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ORIGINAL ARTICLE
Valvular Heart Disease

Impact of Major Vascular Complication Access Site Status on Mortality After Transfemoral Transcatheter Aortic Valve Replacement

— Results From the FinnValve Registry —

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Background: The aim of this study was to investigate the impact of anatomical site status and major vascular complication (MVC) severity on the outcome of transfemoral transcatheter aortic valve replacement (TF-TAVR).

Methods and Results: The FinnValve registry enrolled consecutive TAVR patients from 2008 to 2017. MVC was divided into 2 groups: non-access site-related MVC (i.e., MVC in aorta, aortic valve annulus or left ventricle); and access site-related MVC (i.e., MVC in iliac or femoral arteries). Severity of access site-related MVC was measured as units of red blood cell (RBC) transfusion. Of 1,842 patients who underwent TF-TAVR, 174 had MVC (9.4%; non-access site related, n=29; access site related, n=145). Patients with MVC had a significantly higher 3-year mortality than those without MVC (40.8% vs. 24.3%; HR, 2.01; 95% CI: 1.16–3.62). Adjusted 3-year mortality risk was significantly increased in the non-access site-related MVC group (mortality, 77.8%; HR, 4.30; 95% CI: 2.63–7.02), but not in the access site-related MVC group (mortality, 32.6%; HR, 1.38; 95% CI: 0.86–2.15). In the access site-related MVC group, only those with RBC transfusion ≥4 units had a significantly increased 3-year mortality risk (mortality, 51.8%; HR, 2.18; 95% CI: 1.19–3.89).

Conclusions: In patients undergoing TF-TAVR, MVC was associated with an increased 3-year mortality risk, incrementally correlating with anatomical site and bleeding severity.

Key Words: Bleeding; Major vascular complication; Prognosis; Transfemoral transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is an established treatment for severe aortic stenosis (AS).[1,2] Although the feasibility of TAVR has been proved, there are inherent complications related to the procedure.[3] Vascular complication is a significant cause of death after TAVR via the transfemoral (TF) approach, in association with bleeding complication. Although minor vascular complications do not have an impact on mortality,[4] major vascular complication (MVC) is associated with a significant risk of mortality.[4,5] Although MVC involving

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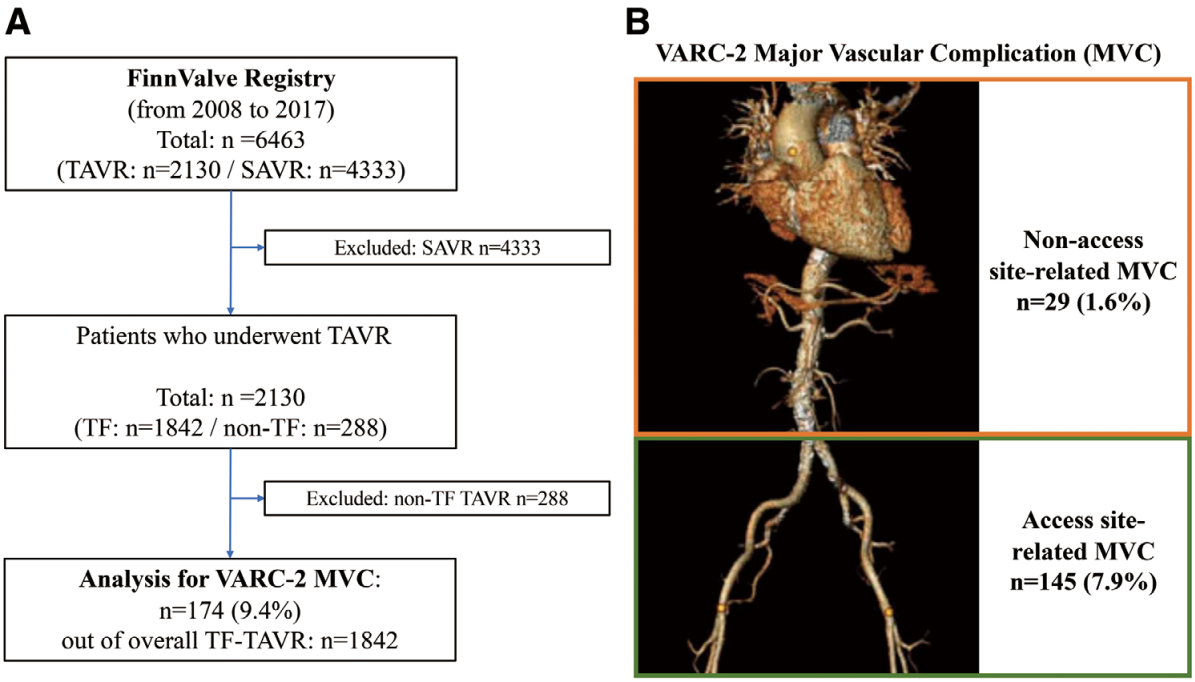

Figure 1. (**A**) Flow chart of patient selection and (**B**) definition of the major vascular complication (MVC) groups (non-access site-related MVC, MVC in aorta, aortic valve annulus, or left ventricle; access site-related MVC, MVC below distal aorta). SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TF, transfemoral; VARC-2, Valve Academic Research Consortium-2.

the aorta, aortic valve annulus, or left ventricle are rare, such complications are potentially catastrophic.[6] Data on MVC stratified by anatomical site with regard to late outcome, however, are still scarce. Moreover, although bleeding complications are commonly associated with vascular complications and the risk for mortality, data on long-term outcomes of MVC stratified by severity of bleeding complication following TF-TAVR are also currently very limited. Therefore, the aim of this study was to comprehensively characterize the impact of MVC, according to anatomical location and bleeding severity, on long-term outcomes after TF-TAVR from the nationwide registry in Finland.

