Journal of the American Heart Association

ORIGINAL RESEARCH

Comparison of Valve Academic Research Consortium (VARC)-2 and VARC-3 Criteria for Bleeding Complications After Transcatheter Aortic Valve Replacement

Stephan Nienaber, MD; Janosch Himken, MD; Max Meertens, MD; Victor Mauri, MD; Samuel Lee, MD; Jonathan Curio, MD; Elmar Kuhn, MD; Richard Nies, MD†; Kaveh Eghbalzadeh, MD; Johannes Dohr, MD; Stephan Baldus, MD; Hendrik Wienemann, MD*; Matti Adam, MD*

BACKGROUND: The Valve Academic Research Consortium (VARC) has updated criteria for periprocedural bleeding after transcatheter aortic valve replacement. However, clinical validation of the VARC-3 bleeding definition is scarce. The aim of this study was to evaluate incidence, associated variables, and clinical impact of VARC-3 bleeding.

METHODS: The study included 2227 patients with severe aortic stenosis undergoing transcatheter aortic valve replacement between 2018 and 2023 at the University Hospital Cologne. VARC-3 bleeding during the index hospitalization were analyzed. Incidence, variables associated with bleeding, and impact on 30-day mortality were evaluated by comparison to the VARC-2 criteria. All data were prospectively collected.

RESULTS: VARC-3 bleeding was 2.5 times more prevalent than VARC-2 (13.9% versus 34.4%), as VARC-3 includes nonattributable blood loss >3 g/dL as a bleeding event. Chronic kidney disease, thoracotomy access, dual antiplatelet therapy (P<0.001 for all), and female sex (P=0.023) were variables associated with VARC-3 bleedings. Type 3 bleeding (VARC-3) was associated with an increased 30-day mortality (hazard ratio [HR], 2.89 [95% CI, 1.35–6.19], P=0.006). VARC-2 major and life-threatening bleeding events were associated with increased 30-day mortality as well (HR, 2.74 [95% CI, 1.26–5.95], P=0.011 and HR, 29.60 [95% CI, 17.42–50.30], P<0.001).

CONCLUSIONS: The VARC-3 criteria present a refined classification for bleeding with prognostic relevance. However, the VARC-2 criteria demonstrate precision and clear correlation with increasing mortality risk proportional to the severity of bleeding too, showing even greater predictive accuracy in the transfemoral cohort. These findings require further validation with similar or even larger patient cohorts.

Key Words: bleeding complications after TAVR ■ prognostic relevance of bleeding ■ VARC-2 ■ VARC-3

Transcatheter aortic valve replacement (TAVR) has become the treatment of choice in older patients with severe aortic stenosis.[1,2] Moreover, the use of TAVR is expanding even in low-risk patients.[3,4] TAVR is associated with similar success but lower periprocedural bleeding rates than surgical aortic valve replacement.[5] Even though periprocedural bleeding was significantly reduced over time due to increasing operator experience and improved transcatheter heart valve technology, periprocedural bleeding remains a relevant drawback after TAVR.[6]

Correspondence to: Stephan Nienaber, MD, Department of Cardiology, Heart Center Cologne, Faculty of Medicine and University Hospital, University of Cologne, Cologne, Kerpener Straße 62, Cologne 50937, Germany. Email: stephan.nienaber@uk-koeln.de

*Hendrik Wienemann and Matti Adam contributed equally.

†R. Nies is only a co-author.

This article was sent to Amgad Mentias, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.039342

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVES

What Is New?

- This analysis provides the first clinical validation of the updated Valve Academic Research Consortium-3 (VARC-3) bleeding criteria in a contemporary transcatheter aortic valve replacement cohort from Germany.

What Are the Clinical Implications?

- Female sex, dual antiplatelet therapy, chronic kidney disease, transaxillary access, thoracotomy access, and larger sheath sizes are variables associated with VARC-3 bleeding.
- The adoption of the new VARC-3 bleeding criteria leads to a substantial increase in bleeding events, and VARC-3 bleeding was associated with increased 30-day mortality.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
TAVR	transcatheter aortic valve replacement
VARC	Valve Academic Research Consortium

The Valve Academic Research Consortium (VARC) has updated criteria for relevant clinical end points and redefined periprocedural bleeding.[7] A prior study found that the VARC-3 bleeding criteria provide an accurate classification system. However, clinical validation of the VARC-3 bleeding definition is available only in a heterogenous patient population treated with outdated transcatheter heart valves and using historical access routes for TAVR.[8] Therefore, the objective of this study was to evaluate incidence, variables associated with bleeding, and clinical impact of VARC-3 bleeding events by analyzing their association with 30-day mortality compared with the earlier VARC-2 criteria in a German cohort receiving current generation transcatheter heart valves mainly via transfemoral access.

