



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

— Results From the FinnValve Registry —

Teemu Laakso, MD; Noriaki Moriyama, MD; Peter Raivio, MD, PhD;
Sebastian Dahlbacka, MD, PhD; Eeva-Maija Kinnunen, MD, PhD; Tatu Juvonen, MD, PhD;
Antti Valtola, MD; Annastiina Husso, MD, PhD; Maina P. Jalava, MD;
Tuomas Ahvenvaara, MD; Tuomas Tauriainen, MD, PhD; Jarkko Piihola, MD, PhD;
Asta Lahtinen, MD; Matti Niemelä, MD, PhD; Timo Mäkikallio, MD, PhD;
Marko Virtanen, MD; Pasi Maaranen, MD; Markku Eskola, MD, PhD;
Mikko Savontaus, MD, PhD; Juhani Airaksinen, MD, PhD;
Fausto Biancari, MD, PhD; Mika Laine, MD, PhD

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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Heart and Lung Center, Helsinki University Hospital, Helsinki (T.L., N.M., P.R., S.D., E.-M.K., T.J., M.L.); Heart Center, Kuopio University Hospital, Kuopio (A.V., A.H.); Heart Center, Turku University Hospital and University of Turku, Turku (M.P.J., M.S., J.A., F.B.); Department of Surgery, Oulu University Hospital and University of Oulu, Oulu (T.A., T.T., F.B.); Department of Internal Medicine, Oulu University Hospital, Oulu (J.P., A.L., M.N., T.M.); Heart Hospital, Tampere University Hospital and Faculty of Medicine and Health Technology, Tampere University, Tampere (M.V., P.M., M.E.); and Department of Surgery, University of Turku, Turku (F.B.), Finland

The first two authors contributed equally to this study (T.L., N.M.).

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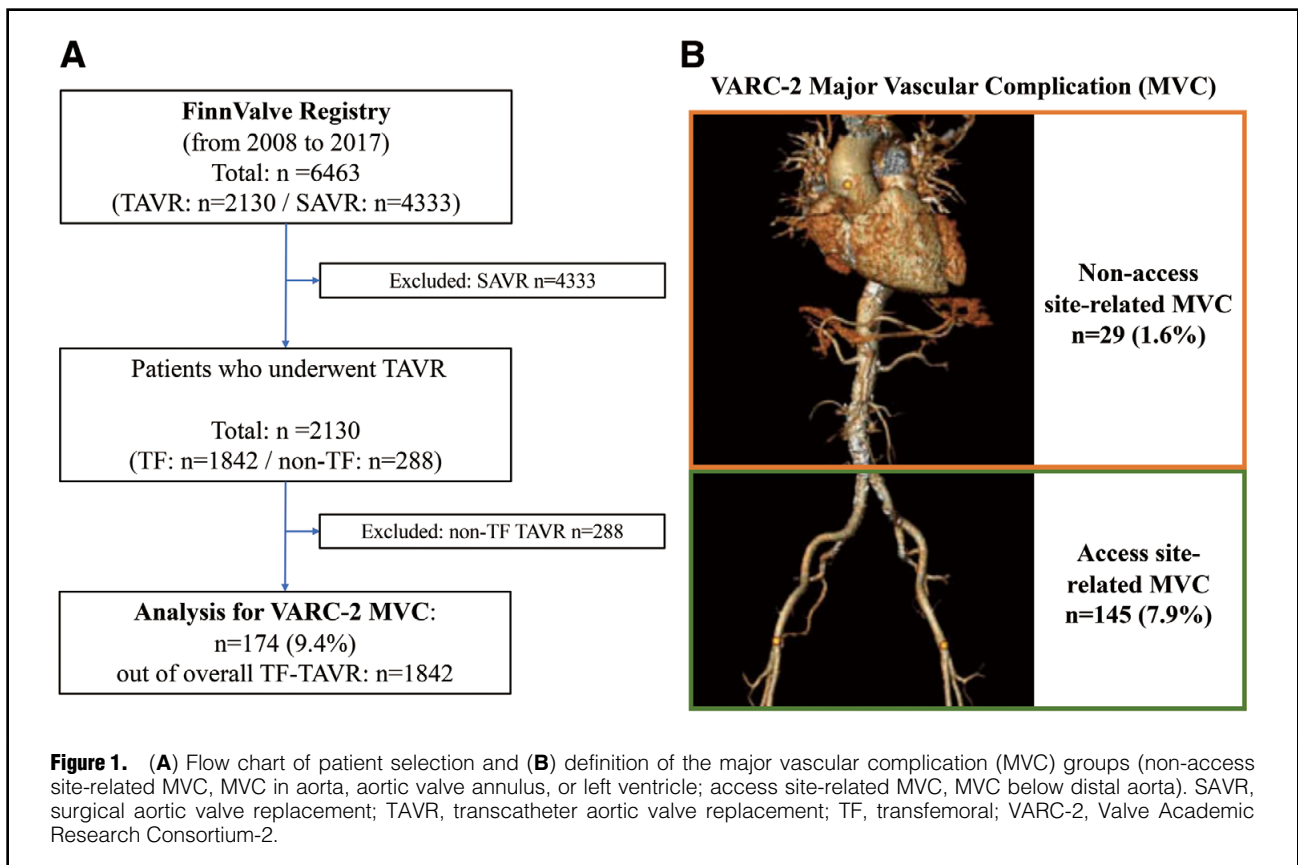
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Mailing address: Mika Laine, MD, PhD, Adjunct Professor of Cardiology, Heart and Lung Center, Helsinki University and Helsinki University Central Hospital, Haartmaninkatu 4, 00290, Helsinki, Finland. E-mail: mika.laine@hus.fi

