

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

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

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

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

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

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

57 **Clinical Perspectives**

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

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

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

68

69 **Condensed Abstract**

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

77

Introduction

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.

95

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

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

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

129

130 **Statistical analysis**

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

135 The association between access and non-access site bleeding and mortality was examined using
136 parametric Weibull survival models in which bleeding was considered as a time-varying covariate.

137 The time in days between the index TAVR procedure and the first bleeding event triggered the
138 status change from the non-bleeding to the bleeding group. Risk estimates are expressed as

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

152

Results

153 From August 2007 through June 2014, 926 consecutive patients with severe AS underwent TAVR.

154 Baseline and procedural characteristics of the study population are summarized in **Table 1** and **2**.

155 In the overall cohort, the mean age was 82.4 ± 5.8 years and 491 patients (53%) were women. The

156 baseline standard predictor of risk was $6.6 \pm 4.4\%$ according to the STS score. Most patients

157 underwent transfemoral TAVR (746 patients or 80.6%) and there was a similar implantation rate

158 of self-expandable and balloon-expandable valve devices. Median follow-up was 2.75 years (IQR

159 [1.17-4.40]).

160

161 **Frequency, Time Course, and Mortality associated with Bleeding Events**

162 As reported in **Table 3**, a total of 285 (30.7%) patients experienced at least one bleeding event up

163 to 5 years, with a similar proportion between access site (145 patients or 51%) and non-access

164 site bleeding (140 patients or 49%). Life threatening or major bleeding was observed in 224

165 (24.2%) patients, representing thus 78.6% of all bleeding events (122 or 84% of access site and

166 102 or 73% of non-access site bleeding events). As shown in **Figure 1**, the adjusted risk of mortality

167 was significantly increased among patients who had life threatening (HR 2.30, 95%CI 1.71-3.08,

168 $p < 0.001$) or major bleeding (HR 1.36, 95%CI 1.02-1.81, $p = 0.034$) compared those who did not

169 experience a bleeding event.

170 The incidence of access and non-access site bleeding during follow-up is shown in **Figure 2**.

171 Approximately 80% of all bleeding events occurred within the first 30 days after TAVR. However,

172 while all access site bleeding events arose within the first 30 days after the index TAVR, late

173 bleeding (>30 days) accounted for 40% of non-access site bleeding. The gastrointestinal tract was

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

176

177 **Clinical and Procedural Characteristics**

178 In univariable analyses (**Table 1**), we found higher risk of bleeding in older patients, those with a
179 lower body mass index, anemic patients, and those with chronic renal failure. As reported in **Table**
180 **2**, bleeding was associated with different prescription of antithrombotic therapy at discharge.
181 **Table 4** describes antithrombotic therapy throughout follow-up. There was an increasing
182 proportion of patients treated with either single antiplatelet therapy or oral anticoagulant
183 starting from 1-year, while dual antiplatelet therapy and the combination of oral anticoagulant
184 with single or dual antiplatelet therapy were less commonly prescribed during long-term follow-
185 up.

186

187 **Impact of Type of Bleeding on Mortality in the Overall Cohort**

188 As shown in **Figure 3**, the rate of all-cause mortality up to 5 years follow-up associated with no
189 bleeding, access site, and non-access site life-threatening or major bleeding amounted to 49%,
190 58.7%, and 72.6%, respectively.

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

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

210

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

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

219 Among patients who underwent transapical TAVR (n=165), neither access-site bleeding (adjusted
220 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-
221 3.61, p=0.27) were associated with a significantly higher risk of death compared with no bleeding
222 (**Online Figure 3**). Consequently, there was no significant difference in the risk of mortality
223 associated with non-access vs. access-site bleeding (adjusted HR 1.23, 95%CI 0.48-3.14, p=0.67)
224 (**Online Figure 4**).

225

226 **Correlates of Life-Threatening or Major Bleeding**

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

233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255

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

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

264

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

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

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

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

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

308
309 The present study should be interpreted in light of the following limitations. First, the study
310 population was based on the experience of a single, tertiary care center and therefore the results
311 might not be extrapolated to other centers with different procedural experience as well as patient
312 selection. Second, the lack of a greater prognostic impact of non-access site compared with access
313 site bleeding among patients who underwent transapical TAVR should be carefully interpreted in
314 view of the relatively small number of patients included in this cohort. The likely underpowered
315 analysis should be therefore considered when potential different mechanisms underlying access-
316 site bleeding are considered in the setting of transapical TAVR. Third, although the risk of
317 mortality for access site and non-access site bleeding was adjusted for relevant covariates, there
318 might have been residual confounders due to unmeasured factors. In this respect, data on sheath
319 size were not available in the registry. Fourth, patients experiencing non-access site bleeding
320 presented a higher risk profile and, therefore, bleeding events may represent in some cases a
321 marker of disease rather than a true mediator of mortality. Fifth, although antithrombotic therapy
322 did not influence the risk of post-discharge non-access site bleeding, results have to be carefully
323 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.