Methods

Study Design and Participants

Details of this registry have been published previously.[7] The Finnish Registry of Transcatheter and Surgical Aortic Valve Replacement for Aortic Valve Stenosis (FinnValve registry) is a nationwide registry of retrospectively collected data from consecutive and unselected patients who have undergone TAVR or surgical aortic valve replacement (SAVR) with a bioprosthesis for AS at 5 Finnish university hospitals (Helsinki, Kuopio, Oulu, Tampere and Turku) between January 2008 and October 2017. This study was approved by the Institutional Review Boards of each participating center and conformed to the Declaration of Helsinki. During the study period, only these 5 university hospitals performed both TAVR and SAVR. The inclusion criteria for study entry were as follows: (1) age >18 years; (2) primary aortic valve procedure with a bioprosthesis for AS with or without aortic valve regurgitation; and (3) TAVR or SAVR with or without associated coronary revascularization. The exclusion criteria were as follows: (1) any prior TAVR or surgical intervention on the aortic valve; (2) concomitant major procedure on the mitral valve, tricuspid valve and/or ascending aorta; (3) any procedure for isolated aortic valve regurgitation; or (4) acute endocarditis; and (5) SAVR with a mechanical valve prosthesis. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[8]

Definitions

Baseline variables were defined according to the EuroSCORE II criteria.[9] Severe frailty was defined according to the geriatric status scale (GSS) as GSS grades 2–3.[10] Coronary artery disease was defined as any stenosis ≥50% of the main coronary branches. For the purpose of this study, patients were divided into quartiles based on the procedure date (timeframe of TAVR: 1st quartile, January 2008–May 2010; 2nd quartile, June 2010–December 2012; 3rd quartile, January 2013–May 2015; and 4th quartile, June 2015–November 2017).

Patient Selection

The FinnValve registry has data on 6,463 patients who underwent primary TAVR or SAVR with a bioprosthesis; 2,130 (33.0%) underwent TAVR and 4,333 (67.0%) underwent SAVR. After the exclusion of SAVR (n=4,333) and non-TF TAVR (n=288), 1,842 patients who had undergone

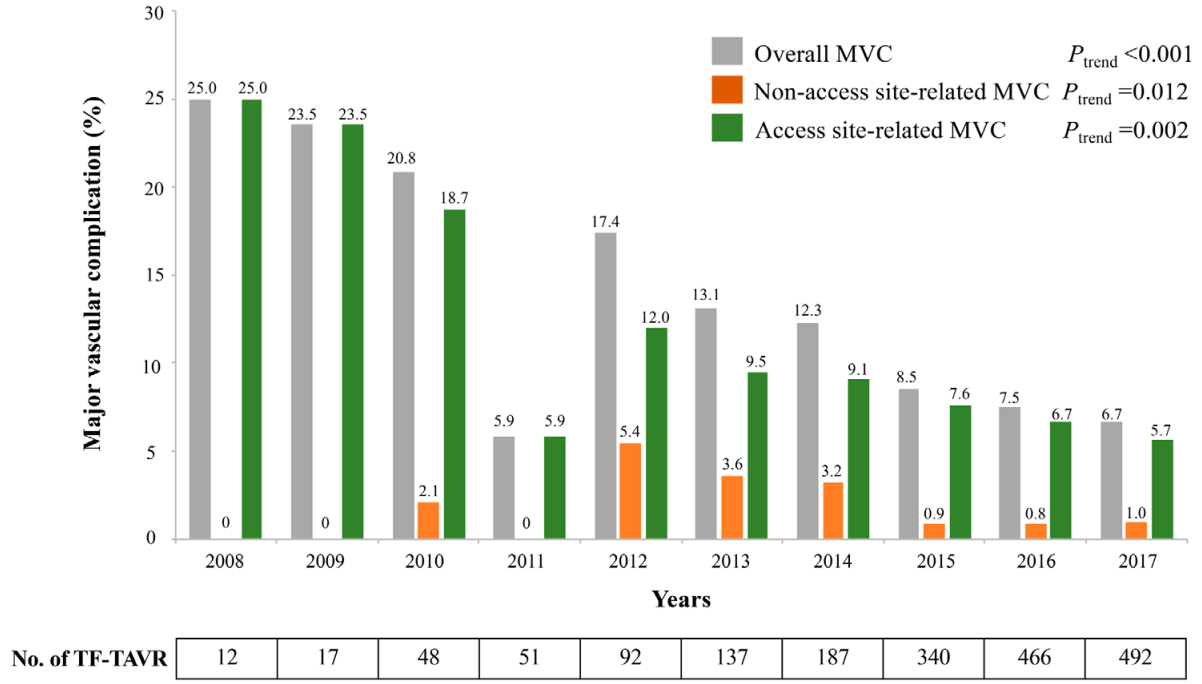

Figure 2. Annual distribution of major vascular complication (MVC). SAVR, surgical aortic valve replacement; TF-TAVR, transfemoral transcatheter aortic valve replacement.

TF-TAVR were included in the present analysis (**Figure 1A**).

Devices

During the study period, patients who underwent TF-TAVR received the Edwards SAPIEN, XT or 3 (Balloon-expandable valve; Edwards Lifesciences, Irvine, CA, USA), the Medtronic CoreValve or Evolut R/Pro (Self-expandable valve; Medtronic, Minneapolis, MN, USA), the Boston ACURATE neo (Self-expandable valve) and LOTUS (Mechanical expandable valve; Boston Scientific, Natick, MA, USA) or the Abbott Portico valve (Self-expandable; Abbott Vascular, Santa Clara, CA, USA).

Outcome Measures

For the purpose of the current analysis, MVC was divided into 2 groups: non-access site-related MVC, defined as MVC in aorta, aortic valve annulus, or left ventricle; and access site-related MVC, defined as MVC below terminal aorta (**Figure 1B**). The early outcomes were defined as peri- and post-procedural outcomes during the hospital stay for the index procedure and 30-day all-cause mortality. Variables were defined according to the Valve Academic Research Consortium (VARC)-2 criteria.[11] Acute kidney injury (AKI) was defined according to the KDIGO classification criteria in this registry.[12] Bleeding complications are the most frequent adverse events in patients with MVC following TAVR. Therefore, bleeding complications were also reported together with number of red blood cell (RBC) transfusions and hemoglobin drop (hemoglobin level before procedure minus the lowest hemoglobin level after procedure during hospital stay). For the purpose of severity analysis, these variables were considered as candidates for indicating severity of MVC.

The primary outcome of this study was to elucidate the impact of MVC stratified by anatomical site (non-access and access site) and bleeding severity on mortality over a 3-year follow-up after TF-TAVR. The secondary outcomes were to identify the early outcomes and the independent predictors of MVC and 3-year mortality.

Statistical Analysis

Categorical variables are presented as n (%) and were compared using the chi-squared test. Continuous variables are presented as mean±SD or median (IQR) and were compared using the Student's t-test or the Wilcoxon rank sum test based on their distributions. Survival curves for time-to-event variables were constructed on the basis of all available follow-up data using Kaplan-Meier estimates, and comparisons were performed using the log-rank test. Multivariate logistic regression was performed to identify independent predictors of MVC and 3-year mortality. The multivariate model was constructed using all baseline and procedural characteristics with $P<0.10$ on univariate analysis. Multivariate logistic regression was performed to determine independent predictors of 3-year all-cause mortality. The multivariate model was built using step-wise selection with all baseline, procedure characteristics and early outcomes. The optimal cut-off of bleeding severity predicting 30-day mortality was evaluated using receiver operating characteristic (ROC) curve analysis. $P<0.05$ was set as statistically significant for all tests. Statistical analysis was performed using JMP version 10.0 (SAS Institute, Cary, NC, USA), and SPSS version 22.0 (IBM, New York, USA).

