes, and the Society of Thoracic Surgeons score (see Methods).

463 **TABLE 4.** Antithrombotic therapy throughout follow-up

464

Antithrombotic therapy throughout follow-up	1 month N = 893	1-Year N = 831	2-Year N = 699	3-Year N = 494	4-Year N = 307	5-Year N = 190
Single antiplatelet therapy, n (%)	79 (10%)	328 (46%)	266 (57%)	256 (60%)	116 (57%)	85 (57%)
Dual antiplatelet therapy, n (%)	495 (60%)	167 (23%)	44 (9%)	29 (7%)	19 (9%)	10 (7%)
Oral anticoagulant, n (%)	57 (7%)	108 (15%)	89 (19%)	96 (22%)	50 (25%)	31 (21%)
Oral anticoagulant plus single or dual antiplatelet therapy, n (%)	182 (22%)	99 (14%)	54 (12%)	35 (8%)	12 (6%)	9 (6%)
None, n (%)	8 (1%)	17 (2%)	11 (2%)	11 (3%)	7 (3%)	15 (10%)

465

TABLE 5. Multivariable analysis for life-threatening or major bleeding events

	HR (95%CI)	P-value
Overall cohort		
Access site bleeding		
Female gender	2.59 (1.10-6.13)	0.030
Non-access site bleeding		
Chronic kidney disease	1.99 (1.02-3.87)	0.043
STS score (per 1% increase)	1.05 (1.00-1.10)	0.047

Chronic kidney disease was defined a glomerular filtration rate <60 ml/min/1.73 m². Candidate variables: Age, female gender, body mass index, diabetes mellitus, previous coronary artery bypass graft, previous percutaneous coronary intervention, previous stroke, peripheral vascular disease, anemia, renal failure, coronary artery disease, atrial fibrillation, aortic regurgitation ≥2 after TAVR, concomitant coronary revascularization, aortic valve area, STS score. Anti-thrombotic therapy at in-hospital admission was included as candidate variable for both access site and non-access site bleeding. Antithrombotic therapy at hospital discharge was additionally included as candidate variable for the analysis of non-access site bleeding.