References

- 335
- 336
- 337 1. Nishimura RA, Otto CM, Bonow RO et al. 2014 AHA/ACC guideline for the management of
338 patients with valvular heart disease: a report of the American College of
339 Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll*
340 *Cardiol* 2014;63:e57-185.
- 341 2. Joint Task Force on the Management of Valvular Heart Disease of the European Society of
342 C, European Association for Cardio-Thoracic S, Vahanian A et al. Guidelines on the
343 management of valvular heart disease (version 2012). *Eur Heart J* 2012;33:2451-96.
- 344 3. Siontis GC, Praz F, Pilgrim T et al. Transcatheter aortic valve implantation vs. surgical aortic
345 valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized
346 trials. *Eur Heart J* 2016;pii: ehw225 - in press.
- 347 4. Siemieniuk RA, Agoritsas T, Manja V et al. Transcatheter versus surgical aortic valve
348 replacement in patients with severe aortic stenosis at low and intermediate risk:
349 systematic review and meta-analysis. *BMJ* 2016;354:i5130.
- 350 5. Rodes-Cabau J, Dauerman HL, Cohen MG et al. Antithrombotic treatment in transcatheter
351 aortic valve implantation: insights for cerebrovascular and bleeding events. *J Am Coll*
352 *Cardiol* 2013;62:2349-59.
- 353 6. Stortecky S, Stefanini GG, Pilgrim T et al. Validation of the Valve Academic Research
354 Consortium Bleeding Definition in Patients With Severe Aortic Stenosis Undergoing
355 Transcatheter Aortic Valve Implantation. *J Am Heart Assoc* 2015;4:e002135.
- 356 7. Stortecky S, Buellesfeld L, Wenaweser P, Windecker S. Transcatheter aortic valve
357 implantation: the procedure. *Heart* 2012;98 Suppl 4:iv44-51.

- 358 8. Kappetein AP, Head SJ, Genereux P et al. Updated standardized endpoint definitions for
359 transcatheter aortic valve implantation: the Valve Academic Research Consortium-2
360 consensus document. *J Am Coll Cardiol* 2012;60:1438-54.
- 361 9. Loscalzo J. From clinical observation to mechanism--Heyde's syndrome. *N Engl J Med*
362 2013;368:579-80.
- 363 10. Natorska J, Mazur P, Undas A. Increased bleeding risk in patients with aortic valvular
364 stenosis: From new mechanisms to new therapies. *Thromb Res* 2016;139:85-9.
- 365 11. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality,
366 postoperative morbidity, and cost after red blood cell transfusion in patients having
367 cardiac surgery. *Circulation* 2007;116:2544-52.
- 368 12. Smith CR, Leon MB, Mack MJ et al. Transcatheter versus surgical aortic-valve replacement
369 in high-risk patients. *N Engl J Med* 2011;364:2187-98.
- 370 13. Leon MB, Smith CR, Mack MJ et al. Transcatheter or Surgical Aortic-Valve Replacement in
371 Intermediate-Risk Patients. *N Engl J Med* 2016;374:1609-20.
- 372 14. Adams DH, Popma JJ, Reardon MJ et al. Transcatheter aortic-valve replacement with a
373 self-expanding prosthesis. *N Engl J Med* 2014;370:1790-8.
- 374 15. Thyregod HG, Steinbruchel DA, Ihlemann N et al. Transcatheter Versus Surgical Aortic
375 Valve Replacement in Patients With Severe Aortic Valve Stenosis: 1-Year Results From the
376 All-Comers NOTION Randomized Clinical Trial. *J Am Coll Cardiol* 2015;65:2184-94.
- 377 16. Wenaweser P, Pilgrim T, Kadner A et al. Clinical outcomes of patients with severe aortic
378 stenosis at increased surgical risk according to treatment modality. *J Am Coll Cardiol*
379 2011;58:2151-62.

- 380 17. Genereux P, Cohen DJ, Williams MR et al. Bleeding complications after surgical aortic valve
381 replacement compared with transcatheter aortic valve replacement: insights from the
382 PARTNER I Trial (Placement of Aortic Transcatheter Valve). *J Am Coll Cardiol*
383 2014;63:1100-9.
- 384 18. Genereux P, Cohen DJ, Mack M et al. Incidence, predictors, and prognostic impact of late
385 bleeding complications after transcatheter aortic valve replacement. *J Am Coll Cardiol*
386 2014;64:2605-15.
- 387 19. Pilgrim T, Stortecky S, Luterbacher F, Windecker S, Wenaweser P. Transcatheter aortic
388 valve implantation and bleeding: incidence, predictors and prognosis. *J Thromb*
389 *Thrombolysis* 2013;35:456-62.
- 390 20. Nuis RJ, Rodes-Cabau J, Sinning JM et al. Blood transfusion and the risk of acute kidney
391 injury after transcatheter aortic valve implantation. *Circ Cardiovasc Interv* 2012;5:680-8.
- 392 21. Borz B, Durand E, Godin M et al. Incidence, predictors and impact of bleeding after
393 transcatheter aortic valve implantation using the balloon-expandable Edwards prosthesis.
394 *Heart* 2013;99:860-5.
- 395 22. Kwok CS, Khan MA, Rao SV et al. Access and non-access site bleeding after percutaneous
396 coronary intervention and risk of subsequent mortality and major adverse cardiovascular
397 events: systematic review and meta-analysis. *Circ Cardiovasc Interv* 2015;8.
- 398 23. Verheugt FW, Steinhubl SR, Hamon M et al. Incidence, prognostic impact, and influence
399 of antithrombotic therapy on access and nonaccess site bleeding in percutaneous
400 coronary intervention. *JACC Cardiovasc Interv* 2011;4:191-7.