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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 $\geq 50\%$ 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

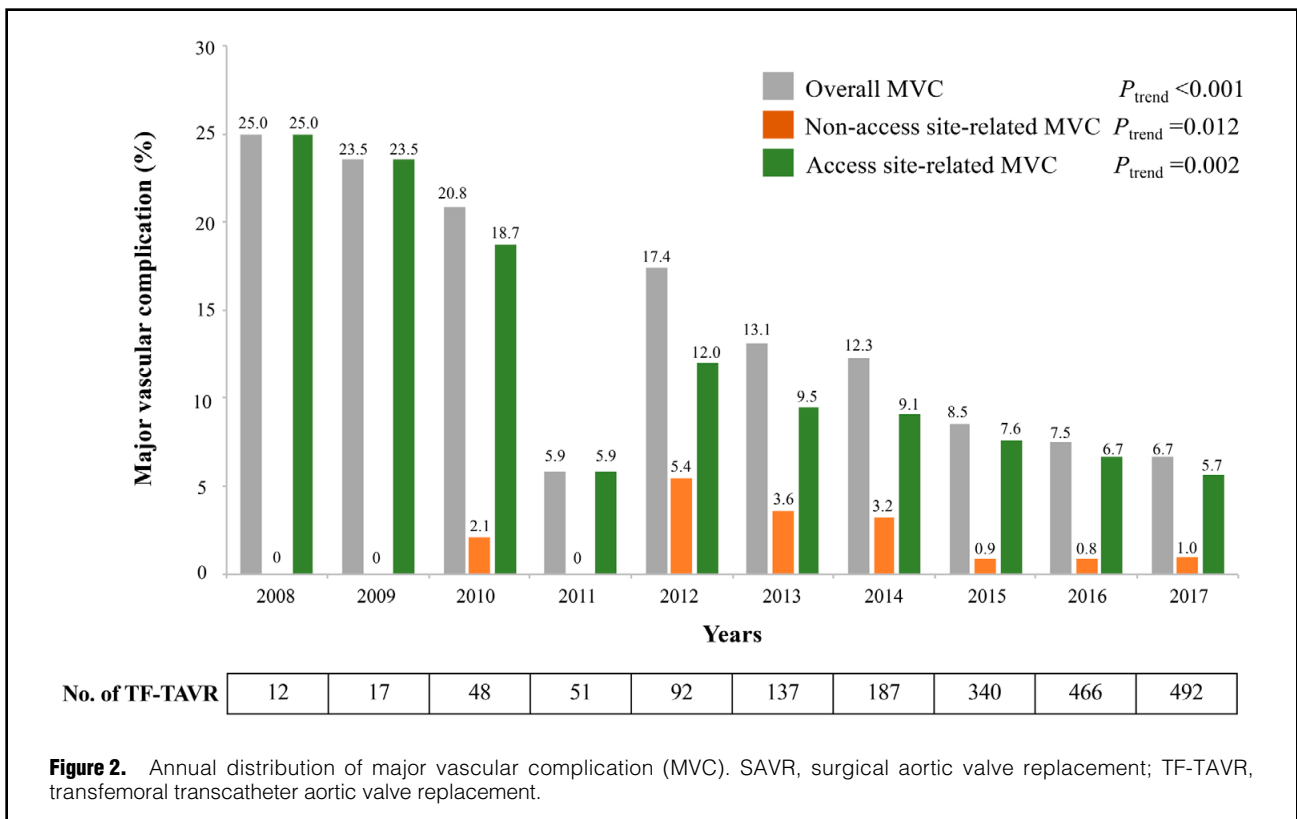


Figure 2. Annual distribution of major vascular complication (MVC). SAVR, surgical aortic valve replacement; TF-TAVR, transfemoral transcatheter aortic valve replacement.