Figure 1

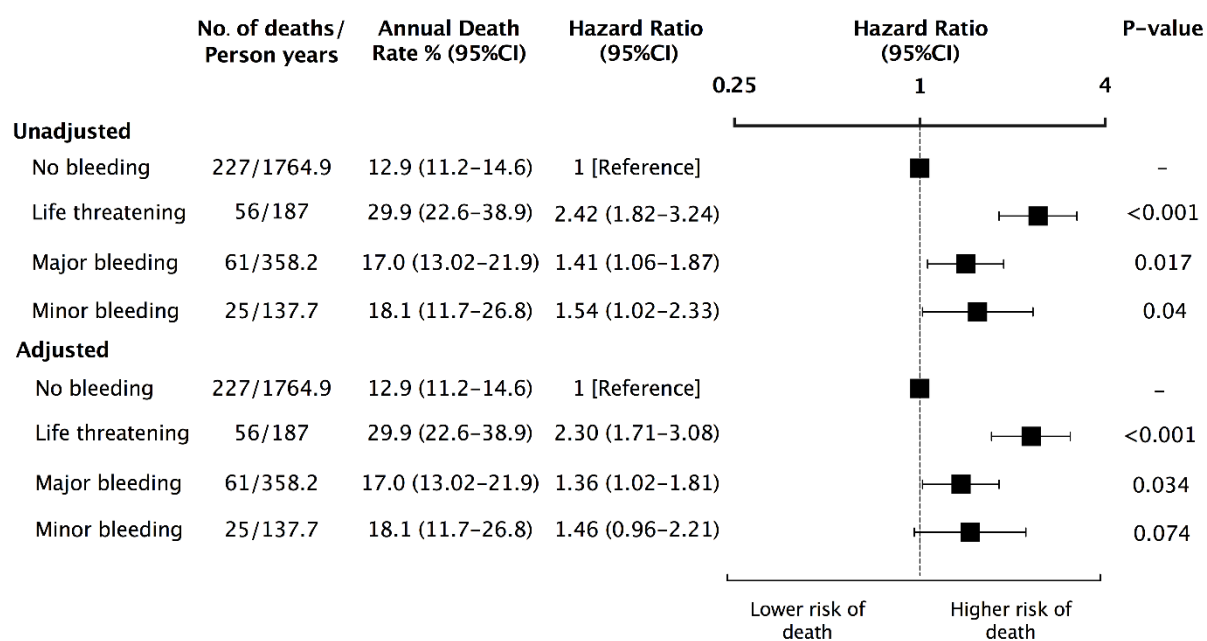


Figure 2

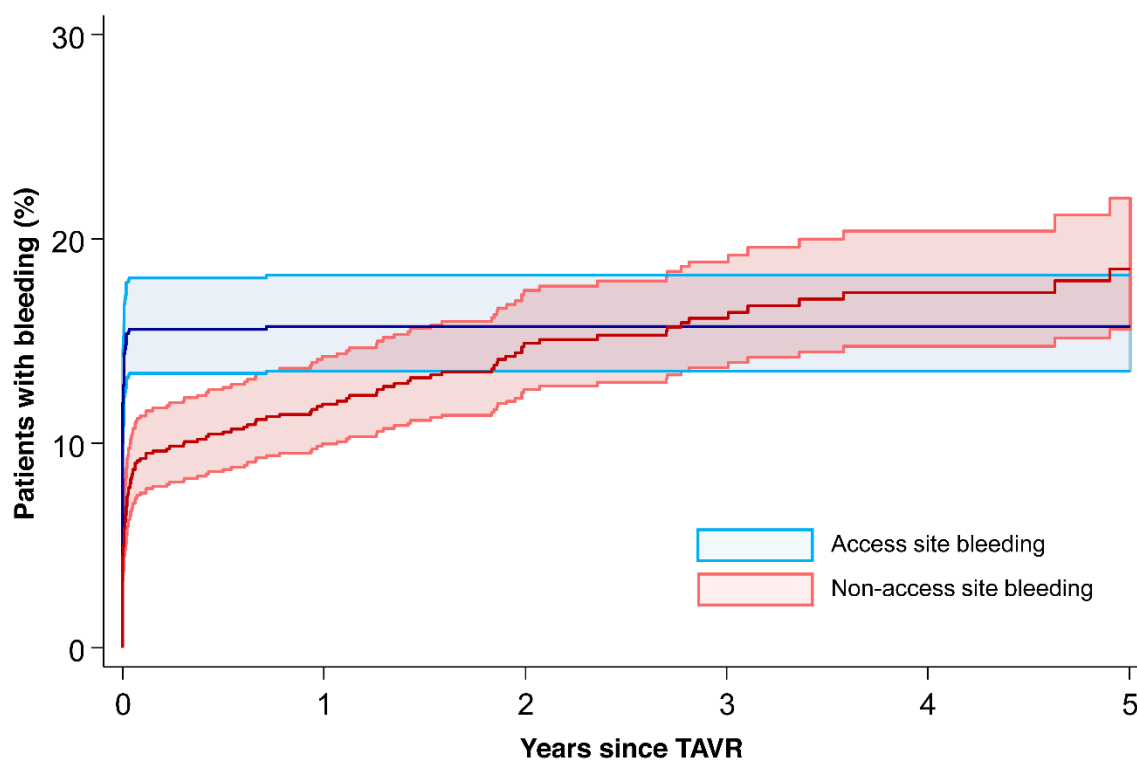


Figure 3

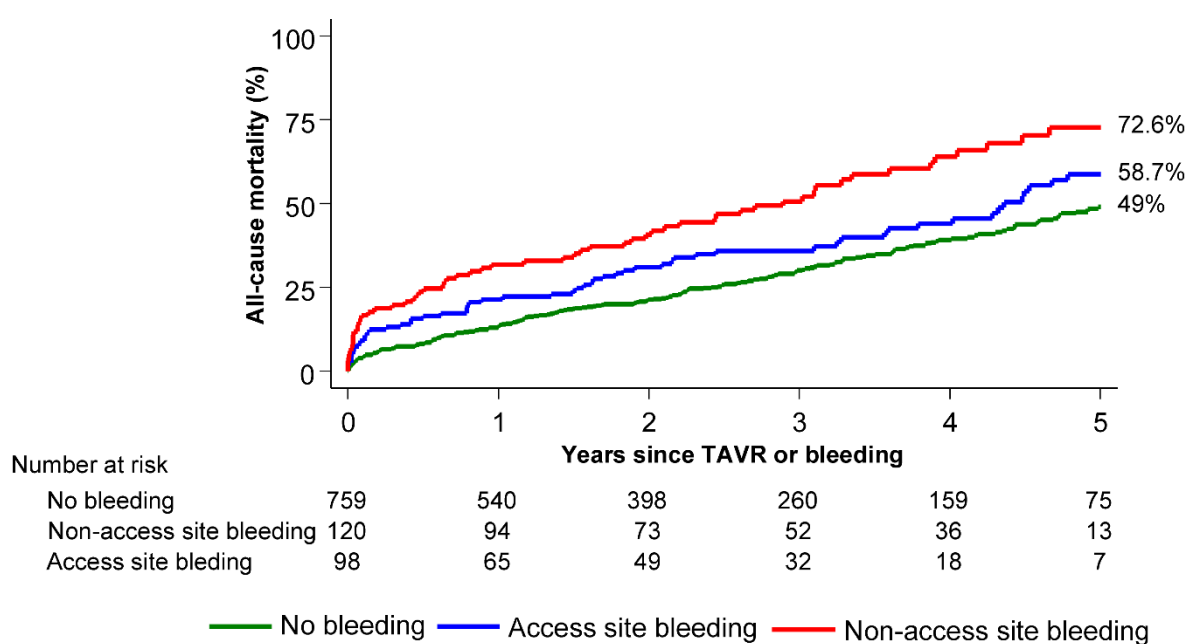


Figure 4

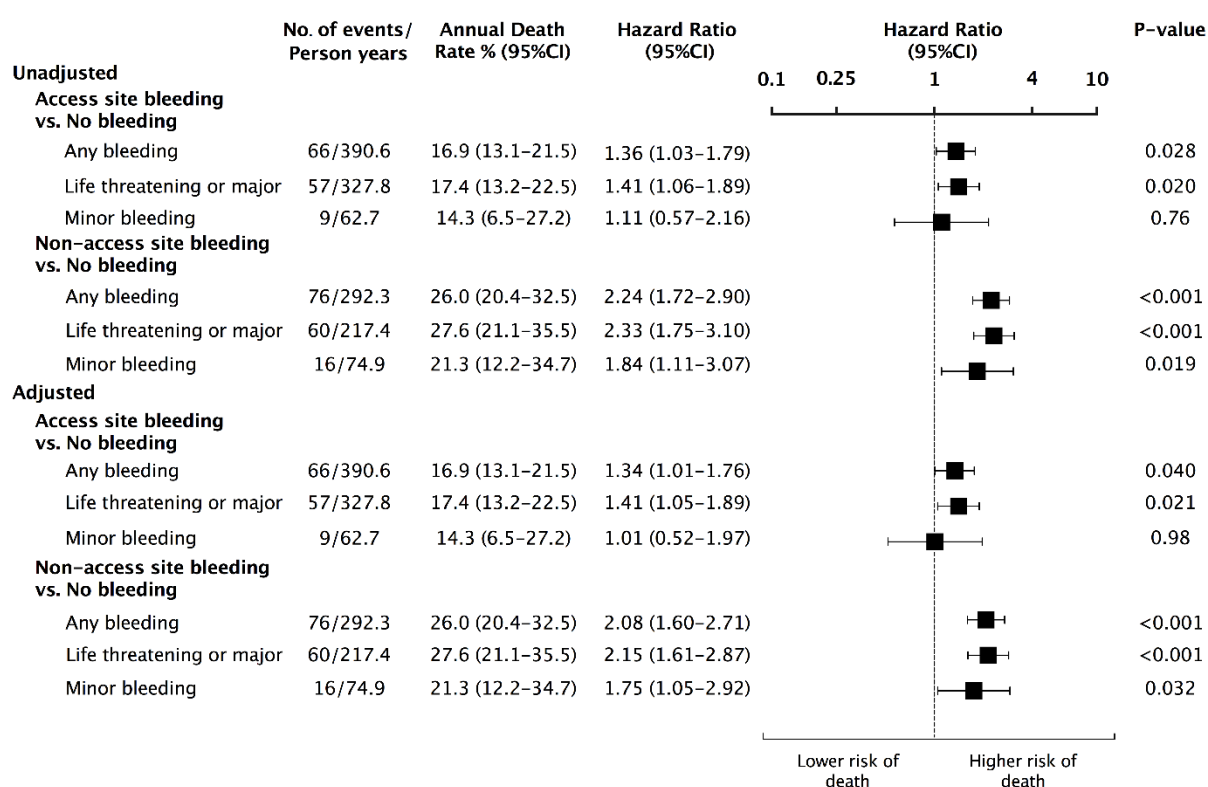
