Bleeding Complications After Surgical Aortic Valve Replacement Compared With Transcatheter Aortic Valve Replacement

Insights From the PARTNER I Trial (Placement of Aortic Transcatheter Valve)

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Objectives   This study sought to identify the incidence, predictors, and prognostic impact of bleeding complications (BC) after surgical aortic valve replacement (SAVR) compared with transcatheter aortic valve replacement (TAVR).

Background   Bleeding complications after SAVR and TAVR are frequent and may be associated with an unfavorable prognosis.

Methods   In the randomized controlled PARTNER (Placement of Aortic Transcatheter Valve) I trial, 657 patients from cohort A (operable high risk) were randomly assigned to SAVR or TAVR (transfemoral [TF] if iliofemoral access was suitable or transapical [TA] if not) and received the designated treatment. First-generation Edwards SAPIEN valves and delivery systems (Edwards Lifesciences, Irvine, California) were used for TAVR, through a 22- or 24-F sheath. The 30-day rates of major BC (modified Valve Academic Research Consortium definitions), predictors of BC, and their association with 1-year mortality were assessed.

Results   A total of 71 (22.7%), 27 (11.3%), and 9 (8.8%) patients had major BC within 30 days of the procedure after SAVR, TF-TAVR, and TA-TAVR, respectively (p < 0.0001). SAVR was associated with a significantly higher 30-day rate of transfusion (17.9%) than either TF-TAVR (7.1%) or TA-TAVR (4.8%; p < 0.0001). Independent predictors of major BC were the occurrence of major vascular complications and use of intraprocedural hemodynamic support among TF-TAVR patients, severe procedural complications requiring conversion to open surgery among TA-TAVR patients, and the presence of low hemoglobin at baseline among SAVR patients. Major BC was identified as the strongest independent predictor of 1-year mortality among the full cohort. However, risk-adjusted analyses demonstrated a significant interaction between BC and treatment strategy with respect to mortality, suggesting that BC after SAVR have a greater impact on prognosis than after TAVR.

Conclusions   Among high-risk aortic stenosis patients enrolled in the PARTNER I randomized trial, BC were more common after SAVR than after TAVR and were also associated with a worse long-term prognosis. (THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial; NCT00530894)   (J Am Coll Cardiol 2014;63:1100–9) © 2014 by the American College of Cardiology Foundation

Transcatheter aortic valve replacement (TAVR) has emerged as an alternative option to surgical aortic valve replacement (SAVR) to treat severe, symptomatic aortic stenosis patients (1–6). Despite high rates of periprocedural complications reported in the early literature, there has been continued enthusiasm for this therapy given its less invasive nature and declining rates of complications in real-world experiences of TAVR (7,8). As TAVR technology evolves

toward smaller device sizes, complications such as vascular complications or major bleeding are expected to decrease significantly. SAVR, a well-established treatment for degenerative aortic valve disease, is associated with a non-negligible risk of bleeding and transfusion of blood products (9).

However, there is a paucity of data (observational or randomized) comparing the occurrence of bleeding events among patients undergoing TAVR or SAVR. In this study, we sought to better characterize and compare the incidence, predictors, and impact of bleeding events on long-term prognosis after SAVR and TAVR using data from the multicenter, randomized PARTNER (Placement of Aortic Transcatheter Valve) I trial.

Methods

Study population. The design and initial results of the randomized PARTNER trial (cohort B and cohort A) have been published previously (5,6). Briefly, the PARTNER trial enrolled patients with severe symptomatic aortic stenosis. Patients were divided into 2 cohorts: 1) those who were considered to be candidates for surgery despite being at high surgical risk, as defined by a Society of Thoracic Surgeons (STS) risk score of 10% or higher or by the presence of coexisting conditions that would be associated with a 15% or greater predicted risk of death by 30 days after surgery (cohort A); and 2) those who were not considered to be suitable candidates for surgery because they had coexisting conditions that would be associated with a predicted probability of 50% or more of either death by 30 days after surgery or a serious irreversible condition (cohort B). The current analysis examines patients from cohort A only, in which randomization to SAVR versus TAVR allowed for comparison of similar populations.

Patients enrolled in cohort A were randomly assigned to TAVR with the SAPIEN heart valve system (Edwards Lifesciences, Irvine, California), using a transfemoral (TF) approach if vascular access was suitable or a transapical (TA) approach if not, or to conventional SAVR. The study was approved by the institutional review board at each participating site, and all patients provided written informed consent.

Study endpoints. All BC were defined according to a modified version of the Valve Academic Research Consortium (VARC) criteria as described in the PARTNER trial protocol (5,6,10,11). Bleeding events were classified as either major or minor. Major BC were defined as a clear site of bleeding that met any of the following criteria: 1) bleeding that caused death; 2) bleeding that caused a new hospitalization or prolonged hospitalization ≥24 h due to treatment; 3) bleeding that required pericardiocentesis or open and/or endovascular procedure for repair or hemostasis; 4) bleeding that caused permanent disability (e.g., blindness, paralysis, hearing loss); and 5) bleeding that required transfusion of >3 U of blood within a 24-h period. Minor bleeding had to meet all of the following criteria: 1) bleeding event that did not meet criteria for major bleeding; 2) clear site for bleeding; and 3) loss of hemoglobin >3 g/dl or loss of hematocrit >9%. Adjustment for transfusions was included at 1 g/dl or 3% for each unit of blood.

The 30-day and 1-year frequency of all-cause mortality, cardiovascular mortality, stroke, major vascular complication, myocardial infarction, and acute kidney injury were reported according to initial VARC definitions (10) or according to a modified version of the VARC criteria as described in the PARTNER trial protocol. An independent clinical events committee adjudicated all adverse events. Further extensive review of the source documents was performed by 2 investigators to better characterize the cause of bleeding events (P.G.) and to subcategorize the cause of death (L.G.S.). Independent core laboratories analyzed all echocardiograms and electrocardiograms. All data were sent for analysis to an independent academic biostatistics group.