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 \pm 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% ($P_{\text{trend}} < 0.001$). This trend was mainly derived by significant reduction of access site-related MVC (from 25.0% to 5.7%, $P_{\text{trend}} = 0.002$; 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/1.73m 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

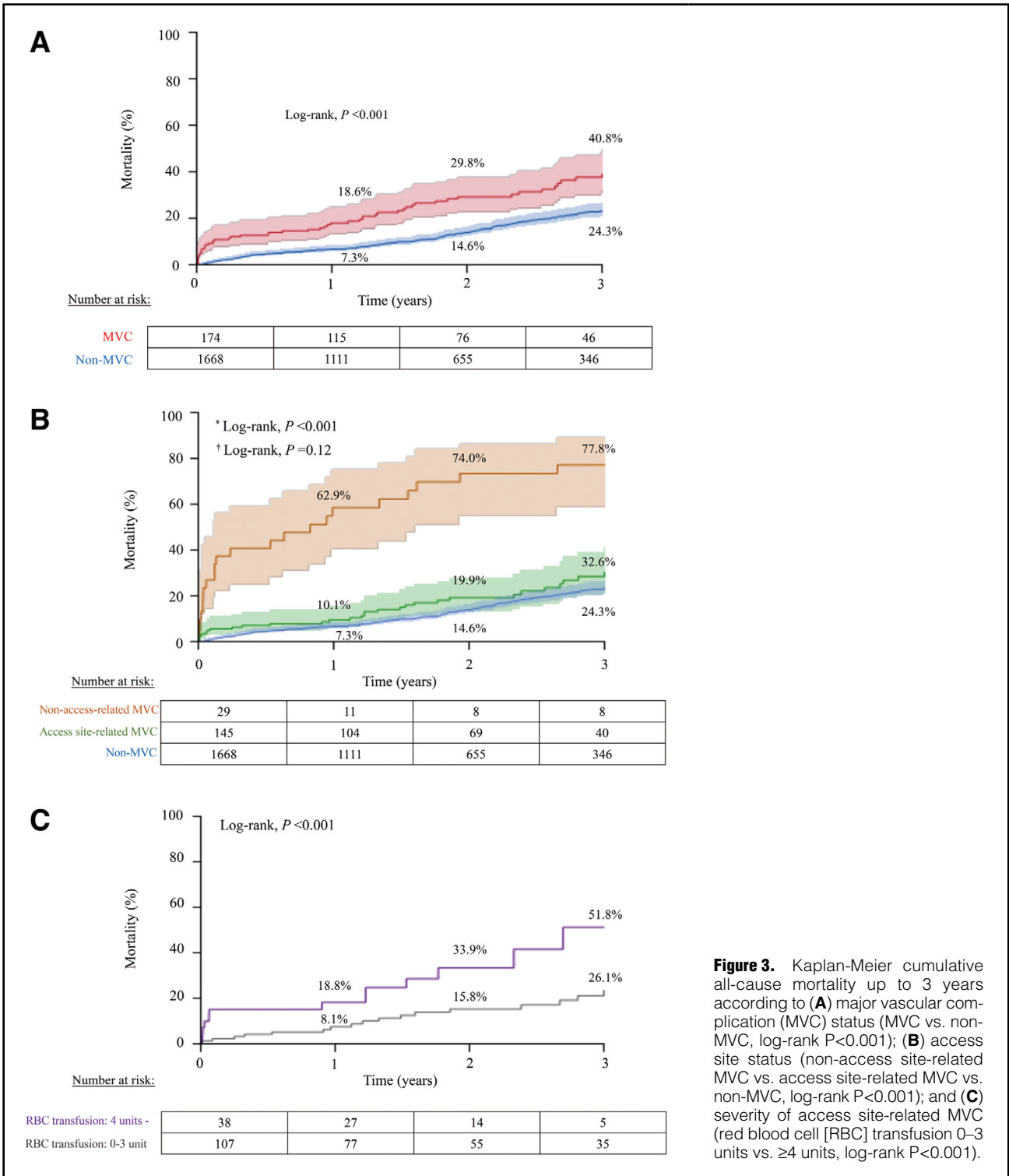


Figure 3. Kaplan-Meier cumulative all-cause mortality up to 3 years according to (A) major vascular complication (MVC) status (MVC vs. non-MVC, log-rank $P < 0.001$); (B) access site status (non-access site-related MVC vs. access site-related MVC vs. non-MVC, log-rank $P < 0.001$); and (C) severity of 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 function²⁷ 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.

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Supplementary Files

Please find supplementary file(s);
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