METHODS

Study Population

All patients with severe aortic stenosis undergoing TAVR between 2018 and 2023 at the University Cologne were included (2405 patients). A total of 178 patients lacking 30-day follow-up were excluded, resulting in 2227 patients (92.6%) for analysis. Specifications of modern transcatheter heart valves were determined in a multidisciplinary heart team. Transfemoral access was standard and used in 93.4%, whereas transaxillary, transaortic, and transapical access were limited to patients with prohibitive peripheral vascular access. Periprocedural anticoagulation and antithrombotic treatment was used according to international guidelines and oral anticoagulation was paused before TAVR.[9] Unfractionated heparin was routinely administered until the activated clotting time exceeded 250 seconds. At the end of the procedure, heparin was partially neutralized with half the dose of protamine. Written informed consent was obtained before TAVR and the local ethics committee provided full board approval for this analysis. The authors declare that all supporting data are available within the article and its online supplementary files.

Data Collection and Clinical End Points

For this observational study baseline clinical, procedural, and follow-up data were prospectively collected in a web-based database held at the clinical trials unit of Cologne heart center. Clinical follow-up data at 30 days were obtained during prescheduled outpatient clinics or by phone contact. If necessary, referring cardiologists were contacted for further information. The primary end point was all-cause mortality at 30 days after TAVR. Procedure-related bleeding events were systemically collected and adjudicated by members of the local heart team according to the VARC definitions at time of the TAVR procedure.[7,10] Every overt bleeding and periprocedural blood loss was reassessed according to both VARC-2 and VARC-3 criteria, respectively.

Bleeding Events Definition

According to the VARC-2 criteria, bleeding events were classified as minor, major, and life threatening. Minor bleeding was defined as any bleeding worth clinical documentation (e.g. access site hematoma). Major bleeding was classified as overt bleeding either associated with a drop in hemoglobin level of at least 3 g/dL or requiring transfusion of 2 or 3 units of whole blood or packed red blood cells (RBCs). Life-threatening bleeding was defined as fatal bleeding or bleeding in a critical organ (e.g. intracranial, intraspinal, intraocular, pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome); bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery; or overt source of bleeding with a drop in hemoglobin of ≥5 g/dL or whole blood or packed RBCs transfusion ≥4 units.[10]

VARC-3 criteria classify bleeding events as type 1, 2, 3 or 4, with type 1 bleeding as any overt bleeding requiring medical intervention or transfusion of 1 unit of whole blood or RBCs. Type 2 bleeding was determined as overt bleeding associated with a hemoglobin drop of >3 g/dL but <5 g/dL or overt bleeding requiring transfusion of 2 to 4 units of whole blood or RBCs. Type 3 bleeding was characterized as overt bleeding in

a critical organ, causing hypovolemic shock or severe hypotension requiring vasopressors or surgery, requiring reintervention or reoperation, or postthoracotomy chest tube output ≥2 L in 24 hours, or associated with a drop in hemoglobin level of ≥5 g/dL or leading to a transfusion of ≥5 units of whole blood or RBCs. Type 4 bleeding was defined as bleeding leading to death.[7,8] Although the VARC-2 document postulates that bleeding has to be the result of overt bleeding, the VARC-3 document declares that any procedural blood loss should be interpreted as overt bleeding, even in the absence of an obvious source of bleeding.[7,10] Thus, type 2 bleeding events were defined as any procedural blood loss with a hemoglobin decrease of 3 to 5 g/dL and type 3 bleeding events were defined as any procedural blood loss with a hemoglobin decrease of ≥5 g/dL. It is important to note that in this article, procedural blood loss (type 2 or type 3 bleeding) is classified as non-attributable bleeding if it is defined solely by a hemoglobin decrease without a clinically apparent source of bleeding. We analyzed hemoglobin levels 1-day prior TAVR and the lowest value within 96 hours after TAVR to identify periprocedural blood loss and the extent of overt bleeding during the index hospitalization. The administration of RBCs during hospitalization and whether it was related to overt bleeding was carefully evaluated to classify bleeding severity. At our institution, patients with hemoglobin levels <7 g/dL usually receive 1 to 2 units of RBCs before TAVR, and patients with renal failure were administered 500 mL of isotonic saline solution before the procedure.

Statistical Analysis

Continuous variables were tested for normality using Kolmogorov–Smirnov test and Shapiro–Wilk test. Differences were tested using the Mann–Whitney *U* test or the Student's *t* test for independent samples, and variables are reported as mean±SD or median (Q1–Q3). Categorical variables are presented as frequencies and percentages using the chi-square test for statistical separation. Baseline characteristics like comorbidities and medication use (antithrombotic agents and oral anticoagulation) as well as procedural data were explored to determine variables associated with VARC-3 bleeding events by univariable logistic regression analysis. Any variable with $P<0.10$ was included in a variable logistic regression model and multivariable variables associated with bleeding are reported as odds ratio (OR; 95% CI). Cox regression analyses were performed separately for VARC-2 and VARC-3 bleeding events to evaluate their effect on 30-day mortality. VARC-2 and VARC-3 bleeding events were included as covariates in the model and the reference category for hazard ratios (HR) was cases without bleeding events. The Cox regression analysis for VARC-2 and VARC-3 bleeding was adjusted for potential confounders, including arterial hypertension, diabetes, peripheral artery disease, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, prior stroke, chronic kidney disease, previous cardiac surgery, and previous myocardial infarction. Kaplan–Meier estimates were performed to build survival curves, which were compared using the log-rank-test. In this article, the term "prognostic relevance" is used to describe the statistical approach for assessing associations between clinical variables and short-term outcomes using Kaplan–Meier-estimates and multivariable Cox regression analysis. All statistical tests were 2 tailed, and $P<0.05$ was considered statistically significant. Calculations were performed using SPSS Version 29.0.2.0 for Mac (IBM SPSS Statistics) and R Version 4.3.3 (R Foundation for Statistical Computing).