Statistical analysis. Continuous variables are summarized as mean ± SD or median (quartile [Q1, Q3]), as appropriate, and were compared using the Student *t* test or Mann-Whitney rank-sum test accordingly. Categorical variables were compared by the chi-square or the Fisher exact tests. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data with the use of Kaplan-Meier estimates, and comparisons were performed using the log-rank test.

Multivariable logistic regression was performed to identify independent predictors of 30-day major BC for each treatment strategy ($\alpha = 0.05$). The multivariable model was built by stepwise selection, with candidate variables being selected if of clinical interest and/or satisfying the entry criterion of p < 0.10 in the univariate analysis. Variables included in the model were carefully selected to avoid overfitting. To assess the association between major

Abbreviations and Acronyms

BC = bleeding complications

CI = confidence interval

HR = hazard ratio

RBC = red blood cells

SAVR = surgical aortic valve replacement

TA = transapical

TAVR = transcatheter aortic valve replacement

TF = transfemoral

VARC = Valve Academic Research Consortium

BC and 1-year rate of all-cause mortality, Cox multivariable regression analyses were performed, with variable selection performed as previously described. A second Cox multivariable regression analyses were performed, with moderate to severe paravalvular leak (at discharge or inside 7 days) and stroke forced into the model given their clinical relevance (Online Appendix). A 2-sided alpha level of 0.05 was used for all superiority testing. We also tested for an interaction between the type of procedure (TAVR vs. SAVR and TF-TAVR vs. SAVR). The association between major bleeding and mortality was assessed, and its impact on 1-year mortality was appraised. Hazard ratios (HRs) were adjusted for independent predictors of 1-year mortality identified in the previous multivariable analysis. All statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

Results

Patients and baseline characteristics. Among the 699 patients enrolled in the PARTNER trial cohort A (high risk but operable), 313 patients were actually treated by SAVR, 240 patients were treated by the TAVR-TF approach, and 104 patients were treated by the TAVR-TA approach, for a total of 657 patients included in the current analysis. Major BC were significantly more frequent in the SAVR group (71 of 313 [22.7%]) compared with patients in the TAVR-TF group (27 of 240 [11.3%]) and the TAVR-TA group (9 of 104 [8.8%]; p < 0.0001) (Fig. 1).

Baseline and procedural characteristics of patients stratified according to the occurrence of major BC within 30 days and by treatment strategy are shown in Tables 1 and 2. Patients with major BC more frequently had diabetes requiring insulin (TF-TAVR), had higher international normalized ratio at baseline (TAVR-TA and SAVR), had

lower hemoglobin at baseline (SAVR), and were less likely to have significant coronary disease at baseline (TAVR-TA). During the procedure, major BC were associated with higher rates of migration or embolization of the prosthesis, use of hemodynamic support devices, conversion to open heart surgery, and use of higher doses of heparin (TAVR-TF and TAVR-TA), resulting in longer procedure times (TAVR-TF). Among TAVR-TA patients, failure to successfully implant a transcatheter heart valve was also associated with major BC. Smaller valve size, longer sternal incisions, and longer procedural times were characteristics associated with major BC among SAVR-treated patients. Interestingly, post-procedure length of stay was not prolonged in association with major BC in either of the TAVR groups, but was significantly prolonged in the SAVR group (11 days vs. 8 days; p = 0.005). Specific causes of major BC stratified by treatment strategy are shown in Online Table 1.

Clinical outcomes. At 30 days, SAVR was associated with a significantly higher rate of transfusions compared with either TAVR-TF or -TA (Fig. 2). Among patients receiving transfusions during the index hospitalization, the proportion of patients receiving ≥4 transfusions was 69.6% in the SAVR group (median: 7.0 [1st, 3rd quartiles: 3.0, 9.0]), 66.7% in the TA-TAVR group (median: 4.0 [1st, 3rd quartiles: 1.0, 7.0]), and 40.5% in the TF-TAVR group (median: 3.5 [1st, 3rd quartiles: 2.0, 5.0]; p for trend = 0.0002).

Clinical outcomes of patients stratified by major BC versus no major BC for each treatment strategy are shown in Table 3. The occurrence of major BC after TAVR-TF was associated with significantly higher 30-day rates of major vascular complications and with a trend toward a higher rate of renal failure requiring dialysis, but no significant increase in all-cause or cardiovascular mortality. The occurrence of major BC after TAVR-TA was associated with a non-significant trend of higher 30-day rates of major vascular complications and cardiovascular mortality. Within the SAVR group, the occurrence of major BC was associated with significantly higher 30-day rates of acute kidney failure requiring dialysis and major vascular complications (such as aortic perforation and aortic dissection), with significantly higher rates of 30-day and 1-year all-cause and cardiac mortality.

Impact of major bleeding on 1-year mortality according to procedure. The impact of 30-day major BC on 1-year mortality is shown in Figure 3. The occurrence of major BC compared with no major BC was associated with an increased rate of 1-year mortality among the total population (Fig. 3A). When stratified by treatment group, major BC were associated with an increased 1-year mortality rate among SAVR-treated patients (Fig. 3B). However, among patients treated by TAVR, there was no difference in 1-year mortality between patients who experienced major BC compared with no major BC regardless of the access site (Figs. 3C to 3E). Specific causes of death among patients with major BC experiencing death, stratified by treatment strategy, are shown as supplementary data (Online Table 2).

p (all) < 0.0001
p (TF-TAVR vs. SAVR) = 0.0004
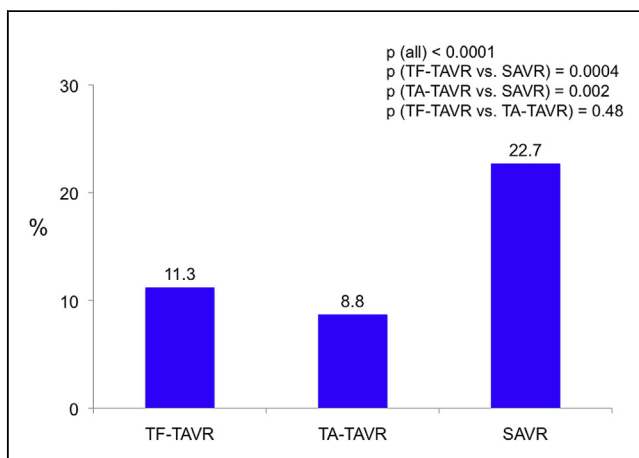p (TA-TAVR vs. SAVR) = 0.002
p (TF-TAVR vs. TA-TAVR) = 0.48