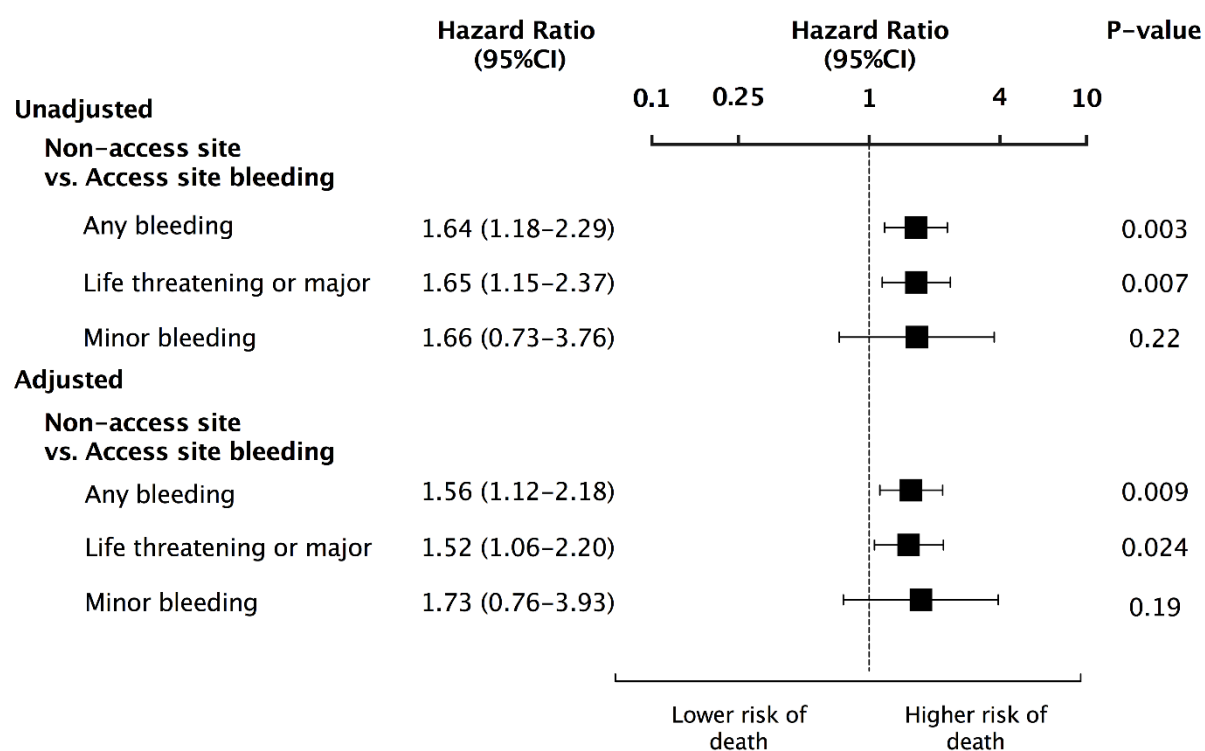


Figure 5



Online Appendix

Online Table 1. Association between access-site and non-access site bleeding with mortality among patients who received packed red blood cell transfusions (PRBCs) or not.

Online Table 2. Use of packed red blood cell transfusions (PRBCs) according to bleeding location and severity.

Online Table 3. Association between antithrombotic therapy and the risk of late post-discharge bleeding.