- 401 24. Dangas GD, Lefevre T, Kupatt C et al. Bivalirudin Versus Heparin Anticoagulation in
402 Transcatheter Aortic Valve Replacement: The Randomized BRAVO-3 Trial. *J Am Coll*
403 *Cardiol* 2015;66:2860-8.
- 404 25. Stortecky S, Wenaweser P, Diehm N et al. Percutaneous management of vascular
405 complications in patients undergoing transcatheter aortic valve implantation. *JACC*
406 *Cardiovasc Interv* 2012;5:515-24.
- 407 26. Barbanti M, Binder RK, Freeman M et al. Impact of low-profile sheaths on vascular
408 complications during transfemoral transcatheter aortic valve replacement.
409 *EuroIntervention* 2013;9:929-35.
- 410 27. Genereux P, Webb JG, Svensson LG et al. Vascular complications after transcatheter aortic
411 valve replacement: insights from the PARTNER (Placement of AoRTic TraNscathetER
412 Valve) trial. *J Am Coll Cardiol* 2012;60:1043-52.
- 413 28. Thourani VH, Kodali S, Makkar RR et al. Transcatheter aortic valve replacement versus
414 surgical valve replacement in intermediate-risk patients: a propensity score analysis.
415 *Lancet* 2016;387:2218-25.
- 416 29. Popma JJ, Reardon MJ, Khabbaz K et al. Early Clinical Outcomes After Transcatheter Aortic
417 Valve Replacement Using a Novel Self-Expanding Bioprosthesis in Patients With Severe
418 Aortic Stenosis Who Are Suboptimal for Surgery: Results of the Evolut R U.S. Study. *JACC*
419 *Cardiovasc Interv* 2017;10:268-275.
- 420 30. O'Connor SA, Morice MC, Gilard M et al. Revisiting Sex Equality With Transcatheter Aortic
421 Valve Replacement Outcomes: A Collaborative, Patient-Level Meta-Analysis of 11,310
422 Patients. *J Am Coll Cardiol* 2015;66:221-8.

- 423 31. Forrest JK, Adams DH, Popma JJ et al. Transcatheter Aortic Valve Replacement in Women
424 Versus Men (from the US CoreValve Trials). *Am J Cardiol* 2016;118:396-402.
- 425 32. Chandrasekhar J, Dangas GD, Yu J et al. Sex-Based Differences in Outcomes With
426 Transcatheter Aortic Valve Therapy. TVT Registry from 2011 to 2014. *J Am Coll Cardiol*
427 2016;68:2733-44.
- 428 33. Nijenhuis VJ, Bennaghmouch N, Hassell M et al. Rationale and design of POPular-TAVI:
429 antiPlatelet therapy fOr Patients undergoing Transcatheter Aortic Valve Implantation. *Am*
430 *Heart J* 2016;173:77-85.
- 431 34. Windecker S, Tijssen J, Giustino G et al. Trial design: Rivaroxaban for the prevention of
432 major cardiovascular events after transcatheter aortic valve replacement: Rationale and
433 design of the GALILEO study. *Am Heart J* 2016;184:81-87.

434

435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450

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 \pm 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		P-value
	Minor bleeding	Major bleeding	Life threatening bleeding	No. events	Adjusted HR of bleeding vs. no bleeding (95%CI)	
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

466 **TABLE 5.** Multivariable analysis for life-threatening or major bleeding events
 467
 468

	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

469
 470 Chronic kidney disease was defined a glomerular filtration rate <60 ml/min/1.73 m². Candidate variables:
 471 Age, female gender, body mass index, diabetes mellitus, previous coronary artery bypass graft, previous
 472 percutaneous coronary intervention, previous stroke, peripheral vascular disease, anemia, renal failure,
 473 coronary artery disease, atrial fibrillation, aortic regurgitation ≥2 after TAVR, concomitant coronary
 474 revascularization, aortic valve area, STS score. Anti-thrombotic therapy at in-hospital admission was
 475 included as candidate variable for both access site and non-access site bleeding. Antithrombotic therapy at hospital
 476 discharge was additionally included as candidate variable for the analysis of non-access site bleeding.