Figure 1   30-Day Major Bleeding Rates According to Treatment Strategy

Major bleeding event rates at 30 days were significantly more frequent with surgical aortic valve replacement (SAVR) than with transfemoral (TF) or transapical (TA) transcatheter aortic valve replacement (TAVR).

| **Table 1** | **Baseline Characteristics of Patients Undergoing TAVR or SAVR According to Occurrence of Major Bleeding Inside 30 Days** | | | | | | | | |

| | TAVR-TF | | | TAVR-TA | | | SAVR | | |
Variables	Major Bleeding (n = 27)	No Major Bleeding (n = 213)	p Value	Major Bleeding (n = 9)	No Major Bleeding (n = 95)	p Value	Major Bleeding (n = 71)	No Major Bleeding (n = 242)	p Value
Age, yrs	83.60 ± 6.62	83.93 ± 6.80	0.84	84.3 ± 6.09	82.8 ± 7.08	0.49	83.7 ± 6.88	84.6 ± 6.17	0.48
Female	12/27 (44.4)	83/213 (39.0)	0.58	4/9 (44.4)	47/95 (49.5)	1.00	30/71 (42.3)	104/242 (43.0)	0.91
BMI, kg/m^2	26.92 ± 4.87	27.56 ± 7.09	0.81	29.63 ± 10.54	27.14 ± 7.12	0.58	26.05 ± 5.15	27.01 ± 5.87	0.21
STS risk score	12.19 ± 3.95	11.79 ± 3.12	0.39	10.9 ± 1.56	11.8 ± 3.77	0.91	11.3 ± 3.21	11.8 ± 3.41	0.07
Logistic EuroSCORE	25.12 ± 16.02	29.65 ± 16.75	0.12	25.88 ± 16.02	30.27 ± 16.08	0.35	29.97 ± 15.75	29.00 ± 14.97	0.59
Diabetes mellitus	13/27 (48.1)	90/213 (42.3)	0.56	3/9 (33.3)	39/95 (41.1)	0.74	29/71 (40.8)	101/242 (41.7)	0.89
Insulin	4/13 (30.8)	7/90 (7.8)	0.03	0/3 (0.0)	0/39 (0.0)	—	1/29 (3.4)	10/101 (9.9)	0.45
CHF	26/27 (96.3)	208/213 (97.7)	0.52	9/9 (100.0)	94/95 (98.9)	1.00	71/71 (100.0)	237/241 (98.3)	0.58
NYHA functional class III	11/27 (40.7)	91/213 (42.7)	0.84	4/9 (44.4)	38/95 (40.0)	1.00	32/71 (45.1)	102/242 (42.1)	0.66
NYHA functional class IV	13/27 (48.1)	113/213 (53.1)	0.63	3/9 (33.3)	51/95 (53.7)	0.31	36/71 (50.7)	127/242 (52.5)	0.79
CAD	19/27 (70.4)	162/213 (76.1)	0.52	4/9 (44.4)	73/95 (76.8)	0.05	58/71 (81.7)	183/242 (75.6)	0.29
Prior PCI	8/26 (30.8)	74/212 (34.9)	0.68	2/9 (22.2)	31/95 (32.6)	0.72	27/71 (38.0)	74/241 (30.7)	0.25
Prior CABG	9/27 (33.3)	88/213 (41.3)	0.43	3/9 (33.3)	48/95 (50.5)	0.49	36/71 (50.7)	104/242 (43.0)	0.25
CVD	8/26 (30.8)	48/201 (23.9)	0.44	2/9 (22.2)	38/87 (43.7)	0.30	18/70 (25.7)	61/222 (27.5)	0.77
PVD	13/27 (48.1)	70/211 (33.2)	0.12	6/9 (66.7)	59/94 (62.8)	1.00	28/71 (39.4)	104/236 (44.1)	0.49
Pulmonary HTN	12/27 (44.4)	105/213 (49.3)	0.63	7/9 (77.8)	48/95 (50.5)	0.17	29/71 (40.8)	121/242 (50.0)	0.17
Permanent pacemaker	6/27 (22.2)	42/213 (19.7)	0.76	1/9 (11.1)	20/95 (21.1)	0.68	19/71 (26.8)	51/242 (21.1)	0.31
COPD	12/27 (44.4)	92/213 (43.2)	0.90	2/5 (40.0)	42/59 (71.2)	0.17	27/47 (57.4)	106/156 (67.9)	0.18
Oxygen dependent	2/27 (7.4)	19/213 (8.9)	1.00	0/2 (0.0)	7/42 (16.7)	1.00	10/27 (37.0)	21/105 (20.0)	0.06
LVEF, %	55.57 ± 15.24	50.47 ± 14.61	0.20	55.53 ± 9.41	53.07 ± 13.40	0.67	53.68 ± 11.28	53.74 ± 12.83	0.89
AV area, cm^2	0.72 ± 0.20	0.65 ± 0.19	0.09	0.71 ± 0.23	0.65 ± 0.20	0.61	0.63 ± 0.19	0.64 ± 0.19	0.37
Mean AV gradient, mm Hg	44.59 ± 14.55	42.92 ± 14.83	0.72	38.66 ± 6.99	41.89 ± 14.29	0.57	42.60 ± 15.39	43.65 ± 14.00	0.48
WBC ×10^3/μl	8.54 ± 4.37	10.61 ± 53.14	0.16	6.81 ± 1.92	7.42 ± 2.28	0.61	7.23 ± 2.17	7.19 ± 2.41	0.62
Hemoglobin, g/dl	11.37 ± 1.25	11.76 ± 2.08	0.26	11.39 ± 0.68	11.87 ± 1.74	0.51	11.38 ± 1.43	11.94 ± 1.78	0.01
Platelets, cells/mm^3	217.0 (147.0–242.0)	201.5 (156.5–283.0)	0.85	207.0 (203.0–244.0)	198.0 (163.0–258.0)	0.23	199.5 (161.0–260.0)	210.00 (159.0–292.0)	0.14
INR	1.28 ± 0.69	1.25 ± 0.79	0.45	1.40 ± 0.44	1.14 ± 0.25	0.01	1.27 ± 1.25	1.22 ± 0.67	0.03
Cr clearance, ml/min	0.88 ± 0.33	0.80 ± 0.40	0.28	0.78 ± 0.44	0.81 ± 0.40	0.82	0.83 ± 0.38	0.81 ± 0.39	0.75