Results

A total of 1,842 patients who underwent TF-TAVR were identified and were the subjects of this analysis (**Figure 1A**). The mean follow-up duration was 2.3±1.6 years (range, 0–9.6 years). A total of 174 patients with MVC following TF-TAVR were identified (9.4%). Of the patients with MVC, 29 patients had non-access site-related MVC (16.6%) and 145 patients had access site-related MVC (83.4%). During a 10-year study period, the incidence of MVC declined from 25.0% to 6.7% ($P_{trend}<0.001$). This trend was mainly derived by significant reduction of access site-related MVC (from 25.0% to 5.7%, $P_{trend}=0.002$; **Figure 2**). Baseline and procedural characteristics of this study populations are listed in **Table 1**. In the overall cohort, the mean age was 81.6±6.4 years, and 1,045 patients (56.7%) were female. There was a similar implantation rate of balloon-expandable, self-expandable and mechanical expandable valve devices between patients with or without MVC (P=0.67).

Predictors of MVC and Early Outcomes

On multivariate analysis, female gender and timeframe of TF-TAVR were identified as the independent predictors of overall MVC (female: OR, 1.56; 95% CI: 1.04–2.34; timeframe: OR, 0.57; 95% CI: 0.34–0.95) and access site-related MVC (female: OR, 1.45; 95% CI: 1.01–2.12; timeframe: OR, 0.31; 95% CI: 0.13–0.75). Use of self-expandable

Table 1. Baseline Clinical and Procedural Characteristics

Variables	Overall (n=1,842)	Non-MVC (n=1,668)	MVC (n=174)	P-value	Non-access site-related MVC (n=29)	Access site-related MVC (n=145)	P-value
Baseline characteristics							
Age (years)	81.6±6.4	81.6±6.4	81.6±6.4	0.96	83.5±7.0	81.2±6.2	0.083
Female	1,045 (56.7)	928 (55.6)	117 (67.2)	0.003	24 (82.8)	93 (64.1)	0.041
BMI (kg/m^2)	27.2±4.9	27.2±4.8	27.1±5.5	0.86	25.4±3.9	27.5±5.7	0.066
BSA (m^2)	1.84±0.22	1.84±0.21	1.80±0.26	0.017	1.72±0.20	1.82±0.27	0.065
Hb (g/L)	125.0±15.5	125.2±15.6	123.7±14.0	0.25	121.3±11.2	124.2±14.5	0.30
eGFR (mL/min/1.73 m^2)	65.6±22.6	65.7±22.5	65.2±23.8	0.077	68.3±20.4	64.6±24.4	0.44
CKD	774 (42.0)	693 (41.6)	81 (46.6)	0.20	9 (31.0)	72 (50.0)	0.067
Dialysis	19 (1.0)	18 (1.1)	1 (0.6)	0.53	0 (0)	1 (0.7)	0.89
Diabetes	505 (27.4)	464 (27.8)	41 (23.6)	0.23	4 (13.8)	37 (25.5)	0.17
Insulin-dependent diabetes	190 (10.3)	179 (10.7)	11 (6.3)	0.069	0 (0)	11 (7.6)	0.13
COPD	372 (20.2)	325 (19.5)	47 (27.0)	0.019	4 (17.8)	43 (30.0)	0.079
AF	796 (43.2)	723 (43.4)	73 (42.0)	0.72	14 (48.3)	59 (40.7)	0.45
Coronary artery disease	498 (27.0)	445 (26.7)	53 (30.5)	0.29	4 (13.8)	49 (33.8)	0.033
Extracardiac arteriopathy	280 (15.2)	251 (15.1)	29 (16.7)	0.57	3 (10.3)	26 (18.0)	0.32
Previous PMI	178 (9.7)	167 (10.0)	11 (6.3)	0.12	1 (3.5)	10 (7.9)	0.49
Previous MI	239 (13.0)	217 (13.0)	22 (12.6)	0.89	0 (0)	22 (15.0)	0.025
Previous cardiac surgery	320 (17.4)	291 (17.5)	29 (16.7)	0.80	2 (6.9)	27 (18.6)	0.12
Previous PCI	385 (20.9)	345 (20.7)	40 (23.0)	0.48	3 (10.3)	37 (25.5)	0.076
Previous stroke	202 (11.0)	178 (10.7)	24 (13.8)	0.21	3 (10.3)	21 (14.5)	0.56
Frailty GSS ≥2	263 (4.3)	234 (14.0)	29 (16.7)	0.34	6 (20.7)	23 (15.9)	0.52
NYHA IV	210 (11.4)	188 (11.3)	22 (12.6)	0.59	6 (20.7)	16 (11.0)	0.15
LVEF ≤50%	479 (26.0)	429 (25.8)	50 (28.9)	0.37	4 (13.8)	46 (31.9)	0.049
Bicuspid aortic valve	105 (5.7)	97 (5.8)	8 (4.6)	0.51	1 (3.5)	7 (4.8)	0.75
Urgent or emergency procedure	132 (7.2)	116 (7.0)	16 (9.2)	0.28	3 (10.3)	13 (9.0)	0.81
Hostile chest	59 (3.2)	55 (3.3)	4 (2.3)	0.48	0 (0)	4 (2.8)	0.37
Porcelain aorta	83 (4.5)	76 (4.6)	7 (4.0)	0.75	1 (3.5)	6 (4.1)	0.86
EuroSCORE II (%)	6.7±6.9	6.6±6.7	7.9±8.9	0.021	5.4±4.0	8.4±9.4	0.098
STS score (%)	4.5±3.2	4.4±3.0	5.2±4.8	0.003	5.0±3.1	5.2±5.1	0.81
Antithrombotic therapy before TAVR							
Antiplatelet therapy	947 (51.4)	856 (51.3)	91 (52.3)	0.81	15 (51.7)	76 (52.4)	0.95
Oral anticoagulant agent	752 (40.8)	679 (40.7)	73 (42.0)	0.75	12 (41.4)	61 (42.1)	0.94
Oral anticoagulant+antiplatelets	93 (5.0)	80 (4.8)	13 (7.5)	0.13	3 (10.3)	10 (6.9)	0.52
None	244 (13.2)	221 (13.3)	23 (13.2)	0.99	5 (17.2)	18 (12.4)	0.48
Timeframe of TAVR				<0.001			0.16
1st quartile	45 (2.4)	34 (75.6)	11 (24.4)		0 (0)	11 (100)	
2nd quartile	312 (16.9)	269 (86.2)	43 (13.8)		11 (25.6)	32 (74.4)	
3rd quartile	723 (39.3)	656 (90.7)	67 (9.3)		11 (16.4)	56 (83.6)	
4th quartile	762 (41.3)	809 (93.0)	53 (7.0)		7 (13.2)	46 (86.8)	

(**Table 1** continued the next page.)