Online Figure 1. Unadjusted and adjusted risk estimates for access site and non-access site bleeding versus no bleeding in the transfemoral cohort. Among patients without any bleeding, there were 180 deaths with 1480.1 person-years, corresponding to an annual mortality rate of 12.1%.

Online Figure 2. Unadjusted and adjusted risk estimates for access site vs. non-access site bleeding in the transfemoral cohort.

Online Figure 3. Unadjusted and adjusted risk estimates for access site and non-access site bleeding versus no bleeding in the transapical cohort. Among patients without any bleeding, there were 47 deaths with 284.8 person-years, corresponding to an annual mortality rate of 16.5%.

Online Figure 4. Unadjusted and adjusted risk estimates for access site vs. non-access site bleeding in the transapical cohort.

Online Table 1. Association between access-site and non-access site bleeding with mortality among patients who received packed red blood cell transfusions (PRBCs) or not.

	Access site bleeding vs. no bleeding		Non-access site bleeding vs. no bleeding		Access-site vs. non-access site bleeding	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Unadjusted						
Patients receiving PRBCs						
Any bleeding	1.75 (1.22 - 2.52)	0.002	2.50 (1.80 - 3.47)	<0.001	1.42 (0.91 - 2.24)	0.13
Life threatening or major bleeding	1.86 (1.29 - 2.70)	0.001	2.54 (1.81 - 3.57)	<0.001	1.36 (0.85 - 2.18)	0.19
Minor bleeding	0.88 (0.22 - 3.55)	0.86	1.96 (0.63 - 6.12)	0.25	2.22 (0.37 - 13.27)	0.38
Patients without PRBCs						
Any bleeding	1.08 (0.74 - 1.56)	0.69	1.99 (1.41 - 2.82)	<0.001	1.85 (1.16 - 2.96)	0.01
Life threatening or major bleeding	1.05 (0.70 - 1.59)	0.81	2.00 (1.30 - 3.07)	0.002	1.90 (1.08 - 3.34)	0.027
Minor bleeding	1.20 (0.57 - 2.55)	0.63	2.01 (1.19 - 3.40)	0.009	1.67 (0.68 - 4.11)	0.26
Adjusted						
Patients receiving PRBCs						
Any bleeding	1.53 (1.06 - 2.21)	0.022	2.59 (1.86 - 3.60)	<0.001	1.67 (1.05 - 2.65)	0.03
Life threatening or major bleeding	1.62 (1.11 - 2.36)	0.011	2.62 (1.86 - 3.69)	<0.001	1.62 (1.00 - 2.60)	0.048
Minor bleeding	0.78 (0.19 - 3.17)	0.73	2.17 (0.69 - 6.80)	0.18	2.77 (0.46 - 16.68)	0.27
Patients without PRBCs						
Any bleeding	1.12 (0.77 - 1.62)	0.55	1.68 (1.18 - 2.39)	0.004	1.54 (0.95 - 2.49)	0.082
Life threatening or major bleeding	1.13 (0.75 - 1.71)	0.56	1.57 (1.00 - 2.47)	0.048	1.39 (0.77 - 2.51)	0.27
Minor bleeding	1.11 (0.52 - 2.35)	0.80	1.86 (1.10 - 3.15)	0.021	1.68 (0.68 - 4.14)	0.26

Analysis includes the first bleeding event at patient-level (each patient counted only once). CI: confidence intervals. HR: hazard ratio.

Online Table 2. Use of packed red blood cell transfusions (PRBCs) according to bleeding location and severity.