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

AV = aortic valve; BMI = body mass index; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CHF = cardiac heart failure; COPD = chronic obstructive pulmonary disease; Cr = creatinine; CVD = cerebrovascular disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HTN = hypertension; INR = international normalized ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TA = transapical; TAVR = transcatheter aortic valve replacement; TF = transfemoral; WBC = white blood cells.

Table 2 Procedural Characteristics of Patients According to Occurrence of Major Bleeding Inside 30 Days

Variables	TAVR-TF			TAVR-TA		
	Major Bleeding (n = 27)	No Major Bleeding (n = 213)	p Value	Major Bleeding (n = 9)	No Major Bleeding (n = 95)	p Value
Valve size, mm						
23	12/27 (44.4)	97/206 (47.1)	0.80	5/9 (55.6)	47/92 (51.1)	1.00
26	15/27 (55.6)	109/206 (52.9)	0.80	4/9 (44.4)	45/92 (48.9)	1.00
Study valve successfully implanted	26/27 (96.3)	202/206 (98.1)	0.46	6/8 (75.0)	90/92 (97.8)	0.03
Migration or embolization	3/23 (13.0)	1/172 (0.6)	0.005	2/5 (40.0)	1/74 (1.4)	0.009
Hemodynamic support, CPB or IABP	5/27 (18.5)	3/207 (1.4)	0.0006	4/9 (44.4)	9/93 (9.7)	0.01
Conversion to open heart surgery	4/27 (14.8)	2/207 (1.0)	0.002	2/9 (22.2)	1/93 (1.1)	0.02
Artery closure						
Surgical cutdown	18/27 (66.7)	150/207 (72.5)	0.53	—	—	—
Closure device	10/27 (37.0)	55/207 (26.6)	0.25	—	—	—
Total procedure time, min	143.00 (111.00–219.00)	114.00 (90.00–154.00)	0.02	122.00 (60.00–267.00)	95.00 (68.00–120.00)	0.42
Heparin administrated, U	9,000.00 (6,500.00–10,000.00)	7,000.00 (5,000.00–10,000.00)	0.04	10,000.0 (10,000.0–30,000.0)	8,000.0 (5,000.0–10,000.0)	0.005
Days in hospital post-procedure	6.00 (4.00–8.00)	5.00 (4.00–7.00)	0.34	7.50 (7.00–8.00)	8.00 (7.00–9.00)	0.80

SAVR Variables	Major Bleeding (n = 71)	No Major Bleeding (n = 242)	p Value
Valve size, mm	21.00 (21.00–23.00)	23.00 (21.00–23.00)	0.04
19	12/71 (16.9)	25/241 (10.4)	0.13
21	30/71 (42.3)	94/241 (39.0)	0.62
23	23/71 (32.4)	86/241 (35.7)	0.61
25	5/71 (7.0)	32/241 (13.3)	0.15
27	0/71 (0.0)	3/241 (1.2)	1.00
Other	1/71 (1.4)	1/241 (0.4)	0.40
Total procedure time, min	351.5 (265.0–461.0)	311.0 (260.0–364.0)	0.01
Total aortic cross-clamp time, min	66.0 (54.0–87.0)	67.0 (57.0–82.0)	0.97
Pump time, min	97.5 (81.5–145.0)	94.0 (79.0–117.0)	0.12
Length of skin incision, mm	19.0 (12.0–24.0)	14.5 (10.0–21.0)	0.04
Heparin administered, U	25,000.0 (20,000.0–32,000.0)	29,000.0 (21,000.0–35,000.0)	0.34
Days in hospital post-procedure	11.0 (8.5–16.5)	8.0 (7.0–10.0)	0.005

Values are n/total N (%) median (interquartile range).

CPB = cardiopulmonary bypass; IABP = intra-aortic balloon pump; other abbreviations as in Table 1.

p (all) < 0.0001
p (TF-TAVR vs. SAVR) = 0.0002
p (TA-TAVR vs. SAVR) = 0.001
p (TF-TAVR vs. TA-TAVR) = 0.44

Figure 2   **Patients Receiving at Least 1 Transfusion Within 30 Days Per Treatment Strategy**

Transfusion rates at 30 days were significantly higher with SAVR than with TF- or TA-TAVR. Abbreviations as in Figure 1.
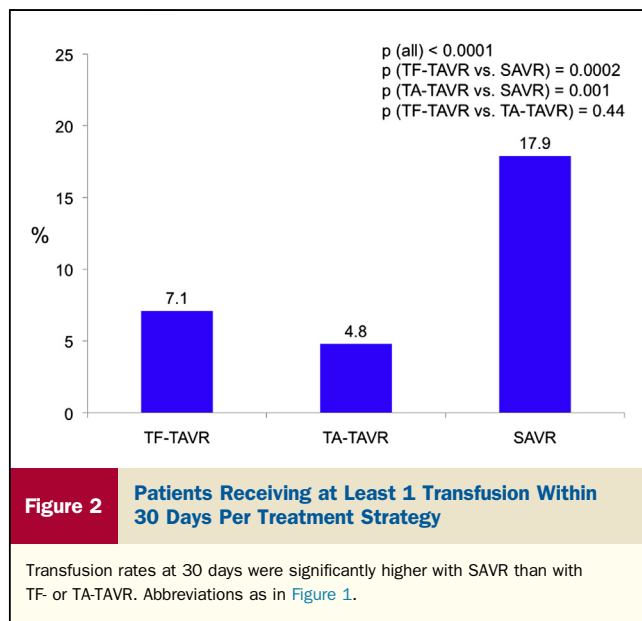
Predictors of bleeding and mortality. Variables associated with major BC are summarized in Table 4. After multivariable analysis, major vascular complications and severe intraprocedural complications leading to the use of hemodynamic support were identified as the strongest independent predictors of major BC in the TAVR-TF group. Similarly, the need for conversion to open surgery was the most significant predictor of bleeding events in the TA-TAVR group. For patients who underwent SAVR, low baseline hemoglobin was the only independent predictor of major BC within 30 days.