Variables	Overall (n=1,842)	Non-MVC (n=1,668)	MVC (n=174)	P-value	Non-access site-related MVC (n=29)	Access site-related MVC (n=145)	P-value
Procedural characteristics							
General anesthesia	406 (22.3)	335 (20.3)	71 (41.8)	<0.001	9 (31.0)	62 (44.0)	0.19
Surgical cut-down approach	293 (15.9)	256 (15.4)	37 (21.3)	0.003	6 (20.7)	31 (21.4)	0.93
Sheath size (Fr)	16.5±2.3	16.4±2.3	17.0±2.4	<0.001	17.3±2.2	17.0±2.4	0.50
THV product				<0.001			0.15
ACURATE neo	157 (8.5)	143 (8.6)	14 (8.1)		1 (3.5)	13 (9.0)	
CoreValve	81 (4.4)	73 (4.4)	8 (4.6)		0 (0)	8 (5.5)	
Evolut R/Pro	167 (9.1)	154 (9.2)	13 (7.5)		0 (0)	13 (9.0)	
LOTUS/Edge	228 (12.4)	209 (12.5)	19 (10.9)		5 (17.2)	14 (9.7)	
Portico	5 (2.7)	4 (0.24)	1 (0.57)		0 (0)	1 (0.69)	
SAPIEN XT	405 (22.0)	343 (20.6)	62 (35.6)		15 (51.7)	47 (32.4)	
SAPIEN 3	799 (43.4)	742 (44.5)	57 (32.8)		8 (27.6)	49 (33.8)	
THV type				0.67			0.032
BE	1,204 (65.3)	1,085 (65.1)	119 (68.4)		23 (79.3)	96 (66.2)	
SE	410 (22.2)	374 (22.4)	36 (20.7)		1 (3.5)	35 (24.1)	
ME	228 (12.4)	209 (12.5)	19 (10.9)		5 (17.2)	14 (9.7)	
Pre-dilatation	967 (52.5)	863 (51.7)	104 (59.8)	0.043	16 (55.2)	88 (60.7)	0.58
Post-dilatation	306 (16.6)	271 (16.3)	35 (20.1)	0.19	12 (41.4)	23 (15.9)	0.002

Data given as n (%) or mean±SD. AF, atrial fibrillation; BE, balloon-expandable (SAPIEN XT and 3); BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; GSS, geriatric status scale; Hb, hemoglobin; LVEF, left ventricular ejection fraction; ME, mechanical expandable (LOTUS/Edge); MI, myocardial infarction; MVC, major vascular complication; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PMI, pacemaker implantation; SE, self-expandable (ACURATE neo, CoreValve, Evolut R/Pro and Portico); STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; THV, transcatheter heart valve.

Table 2. Multivariate Indicators of MVC and 30-Day Mortality

Predictor of MVC	OR (95% CI)	P-value
Overall MVC (n=174)		
Female	1.56 (1.04–2.34)	0.030
4th quartile (vs. 1st quartile)	0.57 (0.34–0.95)	0.029
Non-access site-related MVC (n=29)		
SE valve (vs. BE+ME valve)	0.13 (0.02–0.67)	0.009
Access site-related MVC (n=145)		
Female	1.45 (1.01–2.12)	0.046
4th quartile (vs. 1st quartile)	0.31 (0.13–0.75)	0.011
Predictor of 30-day mortality	**OR (95% CI)**	**P-value**
MVC	6.42 (2.25–20.6)	<0.001
Non-access site-related MVC	39.8 (10.2–92.8)	<0.001
Access site-related MVC	2.63 (1.01–9.3)	0.040

Candidate variables for overall MVC: female, BSA, eGFR, insulin-dependent diabetes, timeframe of procedure, oral anticoagulant+antiplatelet therapy, EuroSCORE II, STS score, general anesthesia, sheath size and balloon pre-dilatation. Candidate variables for non-access site-related MVC: age, female, BMI, BSA, timeframe of procedure, extracardiac arteriopathy, SE vs. BE+ME, and post-dilatation. Candidate variables for access site-related MVC: female, COPD, extracardiac arteriopathy, eGFR, timeframe of procedure, EuroSCORE II, STS score and sheath size. Candidate variables for 30-day mortality: age, eGFR, AF, urgent or emergency procedure, NYHA IV, STS score, PVL grade ≥2, AKI grade ≥2, life-threatening or disabling/major bleeding, timeframe of TAVR and MVC. AKI, acute kidney injury; PVL, paravalvular leak. Other abbreviations as in Table 1.

valve was associated with a significantly lower risk of non-access site-related MVC than balloon- or mechanical expandable valve (OR, 0.13; 95% CI: 0.02–0.67; **Table 2**).

Early outcomes according to MVC status are summarized in **Table 3**. Patients with MVC had a higher 30-day mortality (11.5% vs. 1.6%, P<0.001), and higher prevalence of life-threatening or major bleeds (96.6% vs. 9.8%, P<0.001) with higher risk of RBC transfusion, as well as other complications than those without MVC. Patients with non-access site-related MVC had a significantly higher 30-day mortality (38.9% vs. 6.2%, P<0.001) and longer hospital stay (10.4±3.8 vs. 7.7±3.8 days, P=0.013) than patients with access site-related MVC, and had a tendency towards a higher incidence of stroke (10.3% vs. 3.4%, P=0.061), AKI grade ≥2 (13.8% vs. 5.5%, P=0.091), and paravalvular leak (PVL) grade ≥2 (10.3% vs. 2.8%, P=0.058)