Figure 1

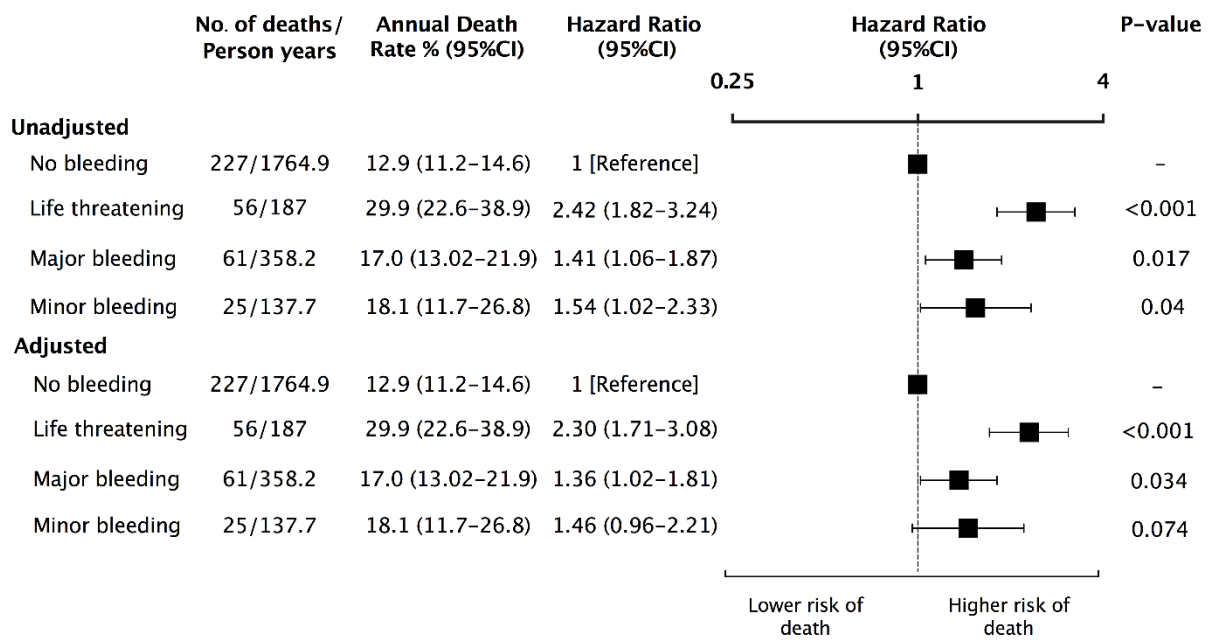


Figure 2

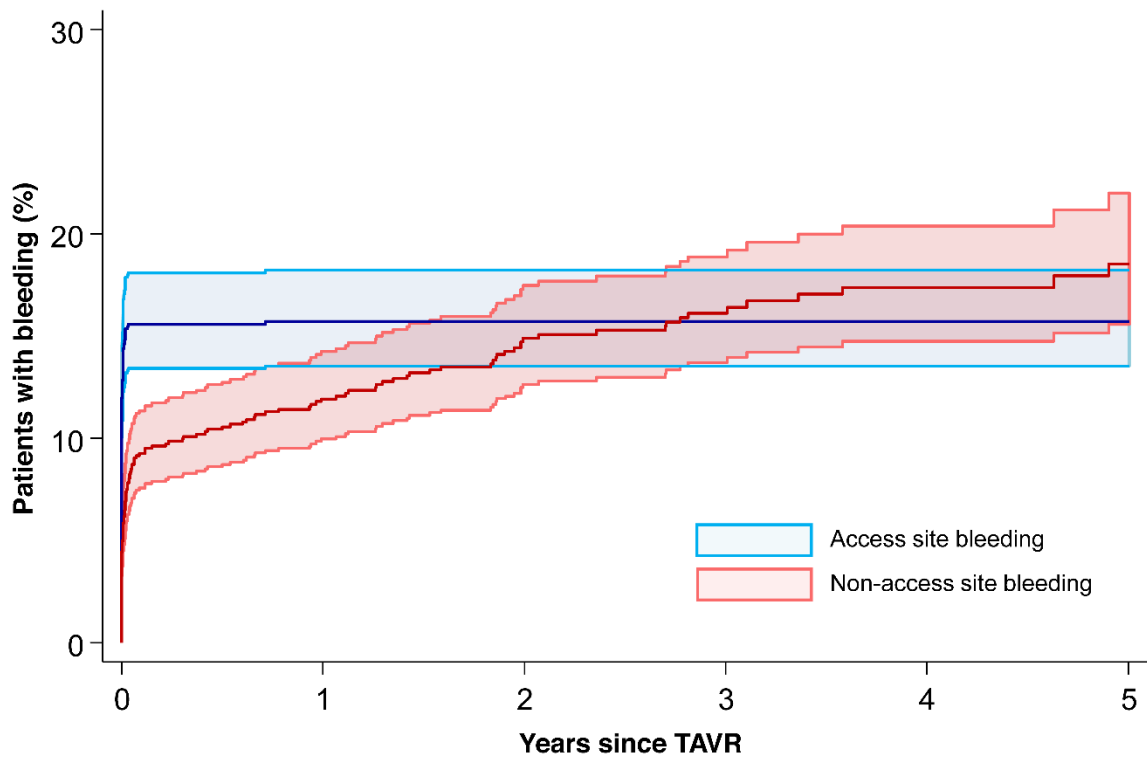


Figure 3