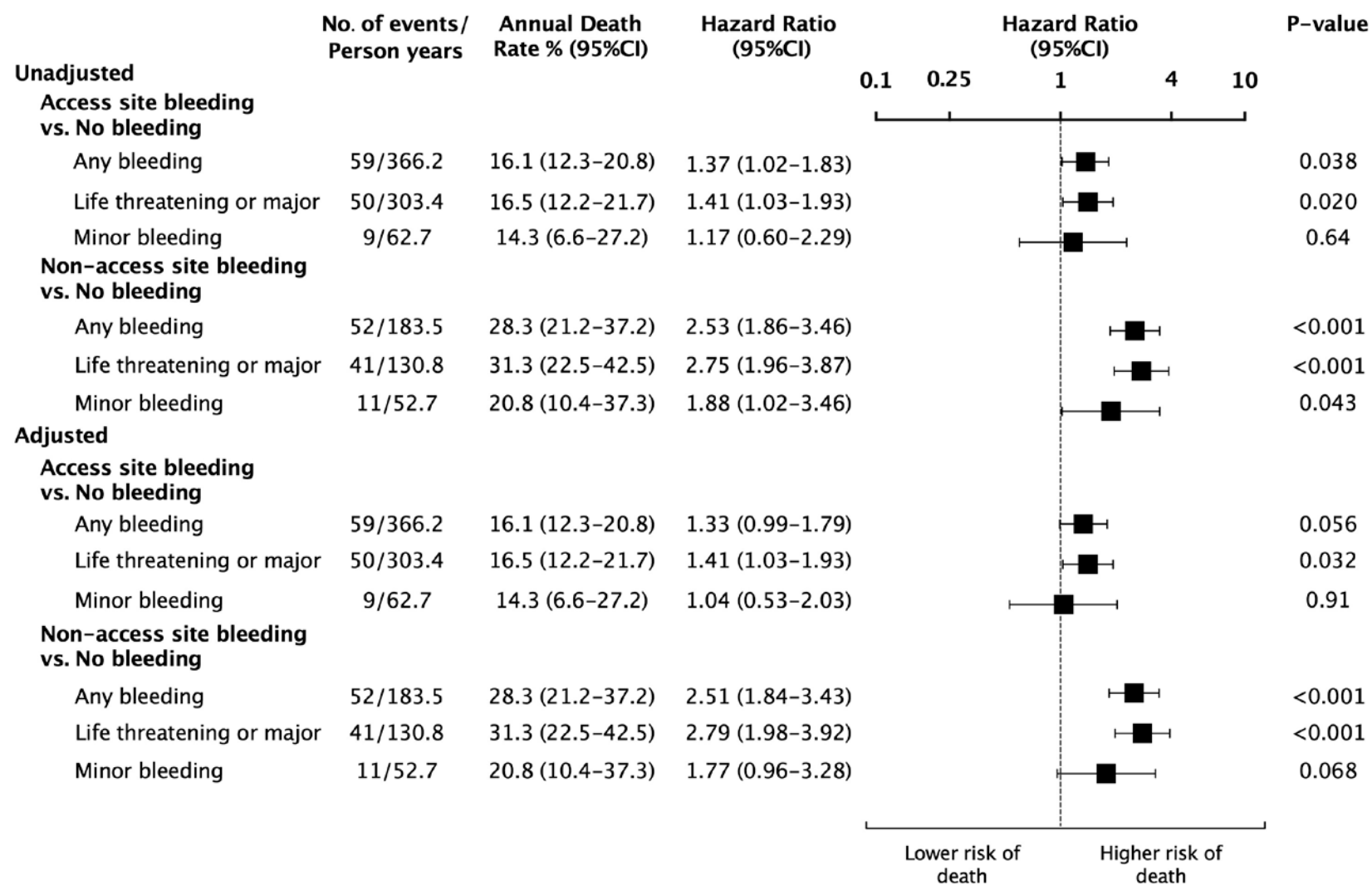
	Life threatening or major or minor bleeding (N =285)	Bleeding severity			P-value
		Life threatening (N=89)	Major (N=135)	Minor (N=61)	
Access or non-access site bleeding	130 (46%)	66 (75%)	55 (41%)	9 (15%)	<0.001
Access site bleeding	64 (44%)	32 (76%)	27 (34%)	5 (22%)	<0.001
Non-access site bleeding	66 (49%)	34 (74%)	28 (52%)	4 (11%)	<0.001

Data show the use of packed red blood cell transfusions according to bleeding location and severity. Analysis includes the first bleeding event at patient-level (each patient counted only once).