Independent predictors of 1-year mortality among the full cohort are summarized in Table 5. Among pre-procedure variables, higher Society of Thoracic Surgeons risk score, lower body mass index, oxygen-dependent chronic obstructive pulmonary disease, and renal dysfunction emerged as independent predictors of mortality. After adjustment for these factors, major bleeding within 30 days was strongly and independently associated with mortality (adjusted HR: 2.49; 95% confidence interval [CI]: 1.85 to 3.37; $p < 0.001$). A second Cox regression analysis was performed with moderate to severe PVL and stroke forced into the model, with major bleeding remaining the strongest predictor of 1-year mortality (adjusted HR: 2.36; 95% CI: 1.68 to 3.31; $p < 0.001$) (Online Table 3). Interaction testing demonstrated that this association differed significantly according to the type of procedure (TAVR vs. SAVR, p value for interaction = 0.046). For patients treated with SAVR, major BC tended to be associated with increased 1-year mortality (adjusted HR: 1.95; 95% CI: 0.95 to 4.01; $p = 0.07$), whereas no such association was apparent for patients treated by TAVR (adjusted HR: 0.86; 95% CI: 0.60 to 1.25; $p = 0.43$) (Fig. 4A). Similarly, interaction testing restricted to TF-TAVR population showed similar results, with major BC after SAVR being associated with increased 1-year

mortality, whereas major BC after TF-TAVR were not (Fig. 4B).

Discussion

The current report is the largest randomized study to specifically evaluate and compare the incidence, predictors, and impact of major BC on long-term prognosis after different treatment strategies for patients with severe aortic stenosis. The main results of the present study are as follows: 1) among a population of high-risk but operable patients, BC and transfusions were more frequent among SAVR-treated patients than among TAVR-treated patients using first-generation devices; 2) the occurrence of major BC after TAVR was associated with vascular complications and important procedural complications, whereas baseline hemoglobin was the main predictor of BC after SAVR; and 3) the impact of major BC on 1-year mortality differed according to treatment strategy, with SAVR being associated with more severe and lethal bleeding than TAVR.

Prior studies have reported high rates of bleeding after TAVR (12,13). Life-threatening and major bleeding after TAVR, defined by VARC criteria (10,11), occurred in approximately 15% and 20% of TAVR procedures, respectively, in the early literature (12). Tchetche et al. (13) recently reported similar rates (13.9% and 20.9%, respectively), with 38.9% of patients undergoing TAVR receiving at least 1 transfusion. Conversely, Tamburino et al. (14) reported lower bleeding event rates, with 30-day rates of life-threatening bleeding of 5.5% and 9.0% after TAVR and SAVR, respectively. More recently, Toggweiler et al. (7) showed that with careful patient selection and advanced interventional techniques, marked reductions in bleeding (and vascular) complications could be achieved, with rates as low as 1% at 30 days after TF-TAVR. However, the heterogeneity of these populations, the lack of independent adjudication of events, and the absence of direct comparison with a surgical cohort of similar risk represent important limitations to these reports.

The current report, derived from the randomized PARTNER trial experience, shows that rates of major BC and transfusions were 2 to 3 times more frequent in the SAVR group than in the TAVR group. This finding is not particularly surprising, given the more invasive nature of surgical AVR as well as the well-documented coagulopathy that occurs after cardiopulmonary bypass. Conversely, the apparent differential prognostic impact of major BC among patients treated with TAVR or SAVR was unexpected. One possible explanation for this finding is that BC after SAVR appear to be more severe, leading to transfusion of a higher number of red blood cell (RBC) units, acute renal failure needing dialysis, reoperation, and consequently, a higher death rate. Taking into consideration that the PARTNER trial represented the earliest TAVR experience of all enrolling centers, that it used the larger first-generation TAVR delivery system (22- and 24-F), and that SAVR