Table 3. Early Outcomes After TF-TAVR

	Non-MVC (n=1,668)	MVC (n=174)	HR (95% CI), P-value (vs. non-MVC)	Non-Access site-related MVC (n=29)	HR (95% CI), P-value (vs. non-MVC)	HR (95% CI), P-value (vs. access site-related MVC)	Access site-related MVC (n=145)	HR (95% CI), P-value (vs. non-MVC)
30-day all-cause death	26 (1.6)	20 (11.5)	7.4 (4.2–12.9), <0.001	11 (38.9)	24.3 (13.3–44.4), <0.001	6.11 (2.8–13.4), <0.001	9 (6.2)	4.0 (1.9–8.4), <0.001
Stroke	37 (2.2)	8 (4.6)	2.1 (0.98–4.4), 0.053	3 (10.3)	4.8 (1.2–12.3), 0.005	3.3 (0.80–7.2), 0.061	5 (3.4)	1.6 (0.71–4.3), 0.35
New PMI	157 (9.4)	16 (9.2)	0.98 (0.60–1.59), 0.93	4 (13.8)	1.5 (0.59–3.7), 0.43	1.67 (0.56–4.8), 0.38	12 (8.3)	0.88 (0.50–1.5), 0.65
Life-threatening or major bleeding	164 (9.8)	168 (96.6)	9.8 (8.5–11.4), <0.001	29 (100)	10.2 (8.8–11.8), <0.001	1.04 (0.98–1.09), 0.29	139 (95.9)	9.7 (8.4–11.3), <0.001
RBC transfusion	173 (10.4)	122 (70.1)	6.8 (5.7–8.0), <0.001	21 (72.4)	7.0 (5.4–9.1), <0.001	1.03 (0.81–1.33), 0.76	101 (70.0)	6.7 (5.6–8.0), <0.001
RBC units	0.23±0.90	2.80±3.10	P<0.001	3.9±4.8	P<0.001	P=0.027	2.6±2.6	P<0.001
RBC transfusion >4 units	13 (0.79)	39 (22.9)	29.1 (15.8–53.4), <0.001	10 (35.7)	45.3 (21.7–94.4), <0.001	1.79 (0.99–3.23), 0.069	29 (20.4)	25.9 (13.8–48.7), <0.001
Hb drop (g/L)†	20.3±12.2	36.8±15.0	P<0.001	32.0±14.5	P<0.001	0.066	37.7±15.0	P<0.001
Unplanned surgical treatment	22 (1.3)	100 (57.5)	P<0.001	21 (72.4)	P<0.001	–	79 (54.5)	P<0.001
Unplanned endovascular treatment	26 (1.6)	41 (23.6)	P<0.001	0 (0)	P=0.89	–	41 (28.3)	P<0.001
AKI grade ≥2	19 (1.1)	12 (6.9)	6.1 (3.0–12.3), <0.001	4 (13.8)	12.1 (4.4–33.4), <0.001	2.6 (1.2–7.8), 0.091	8 (5.5)	4.8 (2.2–10.9), <0.001
PVL grade ≥2	63 (3.8)	7 (4.0)	1.1 (0.5–2.3), 0.87	3 (10.3)	2.7 (0.91–8.2), 0.070	3.75 (0.89–15.9), 0.058	4 (2.8)	0.73 (0.27–2.0), 0.53
LOHS (days)	4.7±4.1	8.1±5.3	P<0.001	10.4±3.8	P<0.001	P=0.013	7.7±4.6	P<0.001

Data given as n (%) or mean±SD unless otherwise indicated. †Hb level before procedure minus the lowest Hb level after procedure during hospital stay. LOHS, length of hospital stay; TF-TAVR, transfemoral transcatheter aortic valve replacement. Other abbreviations as in Tables 1,2.

even compared with those with access site-related MVC. Overall MVC (OR, 6.42; 95% CI: 2.25–20.6) was significantly associated with 30-day mortality on multivariate analysis (**Table 2**). Both types of MVC were associated with increased risk of 30-day mortality (non-access site related: OR, 39.8; 95% CI: 10.2–92.8; access site related: OR, 2.63; 95% CI: 1.01–9.3).

Long-Term Outcomes

The 3-year mortality differed significantly according to MVC status (MVC, 40.8% vs. non-MVC, 24.3%; log-rank P<0.001; **Figure 3A**). Although non-access site-related MVC was significantly associated with higher 3-year mortality compared with non-MVC (77.8% vs. 24.3%, log-rank P<0.001), access site-related MVC was not (32.6% vs. 24.3%, log-rank P=0.12; **Figure 3B**). Cardiac tamponade (79.3%) was the most frequent clinical presentation in patients with non-access site-related MVC (**Table 4**). All-cause mortality at 1 year was 100% in patients with annulus rupture (n=8, 27.6%) and with ventricular septal perforation (n=5, 17.2%), and 87.5% in those with aortic dissection or rupture (n=8, 27.6%). For the purpose of severity analysis, patients with access site-related MVC were divided into 2 groups according to RBC transfusion units (transfusion 0–3 units, and ≥4 units) based on ROC analysis (**Supplementary Figure**). A significant difference in 3-year mortality was observed between these 2 access site-related MVC groups (transfusion 0–3 units, 26.1%; ≥4 units, 51.8%; log-rank P<0.001; **Figure 3C**). On multivariate analysis (**Table 5**), overall MVC was significantly associated with an increased 3-year mortality risk (adjusted hazard ratio [aHR], 2.01; 95% CI: 1.16–3.62). aHR for 3-year mortality was 4.30 (95% CI: 2.63–7.02) for non-access site-related MVC and 1.38 (95% CI: 0.86–2.15) for access site-related MVC. Access site-related MVC requiring ≥4 units RBC transfusion was associated only with an increased risk of 3-year mortality (aHR, 2.18; 95% CI: 1.19–3.89).