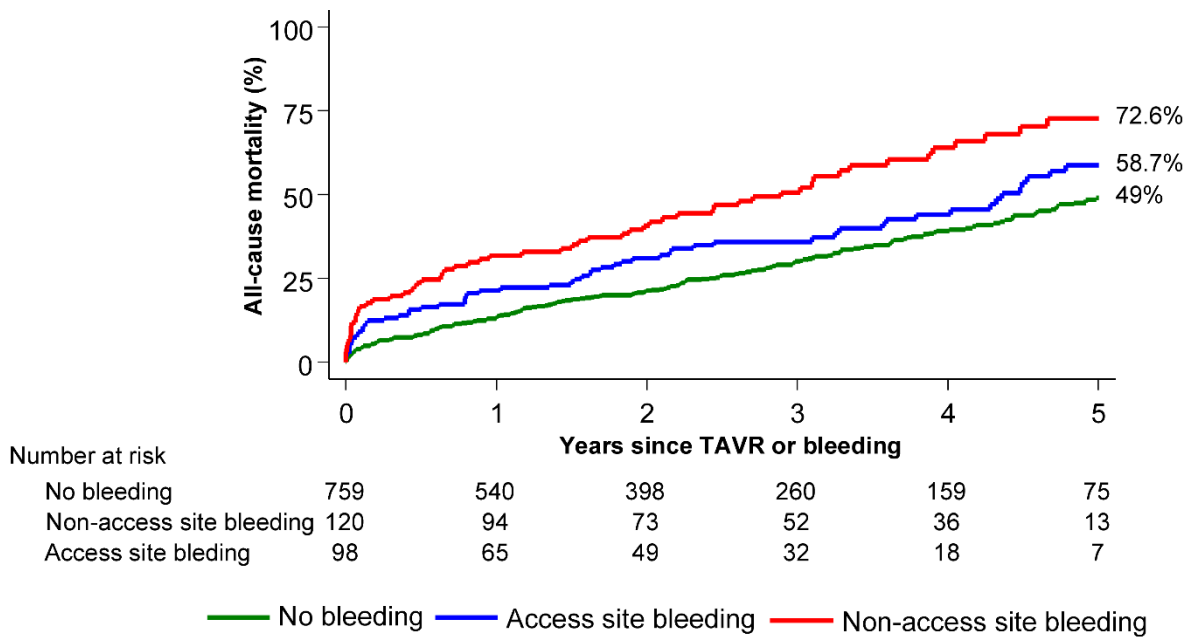


Figure 4

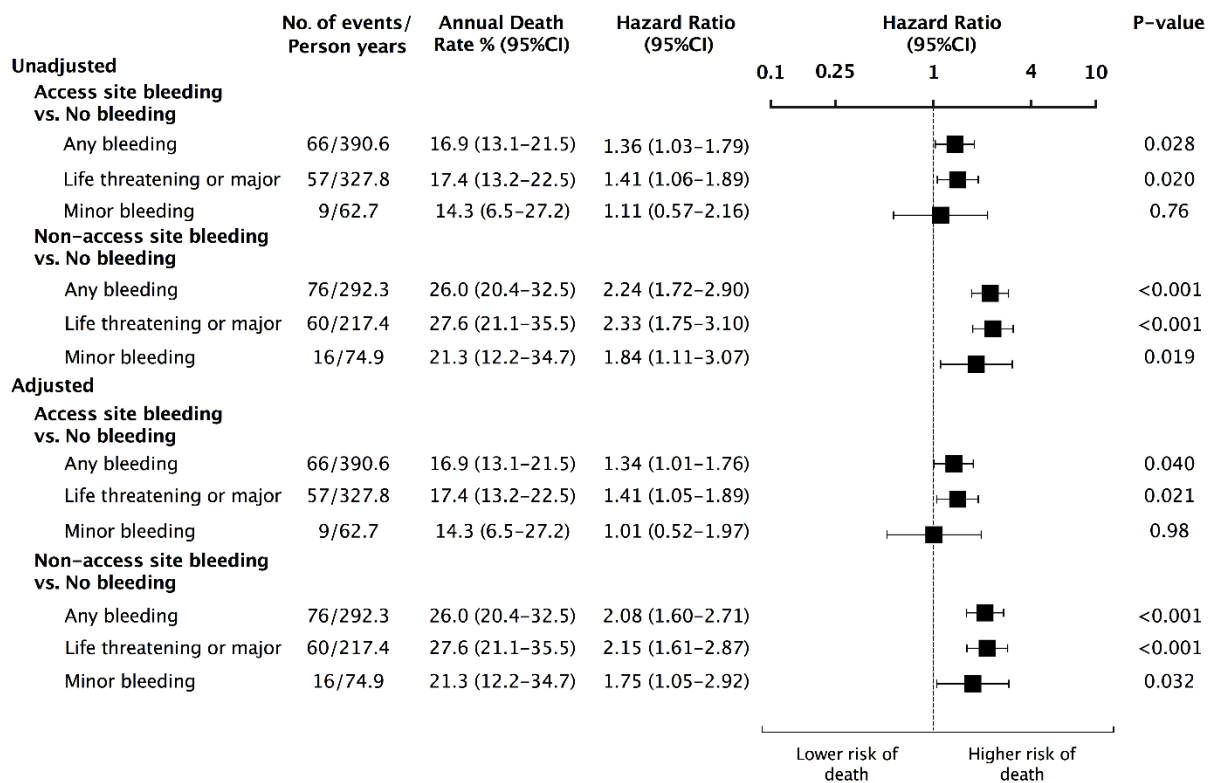
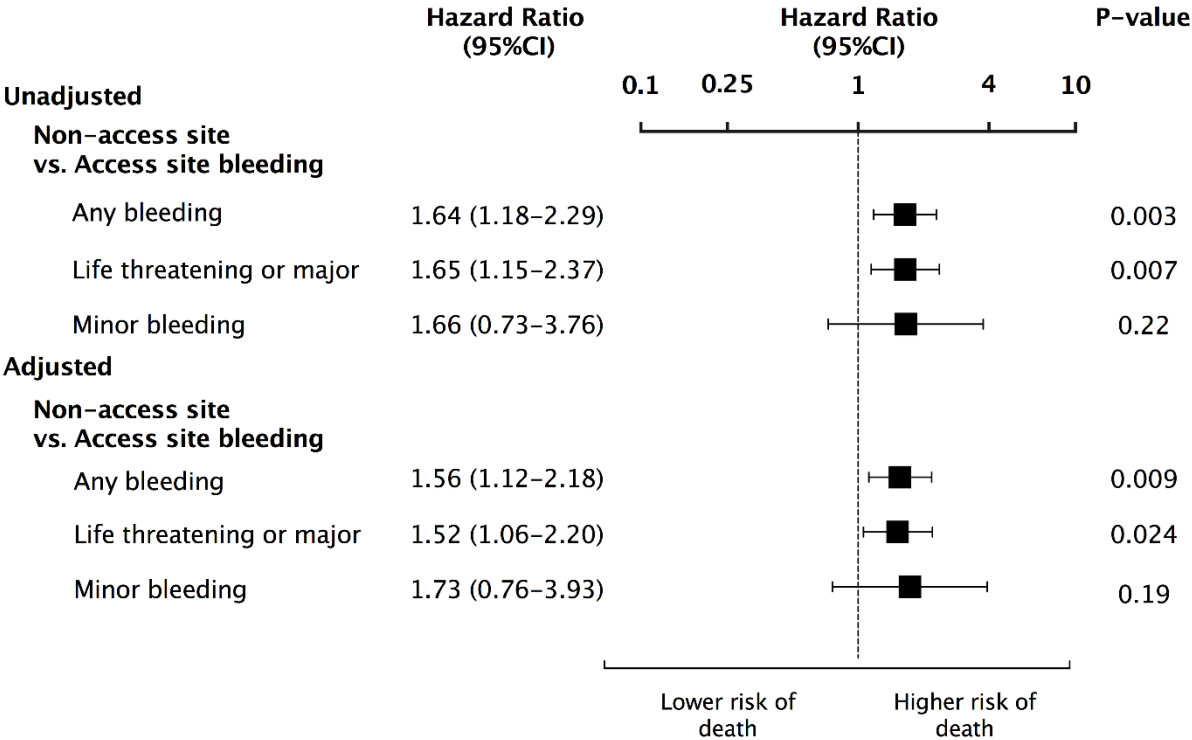