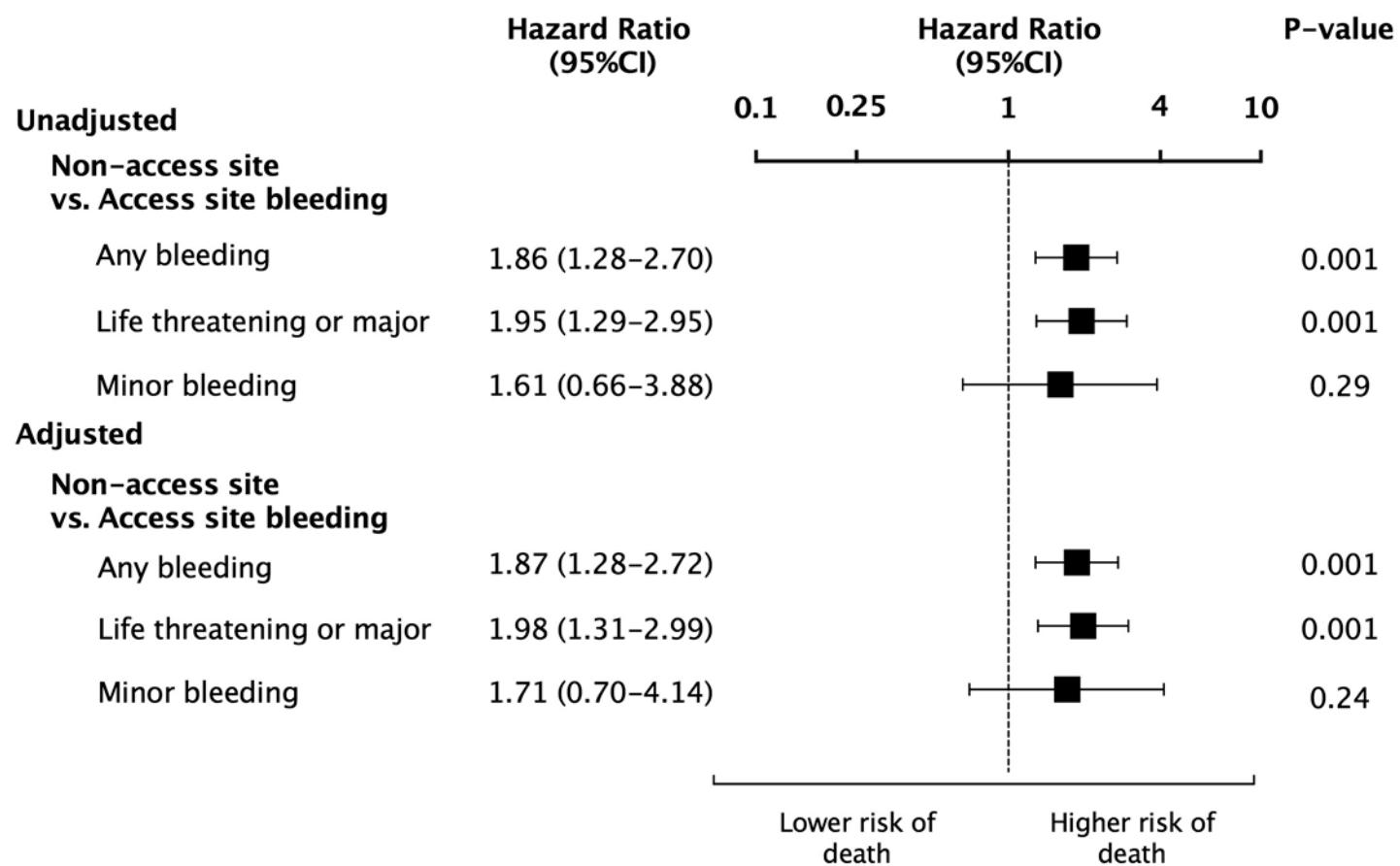
Online Table 3. Association between antithrombotic therapy and the risk of late post-discharge bleeding.

	HR (95% CI)	P-value
Antithrombotic therapy		0.351
Single antiplatelet therapy	1 (reference)	
Dual antiplatelet therapy	0.77 (0.32 - 1.86)	0.56
Oral anticoagulant	1.04 (0.32 - 3.39)	0.946
Oral anticoagulant plus single or dual antiplatelet therapy	1.65 (0.68 - 3.96)	0.267
None	0.71 (0.09 - 5.65)	0.75
Antithrombotic therapy considered as time varying covariate. CI: confidence intervals. HR: hazard ratio.		