Discussion

The present study, which evaluated the prognostic impact of MVC with regard to anatomical location and bleeding severity in 1,842 patients after TF-TAVR, can be summarized as follows: (1) overall MVC after TF-TAVR was observed in 9.4% of patients, with a significant tendency to decrease during the 10-year period at the same time as a steady increase in the number of TF-TAVR cases; (2) overall

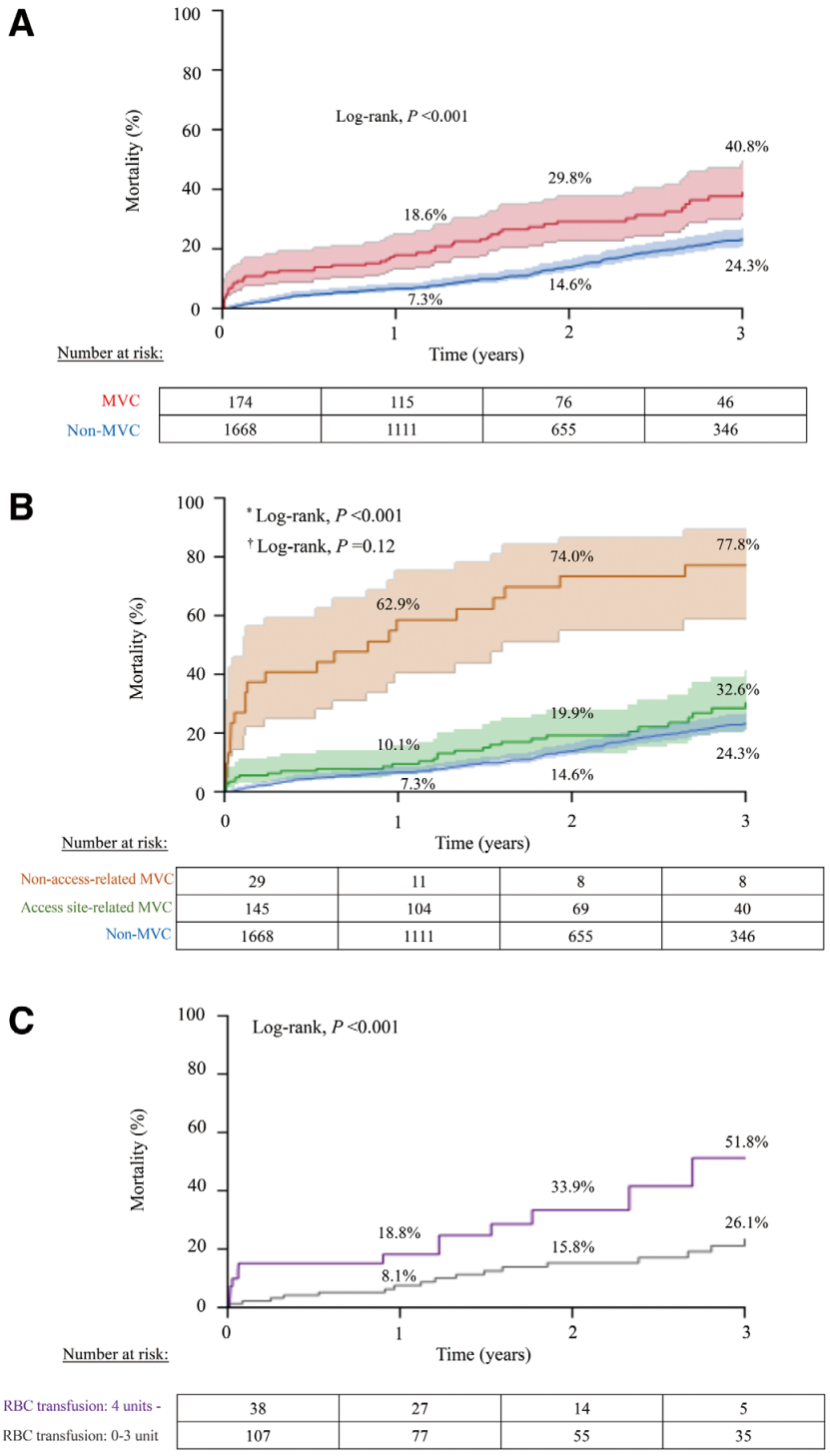

Figure 3. Kaplan-Meier cumulative all-cause mortality up to 3 years according to (**A**) major vascular complication (MVC) status (MVC vs. non-MVC, log-rank P<0.001); (**B**) access site status (non-access site-related MVC vs. access site-related MVC vs. non-MVC, log-rank P<0.001); and (**C**) severity of access site-related MVC (red blood cell [RBC] transfusion 0–3 units vs. ≥4 units, log-rank P<0.001).

MVC was an independent predictor of 30-day and 3-year all-cause mortality; and (3) non-access site-related MVC was associated with an increased risk of 3-year all-cause mortality. In contrast, access site-related MVC worsened 3-year outcomes only in association with severe bleeding complication requiring ≥4 units RBC transfusion.

Impact of MVC on Late Outcome

Several post-TAVR complications have been reported as independent predictors for late mortality. With regard to early TAVR experience, MVC was associated with a significant risk of early and late mortality.[4,5] Recently, Arnold et al reported the impact of short-term complications on 1-year mortality in 3,763 TAVR patients enrolled in the PARTNER 2 trial.[13] Stroke, AKI, and moderate to

Table 4. Non-Access Site-Related MVC: All-Cause Mortality Rates

Non-access site-related MVC, n=29	All-cause mortality (%) (95% CI)†			
	30 days	1 year	2 years	3 years
Annulus rupture, n=8 (27.6%)	75.0 (59.7–90.3)	100	–	–
Aortic dissection or rupture, n=8 (27.6%)	62.5 (45.4–79.6)	87.5 (75.8–99.2)	87.5 (75.8–99.2)	87.5 (75.8–99.2)
Ventricular-septal perforation, n=5 (17.2%)	60.0 (38.1–81.9)	100	–	–
Cardiac tamponade, n=23 (79.3%)	26.1 (16.9–35.3)	48.2 (37.7–58.7)	67.0 (56.9–77.1)	71.7 (62.0–81.4)
Surgical treatment, n=21 (72.4%)	23.8 (14.5–33.1)	43.3 (32.4–54.2)	63.9 (53.1–74.7)	69.1 (58.7–79.5)
Non-invasive treatment, n=8 (27.6%)	75.0 (59.7–90.3)	100	–	–

†Kaplan-Meier analysis. MVC, major vascular complication.