Figure 5



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

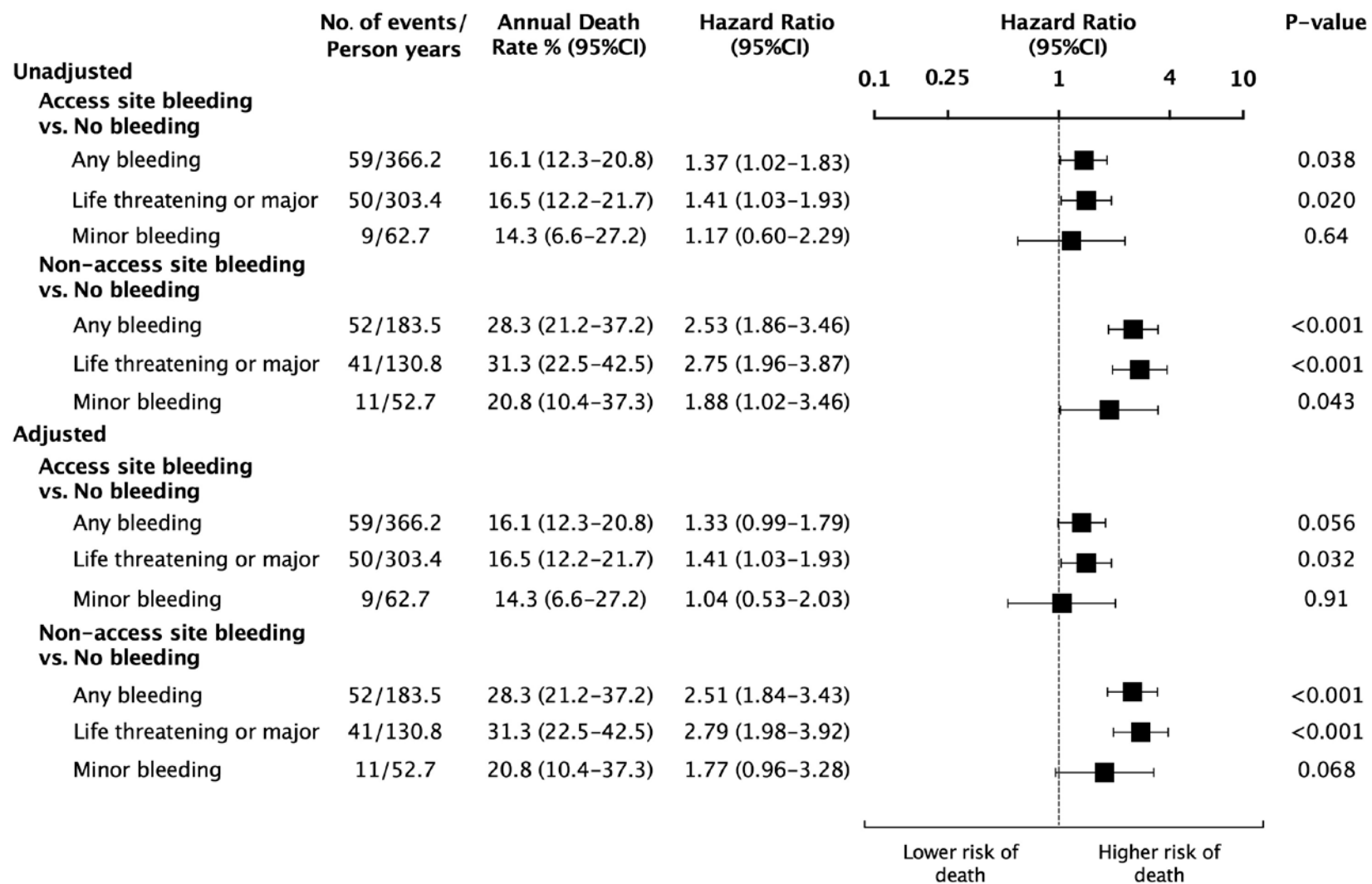
Data show the use of packed red blood cell transfusions according to bleeding location and severity. Analysis includes the first bleeding event at patient-level (each patient counted only once).