Table 3	30-Day and 1-Year Adverse Event Rates According to Occurrence of Major Bleeding Inside 30 Days								
	TAVR-TF			**TAVR-TA**			**SAVR**		
Variables	**Major Bleeding (n = 27)**	**No Major Bleeding (n = 213)**	**p Value**	**Major Bleeding (n = 9)**	**No Major Bleeding (n = 95)**	**p Value**	**Major Bleeding (n = 71)**	**No Major Bleeding (n = 242)**	**p Value**
30-day events									
Death									
From any cause	3.7 (1)	3.8 (8)	1.00	11.1 (1)	8.4 (8)	0.76	21.2 (15)	4.1 (10)	<0.0001
From CV cause	3.7 (1)	3.3 (7)	0.90	11.1 (1)	4.2 (4)	0.35	7.5 (5)	1.7 (4)	0.01
Repeat hospitalization	0.0 (0)	6.2 (13)	0.20	0.0 (0)	5.5 (5)	0.50	6.7 (4)	6.0 (14)	0.88
Stroke or TIA	3.7 (1)	4.7 (10)	0.82	0.0 (0)	7.6 (7)	0.43	4.4 (3)	2.1 (5)	0.28
TIA	3.7 (1)	1.0 (2)	0.22	0.0 (0)	0.0 (0)	—	0.0 (0)	0.4 (1)	0.60
Stroke	0.0 (0)	3.8 (8)	0.31	0.0 (0)	7.6 (7)	0.43	4.4 (3)	2.1 (5)	0.28
Major	0.0 (0)	2.8 (6)	0.38	0.0 (0)	6.5 (6)	0.46	4.4 (3)	1.7 (4)	0.17
Minor	0.0 (0)	0.9 (2)	0.61	0.0 (0)	1.1 (1)	0.77	0.0 (0)	0.4 (1)	0.60
Myocardial infarction	0.0 (0)	0.0 (0)	—	0.0 (0)	0.0 (0)	—	1.4 (1)	0.0 (0)	0.06
Vascular complications	67.4 (18)	18.3 (39)	<0.0001	11.1 (1)	4.2 (4)	0.34	11.3 (8)	2.5 (6)	0.002
Major	67.4 (18)	7.0 (15)	<0.0001	11.1 (1)	3.2 (3)	0.22	11.3 (8)	1.7 (4)	0.0002
Renal failure, dialysis required	7.6 (2)	2.8 (6)	0.21	0.0 (0)	5.5 (5)	0.50	8.9 (6)	3.3 (8)	0.05
Dialysis >30 days	0.0 (0)	0.5 (1)	0.72	0.0 (0)	1.1 (1)	0.77	1.5 (1)	2.1 (5)	0.79
PVL moderate-severe*	8.7 (2)	8.1 (16)	1.00	0.0 (0)	5.7 (5)	1.00	0.0 (0)	0.5 (1)	1.00
1-year events									
Death									
From any cause	22.4 (6)	21.2 (45)	0.81	44.4 (4)	27.6 (26)	0.27	44.2 (31)	19.7 (47)	<0.0001
From CV cause	12.1 (3)	8.0 (16)	0.48	11.1 (1)	8.9 (8)	0.76	12.7 (8)	6.2 (14)	0.04
Repeat hospitalization	23.1 (5)	17.0 (34)	0.78	25.0 (2)	15.8 (13)	0.48	17.7 (9)	16.4 (36)	0.88
Stroke or TIA	3.7 (1)	6.4 (13)	0.63	0.0 (0)	15.7 (13)	0.28	4.4 (3)	4.1 (9)	0.66
TIA	3.7 (1)	2.1 (4)	0.51	0.0 (0)	4.0 (3)	0.62	0.0 (0)	1.9 (4)	0.34
Stroke	0.0 (0)	4.3 (9)	0.28	0.0 (0)	11.7 (10)	0.34	4.4 (3)	2.6 (6)	0.36
Major	0.0 (0)	3.4 (7)	0.35	0.0 (0)	10.6 (9)	0.37	4.4 (3)	2.2 (5)	0.25
Minor	0.0 (0)	0.9 (2)	0.61	0.0 (0)	1.1 (1)	0.77	0.0 (0)	0.4 (1)	0.60
Myocardial infarction	0.0 (0)	0.0 (0)	—	0.0 (0)	0.0 (0)	—	1.4 (1)	0.0 (0)	0.06

Values are % (n). *At discharge or inside 7 days of the procedure as evaluated by echocardiogram.

CV = cardiovascular; PVL = paravalvular leak; TIA = transient ischemic attack; other abbreviations as in Table 1.

was performed by the most experienced and high-volume surgeons, upcoming studies using smaller TAVR devices, more experienced operators, and lower-risk populations (8) may potentially increase the magnitude of benefit of TAVR over SAVR regarding rates of transfusion and bleeding complications.

In the current report, the occurrence of major BC did not seem to impact long-term prognosis in patients treated by TF- or TA-TAVR. Conversely, the 30-day mortality rate among patients undergoing SAVR and experiencing major bleeding was high compared with TA- or TF-TAVR (21.2%, 11.1%, and 3.7%, respectively), potentially underlining the severity of the initial bleeding events in the surgical cohort.

Predictors of BC and RBC transfusions have been identified by several groups. Among them, vascular complications, major intraprocedural complications, female sex, and baseline anemia have been most frequently reported (13,15,16). Not surprisingly, in our cohort, major vascular complications were present in approximately two-thirds of patients who had BC in the TF-TAVR population, but in a lower proportion of patients who underwent TA-TAVR

or SAVR. These results have been previously demonstrated by several investigators who have reported that the need for transfusion after major vascular complications, especially in the early TAVR experience, varied between 40.7% and 78.0% (13,17–19). Catastrophic events, such as migration and embolization of prosthesis, requirement of hemodynamic/cardiopulmonary support, and the need to convert to open surgery also explained some of the major bleeding events after TAVR. However, the occurrence of such dramatic complications is expected to decrease with smaller devices and more experienced operators. Reasons for transfusion after SAVR remain difficult to define. The only identifiable predictor of major bleeding after SAVR in the current report was the presence of baseline anemia. Paired with procedural blood loss and compensated by equivalent blood transfusion, these 2 factors potentially remain the main determinant of major bleeding events after SAVR. Strategies to better capture, characterize, and prevent these blood losses/transfusions after SAVR are warranted.