Table 5. Effect of MVC on 3-Year All-Cause Mortality

	Cumulative mortality rate at 3 years (%) (95% CI)	Unadjusted HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
Non-MVC	24.3 (22.8–25.8)	1 (Ref.)	–	1 (Ref.)	–
MVC	40.3 (39.6–44.9)	2.20 (1.71–2.81)	<0.001	2.01 (1.16–3.62)	<0.001
Non-access site-related MVC	77.8 (69.8–85.6)	5.27 (4.16–6.68)	<0.001	4.30 (2.63–7.02)	<0.001
Access site-related MVC	32.6 (26.7–36.9)	1.58 (1.15–2.18)	0.007	1.38 (0.86–2.15)	0.18
RBC transfusion 0–3 units	26.1 (20.5–31.6)	1.21 (0.82–2.03)	0.22	1.08 (0.59–2.00)	0.52
RBC transfusion ≥4 units	51.8 (39.2–64.5)	2.38 (1.51–3.75)	<0.001	2.18 (1.19–3.89)	0.013

Adjusted HR generated from Cox models that included the following covariates: age, gender, BSA, extracardiac arteriopathy, frailty geriatric status scale ≥2, previous MI, previous cardiac surgery, LVEF ≤50%, STS score, PVL grade ≥2, AKI grade ≥2 and MVC. Abbreviations as in Tables 1–3.

severe PVL, and life-threatening or major bleeding were associated with an increased risk for 1-year mortality, but MVC were not. This, however, does not mean that vascular complications are benign, because in the present study MVC itself was highly associated with other short-term complications such as life-threatening or major bleeding and AKI (**Table 3**). Therefore, the Arnold et al results could instead indicate that if a vascular complication can be corrected quickly and does not result in severe bleeding or AKI, then it has little impact on late outcomes. The present study included data on the early experience of TAVR before the introduction of established management for vascular complications. This could explain the discrepancy between these studies.

Non-Access Site-Related MVC

In the present study 29 patients had non-access site-related MVC (1.6% of 1,842 TF-TAVR patients). Despite increased case volume, and evolution of the technique and device technology, non-access site-related MVC still occurred in 0.8–1.0% of patients between 2015 and 2017 (**Figure 2**). In the transcatheter valve therapy (TVT) registry, the incidence of MVC involving the aorta, aortic valve annulus, or left ventricle was between 0.2% and 1.1% from 2012 to 2014.[14] Annular rupture is most commonly reported as a critical complication especially during balloon-expandable valve implantation, occurring in ≤1.0% of TAVR.[15,16] In the present study the rate of annular rupture (n=8, 0.43%) was similar to that of the previous reports, and may indicate that balloon- or mechanical expandable valve deployment carries a higher risk of non-access site-related MVC than does self-expandable valve. In the present study, 30-day mortality occurred in 75.0% of patients with annular rupture, whereas a wide range of 30-day mortality has been reported in the literature, between 50% and 100%.[15,17] Although several treatment options following annular complications, such as valve-in-valve technique and *N*-butyl-2-cyanoacrylate glue use, besides emergency surgical repair, have been reported, annular rupture is still associated with a significant risk of mortality.[18,19] In terms of aortic dissection during TAVR, there have been no systematic studies on outcomes, but outcomes could be generalized from a large study of patients with iatrogenic aortic root complications. In terms of in-hospital outcomes, Mehta et al reported a 52.5% in-hospital mortality for medically treated for type A aortic dissection, and 37.5% for those treated surgically.[20]

Importantly, non-access site-related MVC were associated with a greater risk of post-procedural stroke (10.3%), bleeding (100%) and AKI grade ≥2 (13.8%; **Table 3**), which obviously worsen short- and even long-term outcomes after TAVR. This could suggest that, even if bail-out treatment is successful, the prognosis of non-access site-related MVC is worsened. Therefore, considering the seriousness of these complications, further pre-procedural evaluation and dedicated valve selection are still needed in order to avoid the incidence of non-access site-related MVC.

Access Site-Related MVC

In the present study, 145 patients had access site-related MVC (7.9% of 1,842 TF-TAVR patients). Access site-related MVC after TF-TAVR varies from 2.0% to 17.1% depending on operator experience, center volume, type of percutaneous vascular closure device, and reduction of sheath/device size.[21–23] Probably with these improvement, the incidence of access site-related MVC decreased from 25.0% to 5.7% during a 10-year period in this registry. Previously, a significant association of MVC with mortality

up to 1-year follow-up was noted.[4,5] In contrast, van Kesteren et al confirmed that MVC influence survival only in the direct postoperative period in the first 30 days.[24] An actual impact of only access site-related MVC on long-term prognosis, however, has not been described to date. Importantly, we identified that (1) access site-related MVC does not have a significant impact on 3-year mortality, unlike non-access site-related MVC; and (2) access site-related MVC with severe bleeding requiring ≥4 units RBC transfusion is associated with an increased risk of early and late mortality. The association between access-site bleeding and mortality has been reported previously.[25] That could support the present results. The increasing units of RBC transfusion can be simply considered as a marker of bleeding severity leading to poor outcomes. In contrast, RBC transfusion itself is independently associated with early and late mortality after TAVR.[26] The transfusion-related immunomodulation leading to acute, and even chronic impairment of macrophage function[27] may partly explain the increase in mortality as the units of RBC transfusion increased in the present study. Unsurprisingly, female sex was associated with access site-related MVC. The mechanisms are likely multifactorial and include a lower body surface area and small iliofemoral artery in female compared with male undergoing TF-TAVR.[28,29] Refinements in femoral access technique, percutaneous closure device and the lower delivery sheath profile play an important role in the prevention of access site-related complications.[21,22] Furthermore, Sedaghat et al recently demonstrated that the use of self-expanding stent graft is associated with favorable short- and mid-term outcomes in patients with access site-related MVC.[30] Early recognition and quick endovascular treatment avoiding huge blood loss might improve the prognosis of access site-related MVC.

Study Limitations

Several limitations of the present study should be acknowledged. First, the results concerning predictive factors of non-access site-related MVC have to be interpreted with caution in the view of the small number of patients included in this registry. Similarly, although the risk for mortality for MVC was adjusted for relevant covariates, there might have been residual confounders due to unmeasured factors. In this respect, data on annular size, calcification and access-route vessel size on computed tomography were not available in the registry. Second, events were adjudicated by investigators from each participating center. Therefore, a certain degree of underreporting of events cannot be completely ruled out. Finally, 3-year follow-up was not available in all patients, and hence this might have affected the event rate up to 3 years.

Conclusions

MVC following TF-TAVR was frequent, but was decreasing over time. MVC was significantly associated with an increased risk of all-cause mortality up to 3 years, and non-access site-related MVC conferred a significantly greater magnitude of risk than access site-related MVC. When associated with severe bleeding, access site-related MVC worsened early and late outcomes after TF-TAVR.

Data Availability

The de-identified participant data will not be shared.

Disclosures

The authors declare no conflicts of interest.