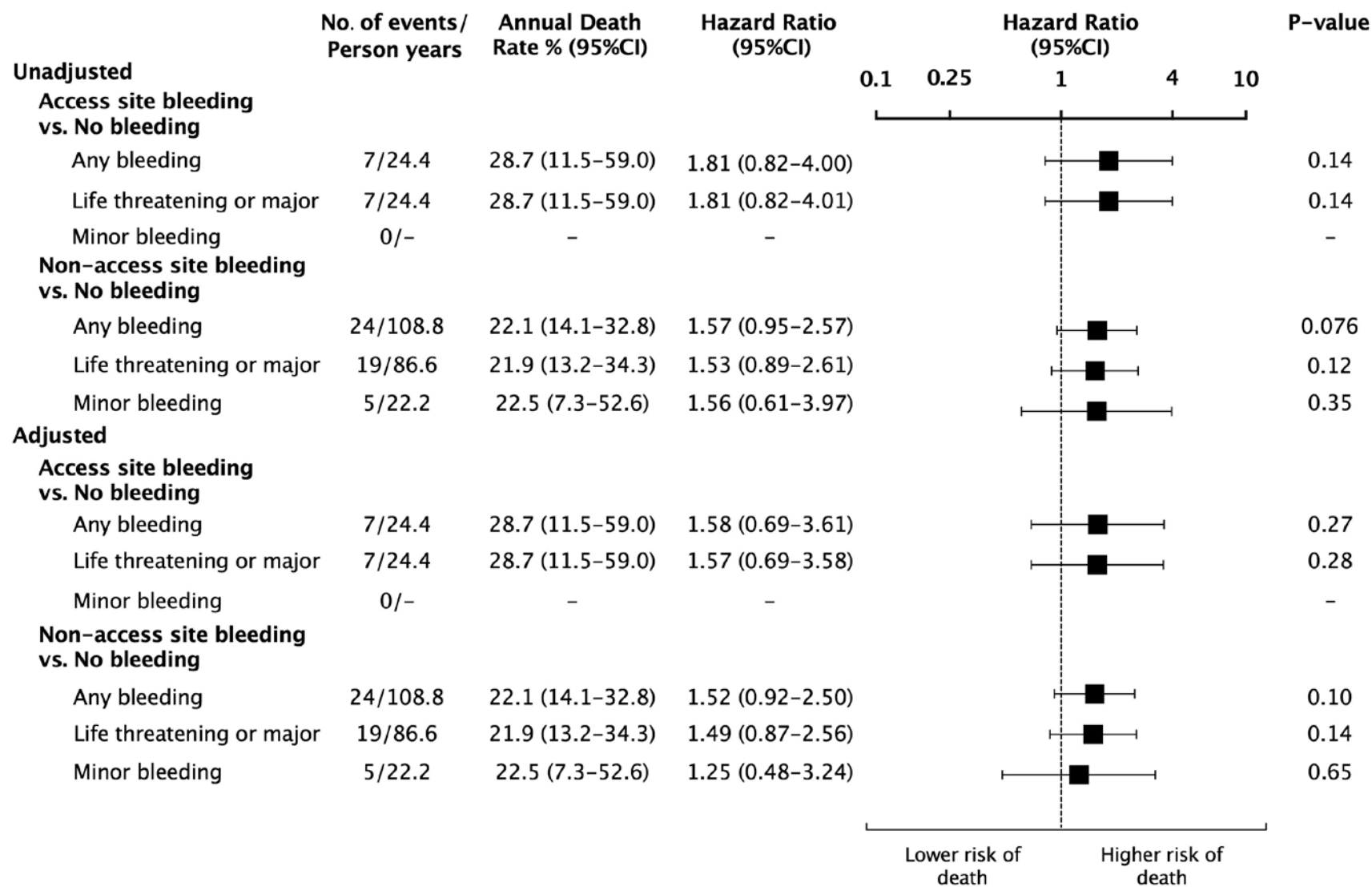
Online Figure 1



Online Figure 2



Online Figure 3



Online Figure 4