Several previous studies have established the deleterious effect of RBC transfusions after a cardiovascular procedure (9,15,20). Murphy et al. (9) reported that the short- and
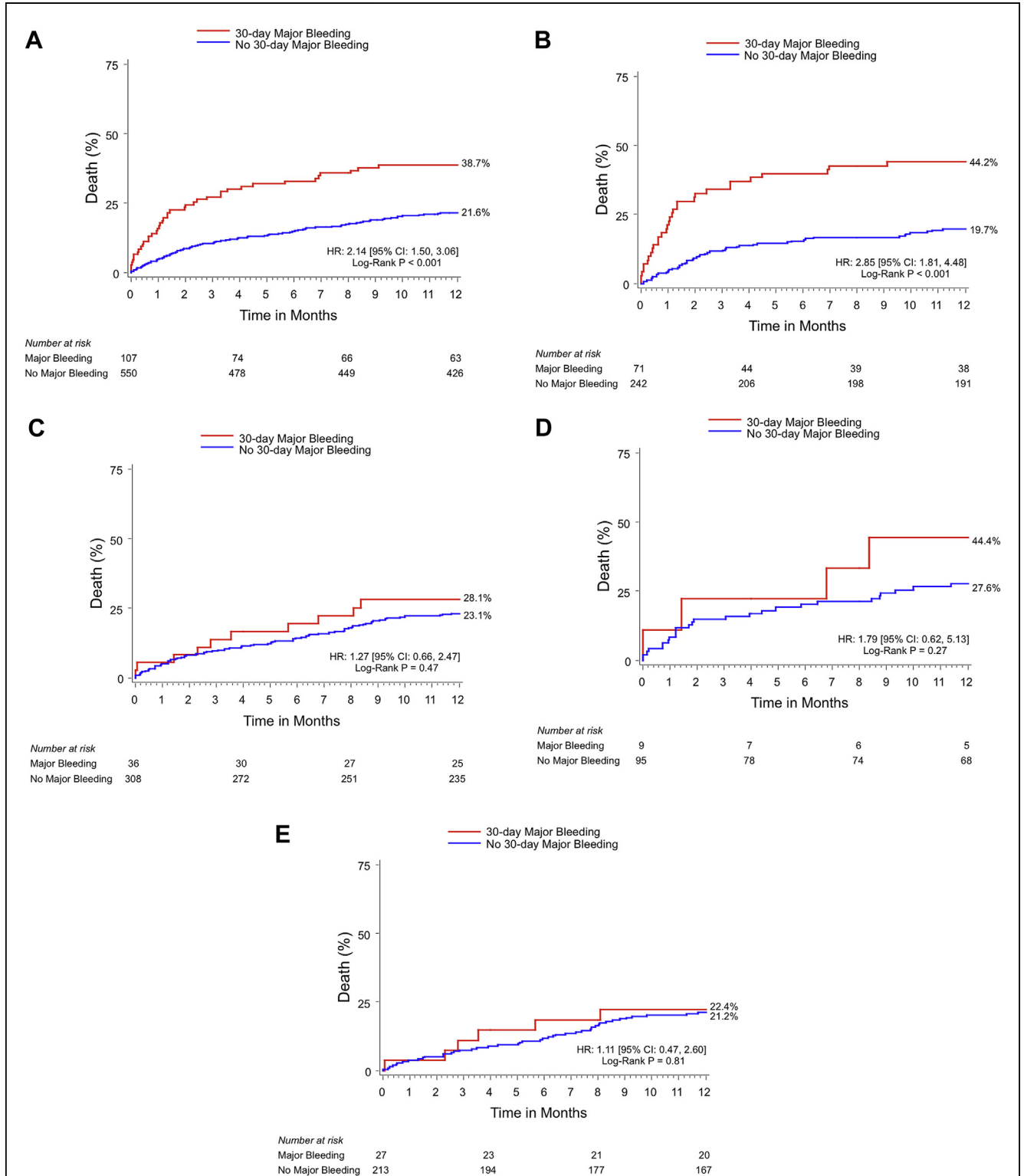
Figure 3 **Kaplan-Meier Curves Showing Cumulative Death Rates Through 1 Year**

Comparison of the cumulative death rate through 1 year between patients with 30-day major bleeding **(red lines)** and with no 30-day major bleeding **(blue lines)**, according to procedure performed: **(A)** among the complete population; **(B)** among SAVR patients; **(C)** among both TF- and TA-TAVR patients; **(D)** among TA-TAVR patients; and **(E)** among TF-TAVR patients. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

Table 4	Independent Clinical Predictors of Major Bleeding Events According to Treatment Strategy	
Predictors	**Adjusted HR (95% CI)**	**p Value**
TAVR-TF		
Major vascular complications	11.64 (6.83–19.87)	<0.0001
Use of intraprocedural hemodynamic support	2.56 (1.18–5.56)	0.02
TAVR-TA		
Conversion to open surgery	58.49 (6.82–502.0)	0.0002
Coronary disease at baseline	0.14 (0.03–0.73)	0.02
SAVR		
Baseline hemoglobin	0.84 (0.72–0.98)	0.03

Candidate variables were female sex, insulin-dependent diabetes mellitus, baseline hemoglobin, use of intraprocedural hemodynamic support, major vascular complications, migration or embolization of prosthesis, and conversion to open surgery for the TAVR-TF model; conversion to open surgery, migration or embolization of prosthesis, and coronary disease at baseline for the TAVR-TA model; and female sex, body mass index, baseline hemoglobin, international normalized ratio at baseline, valve size, and oxygen-dependent chronic obstructive pulmonary disease for the SAVR model.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

long-term risk of infection and ischemic events, length of stay, and hospital cost increased proportionately with the number of transfusions received after heart surgery. In the current report, transfusion of RBC units were almost 4 and 3 times more frequent among SAVR patients compared with operable TA- and TF-TAVR patients. These findings are in line with a recently published report showing that SAVR patients received a mean of 2.5 RBC units after surgery compared with 0.5 after TAVR. Approximately 30% of patients in the SAVR arm received ≥4 RBC units compared with <4% for TAVR patients (21). Of note, the significantly higher number of transfusions evidenced in our report for both the TAVR and SAVR cohort may be explained not only by the higher-risk population treated, but also by a more assiduous capture and reporting of all adverse events in the context of a well-conducted randomized trial.

A recent study, published by Nuis et al. (15), demonstrated the relationship between RBC units transfused and the occurrence of acute kidney injury after TAVR. These findings are consistent with our observation of higher rates of acute renal failure requiring dialysis after SAVR compared with after TAVR. These reports, as well as our study, underline the close relationship among the severity of the

Figure 4 Adjusted Interaction Between Treatment Strategy and 30-Day Major Bleeding and Impact on 1-Year Mortality

(A) Adjusted interaction between TAVR (TA and TF combined), versus SAVR, and major bleeding at 30 days and its impact on 1-year mortality. **(B)** Adjusted interaction between TF-TAVR versus SAVR and major bleeding at 30 days and its impact on 1-year mortality. A significant interaction exists between the type of treatment (TAVR or TF-TAVR vs. SAVR) and bleeding events at 30 days, and modulated the impact of major bleeding on 1-year mortality. Bleeding events occurring in the TAVR group, and specifically in the TF-TAVR group, have a significantly less important impact on 1-year mortality compared with bleeding events occurring among SAVR patients, suggesting that bleeding events were less severe and potentially more easily managed among TAVR (and TF-TAVR) patients compared with SAVR patients. Adjusted for body mass index, Society of Thoracic Surgeons (STS) risk score, renal disease at baseline, and chronic obstructive pulmonary disease oxygen dependent. Abbreviations as in Figures 1 and 3.