References

1. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al; PARTNER 3 Investigators. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019; **380:** 1695–1705.
2. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al; Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. *N Engl J Med* 2019; **380:** 1706–1715.
3. Beohar N, Kirtane AJ, Blackstone E, Waksman R, Holmes D Jr, Minha S, et al. Trends in complications and outcomes of patients undergoing transfemoral transcatheter aortic valve replacement: Experience from the PARTNER Continued Access Registry. *JACC Cardiovasc Interv* 2016; **9:** 355–363.
4. Généreux P, Webb JG, Svensson LG, Kodali SK, Satler LF, Fearon WF, et al; PARTNER Trial Investigators. Vascular complications after transcatheter aortic valve replacement: Insights from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial. *J Am Coll Cardiol* 2012; **60:** 1043–1052.
5. Tchetche D, Dumonteil N, Sauguet A, Descoutures F, Luz A, Garcia O, et al. Thirty-day outcome and vascular complications after transarterial aortic valve implantation using both Edwards Sapien and Medtronic CoreValve bioprostheses in a mixed population. *EuroIntervention* 2010; **5:** 659–665.
6. Langer NB, Hamid NB, Nazif TM, Khalique OK, Vahl TP, White J, et al. Injuries to the aorta, aortic annulus, and left ventricle during transcatheter aortic valve replacement: Management and outcomes. *Circ Cardiovasc Interv* 2017; **10:** e004735.
7. Moriyama N, Laakso T, Biancari F, Raivio P, Jalava MP, Jaakkola J, et al. Prosthetic valve endocarditis after transcatheter or surgical aortic valve replacement with a bioprosthesis: Results from the FinnValve Registry. *EuroIntervention* 2019; **15:** e500–e507.
8. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Prev Med* 2007; **45:** 247–251.
9. Nashef SA, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. *Eur J Cardiothorac Surg* 2012; **41:** 734–744; discussion 744–745.
10. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hébert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. *Lancet* 1999; **353:** 205–206.
11. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012; **60:** 1438–1454.
12. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (Part 1). *Crit Care* 2013; **17:** 204.
13. Arnold SV, Zhang Y, Baron SJ, McAndrew TC, Alu MC, Kodali SK, et al. Impact of short-term complications on mortality and quality of life after transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2019; **12:** 362–369.
14. Holmes DR Jr, Nishimura RA, Grover FL, Brindis RG, Carroll JD, Edwards FH, et al; STS/ACC TVT Registry. Annual outcomes with transcatheter valve therapy: From the STS/ACC TVT Registry. *J Am Coll Cardiol* 2015; **66:** 2813–2823.
15. Pasic M, Unbehaun A, Buz S, Drews T, Hetzer R. Annular rupture during transcatheter aortic valve replacement: Classification, pathophysiology, diagnostics, treatment approaches, and prevention. *JACC Cardiovasc Interv* 2015; **8:** 1–9.
16. Langer NB, Hamid NB, Nazif TM, Khalique OK, Vahl TP, White J, et al. Injuries to the aorta, aortic annulus, and left ventricle during transcatheter aortic valve replacement: Management and outcomes. *Circ Cardiovasc Interv* 2017; **10:** e004735.
17. Eggebrecht H, Mehta RH, Kahlert P, Schymik G, Lefèvre T, Lange R, et al. Emergent cardiac surgery during transcatheter aortic valve implantation (TAVI): Insights from the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry. *EuroIntervention* 2014; **10:** 975–981.
18. Yu Y, Vallely M, Ng MK. Valve-in-valve implantation for aortic annular rupture complicating transcatheter aortic valve replacement

(TAVR). *J Invasive Cardiol* 2013; **25:** 409–410.
19. Piliero N, Thony F, Vanzetto G, Barone-Rochette G. Gluing of an aortic perforation during transcatheter aortic valve replacement: An alternative treatment for annular rupture? *JACC Cardiovasc Interv* 2015; **8:** 2037–2038.
20. Mehta RH, O'Gara PT, Bossone E, Nienaber CA, Myrmel T, Cooper JV, et al; International Registry of Acute Aortic Dissection (IRAD) Investigators. Acute type A aortic dissection in the elderly: Clinical characteristics, management, and outcomes in the current era. *J Am Coll Cardiol* 2002; **40:** 685–692.
21. Stortecky S, Wenaweser P, Diehm N, Pilgrim T, Huber C, Rosskopf AB, et al. Percutaneous management of vascular complications in patients undergoing transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2012; **5:** 515–524.
22. Barbanti M, Binder RK, Freeman M, Wood DA, Leipsic J, Cheung A, et al. Impact of low-profile sheaths on vascular complications during transfemoral transcatheter aortic valve replacement. *EuroIntervention* 2013; **9:** 929–935.
23. Popma JJ, Reardon MJ, Khabbaz K, Harrison JK, Hughes GC, Kodali S, et al. Early clinical outcomes after transcatheter aortic valve replacement using a novel self-expanding bioprosthesis in patients with severe aortic stenosis who are suboptimal for surgery: Results of the Evolut R U.S. Study. *JACC Cardiovasc Interv* 2017; **10:** 268–275.
24. van Kesteren F, van Mourik MS, Vendrik J, Wiegerinck EMA, Henriques JPS, Koch KT, et al. Incidence, predictors, and impact of vascular complications after transfemoral transcatheter aortic valve implantation with the SAPIEN 3 prosthesis. *Am J Cardiol* 2018; **121:** 1231–1238.
25. Piccolo R, Pilgrim T, Franzone A, Valgimigli M, Haynes A, Asami M, et al. Frequency, timing, and impact of access-site and non-access-site bleeding on mortality among patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv* 2017; **10:** 1436–1446.
26. Maaranen P, Husso A, Tauriainen T, Lahtinen A, Valtola A, Ahvenvaara T, et al. Blood transfusion and outcome after transfemoral transcatheter aortic valve replacement. *J Cardiothorac Vasc Anesth* 2019; **33:** 2949–2959.
27. Youssef LA, Spitalnik SL. Transfusion-related immunomodulation: A reappraisal. *Curr Opin Hematol* 2017; **24:** 551–557.
28. O'Connor SA, Morice MC, Gilard M, Leon MB, Webb JG, Dvir D, et al. Revisiting Sex equality with transcatheter aortic valve replacement outcomes: A collaborative, patient-level meta-analysis of 11,310 patients. *J Am Coll Cardiol* 2015; **66:** 221–228.
29. Forrest JK, Adams DH, Popma JJ, Reardon MJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic valve replacement in women versus men (from the US CoreValve Trials). *Am J Cardiol* 2016; **118:** 396–402.
30. Sedaghat A, Neumann N, Schahab N, Sinning JM, Hammerstingl C, Pingel S, et al. Routine endovascular treatment with a stent graft for access-site and access-related vascular injury in transfemoral transcatheter aortic valve implantation. *Circ Cardiovasc Interv* 2016; **9:** e003834.

Supplementary Files

Please find supplementary file(s);
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