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

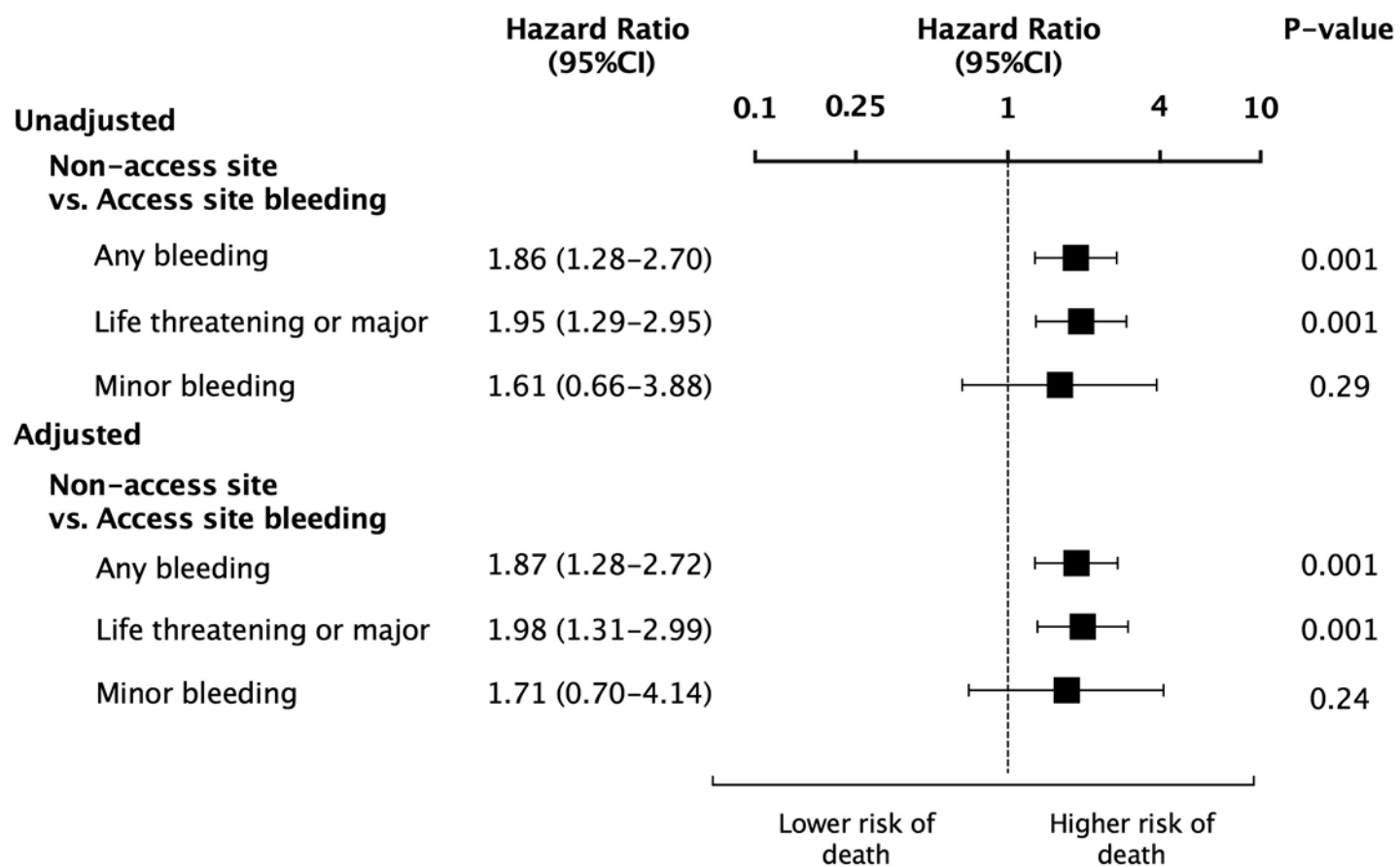
	HR (95% CI)	P-value
Antithrombotic therapy		0.351
Single antiplatelet therapy	1 (reference)	
Dual antiplatelet therapy	0.77 (0.32 - 1.86)	0.56
Oral anticoagulant	1.04 (0.32 - 3.39)	0.946
Oral anticoagulant plus single or dual antiplatelet therapy	1.65 (0.68 - 3.96)	0.267
None	0.71 (0.09 - 5.65)	0.75