Table 5	Independent Predictors of 1-Year Mortality Among the Total Population	
Predictors	**Adjusted HR (95% CI)**	**p Value**
Major bleeding at 30 days	2.49 (1.85–3.37)	<0.0001
STS risk score	1.07 (1.03–1.10)	<0.0001
Body mass index	0.96 (0.94–0.98)	0.001
Oxygen-dependent COPD	1.65 (1.13–2.41)	0.01
Baseline renal disease	1.31 (0.95–1.80)	0.10

Candidate variables for the model were age, female sex, body mass index, Society of Thoracic Surgeons risk score, prior coronary artery bypass graft surgery, permanent pacemaker, renal disease, malignant tumors, liver disease, oxygen-dependent chronic obstructive pulmonary disease, left ventricular ejection fraction, baseline hemoglobin, baseline platelet; and major bleeding at 30 days (as time-dependent covariable).

Abbreviations as in Tables 1 and 4.
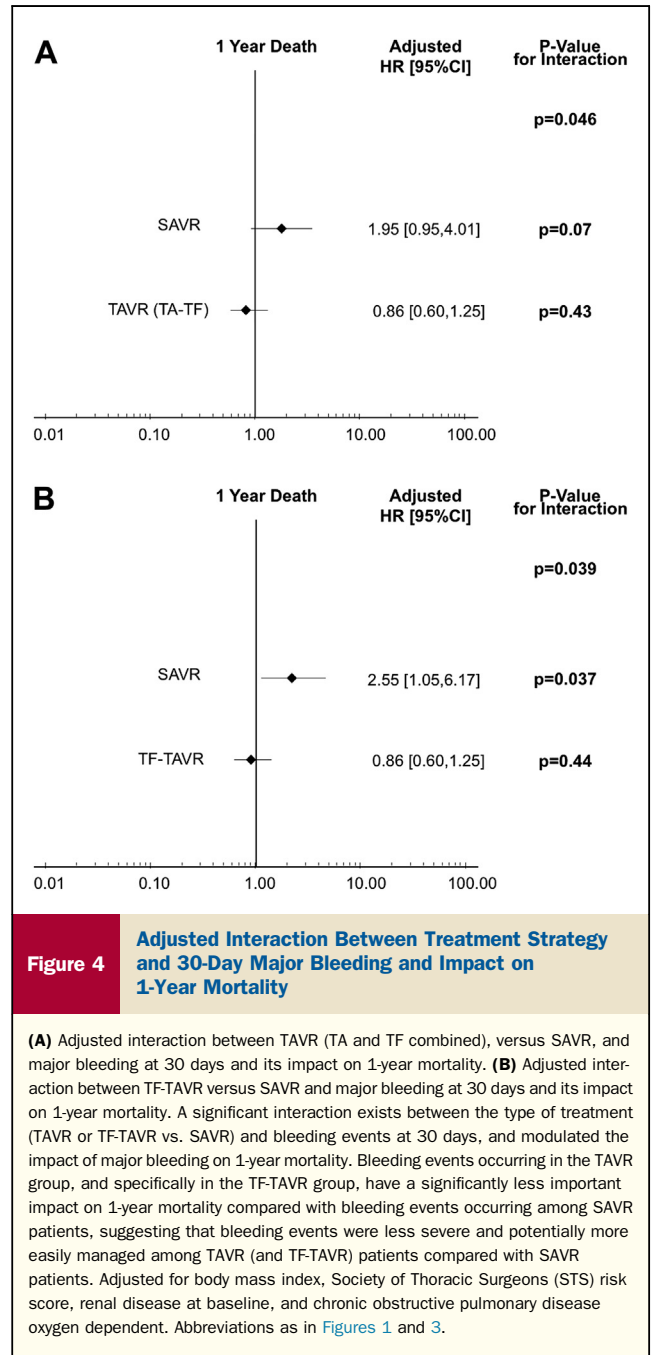
initial bleeding event, the use of exogenous blood product, and impact on mid-term and long-term outcomes, and the need to prevent and decrease unnecessary post-procedural RBC transfusions.

Study limitations. The PARTNER trial was performed using first-generation devices (large 22- and 24-F introducer sheath diameter for TF approaches and 29-F for TA access) with operators and sites at the beginning of the learning curve. Taking into account the ongoing evolution toward lower-profile TAVR devices, it is likely that even greater differences between TAVR and SAVR in rates of BC and transfusions might be seen in the future. Whereas

major complications and adverse outcomes were collected by enrolling sites and adjudicated by an independent committee, specific causes of bleeding (i.e., gastrointestinal bleed) and reasons for transfusions were not systematically documented. Baseline anemia was frequent in both groups, and the exact etiology, although most likely multifactorial and less likely to have precluded enrollment, is unknown. The current report used a modified version of VARC-1 (10) and -2 (11) criteria. Although the use of VARC-2 criteria to report adverse events is strongly recommended in any TAVR study, those criteria were not available at the time of the initiation of the PARTNER IA trial. However, the strong relationship between major bleeding events, death, and treatment strategy is less likely to have been affected. Access and closure were performed by surgical cut-down in approximately 70% of patients and were fully percutaneous in approximately 30% of PARTNER trial cohort A patients (19). The severity and impact of bleeding in the context where TF-TAVR procedure would be performed fully percutaneously is still to be determined. Finally, although we adjusted for imbalances in a number of important covariates, potential unmeasured confounders may still be present. The results of this observational post-hoc analysis should therefore be considered hypothesis generating.

Conclusions

Major BC were frequent after SAVR and TAVR using first-generation devices. However, among a cohort of patients with similar risk profiles, major BC and the need for transfusions were significantly higher after SAVR than after TAVR. In addition to their greater frequency, the adverse prognostic impact of major BC was substantial among patients treated with SAVR, but negligible among patients receiving TAVR.

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▶ **APPENDIX**

For supplemental tables, please see the online version of this article.