Antithrombotic therapy considered as time varying covariate. CI: confidence intervals. HR: hazard ratio.

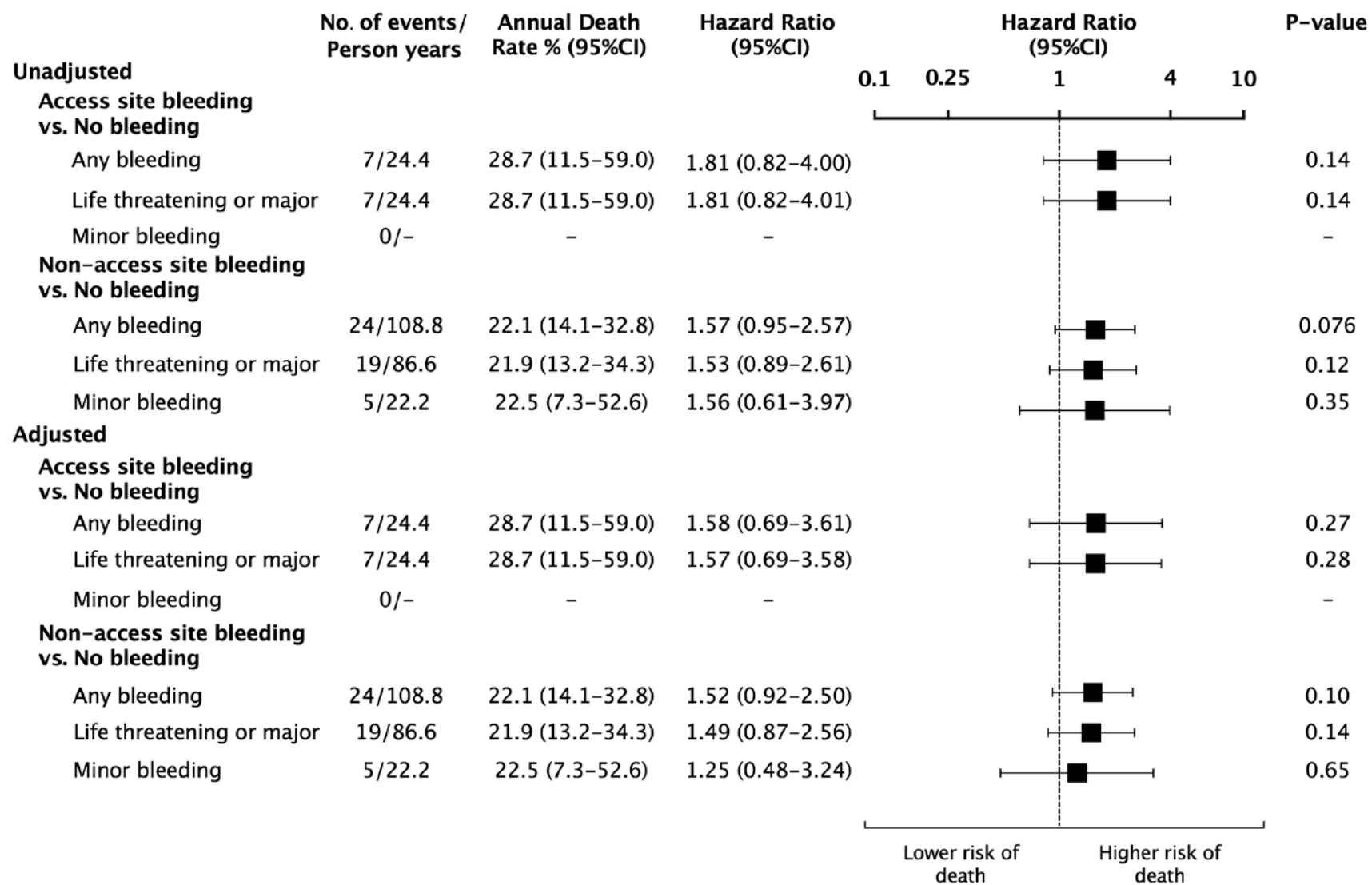
Online Figure 1



Online Figure 2



Online Figure 3



Online Figure 4