RESULTS

Baseline Characteristics

The analysis included 2227 patients undergoing TAVR at the University Heart Center Cologne between 2018 and 2023. The median age was 82.3 (Q1–Q3: 78.4–85.4) years and 46.7% were women. The median Society of Thoracic Surgeons Predicted Risk of Mortality score was 3.25% (Q1–Q3: 2.24%–4.98%). Transfemoral TAVR was performed in 93.4% of the procedures; 63.6% of the patients were treated with self-expanding valves. Transaxillary, transapical, and transaortic access was used in 4.5%, 1.8%, and 0.4% of patients, respectively. Baseline and procedural characteristics including antithrombotic treatment and anticoagulation are shown in Tables 1 and 2.

Incidence and Severity of Bleeding

VARC-2 bleeding complications occurred in 13.9% of patients. Most patients (133, 6.0%) experienced major bleeding. An additional 72 patients (3.2%) suffered life-threatening bleeding and 26 of these patients died within 30 days.104 patients (4.7%) had minor bleeding. When applying the VARC-3 criteria significantly more bleeding events were captured (13.9% versus 34.4%, $P<0.001$) (Figure 1). Type 2 and type 3 bleedings were frequent subtypes with 24.2% and 6.6%, respectively. A total of 54 patients (2.4%) experienced type 1 bleeding, and 24 patients (1.1%) had fatal bleeding (type 4 bleeding). Table 3 illustrates the reclassification of VARC-2 bleeding events under the new VARC-3 criteria, largely driven by the inclusion of non-attributable periprocedural blood loss. Nearly 21% (460 patients) of patients experienced VARC-3 bleedings resulting from non-attributable periprocedural blood loss, representing 60% of all VARC-3 bleedings.

Table 1. Baseline Characteristics, Overall and According to the Presence of VARC-3 Bleeding

Baseline characteristics	Total (N=2227)	No bleeding (N=1462, 65.6%)	Bleeding (N=765, 34.4%)	*P* value
Age, y	82.3 (78.4–85.4)	82.2 (78.2–85.2)	82.3 (78.8–85.7)	0.252
Female sex	1039 (46.7%)	650 (44.5%)	389 (50.8%)	0.004
Body mass index, kg/m^2	26.1 (23.6–29.4)	26.3 (23.7–29.7)	26.0 (23.4–29.3)	0.108
Diabetes	620 (27.8%)	411 (28.1%)	209 (27.3%)	0.692
Hypertension	1908 (85.7%)	1262 (86.3%)	646 (84.4%)	0.230
Peripheral artery disease	373 (16.7%)	232 (15.9%)	141 (18.4%)	0.124
Coronary artery disease	1344 (60.4%)	866 (59.2%)	478 (62.5%)	0.137
Previous myocardial infarction	215 (9.7%)	131 (9.0%)	84 (11.0%)	0.125
Previous cardiac surgery	232 (10.4%)	143 (9.8%)	89 (11.6%)	0.174
Previous stroke	200 (9.0%)	127 (8.7%)	73 (9.5%)	0.502
Chronic obstructive pulmonary disease	252 (11.3%)	154 (10.5%)	98 (12.8%)	0.107
Atrial fibrillation/flutter	874 (39.2%)	594 (40.6%)	280 (36.6%)	0.065
Chronic kidney disease	1151 (51.7%)	714 (48.8%)	437 (57.1%)	<0.001
Dialysis	52 (2.3%)	34 (2.3%)	18 (2.4%)	0.968
Previous pacemaker	243 (10.9%)	176 (12.0%)	67 (8.8%)	0.018
Left ventricular ejection fraction category				0.600
>50%	1760 (79.0%)	1144 (78.2%)	616 (80.5%)	
41%–50%	210 (9.4%)	140 (9.6%)	70 (9.2%)	
31%–40%	144 (6.5%)	97 (6.6%)	47 (6.1%)	
<31%	108 (4.8%)	78 (5.3%)	30 (3.9%)	
New York Heart Association functional class III/IV	1496 (67.2%)	968 (66.2%)	528 (69.0%)	0.180
European System for Cardiac Operative Risk Evaluation score II	3.44 (2.06–5.50)	3.19 (1.99–5.39)	3.75 (2.16–5.85)	<0.001
Society of Thoracic Surgeons score	3.25 (2.24–4.98)	3.15 (2.20–4.75)	3.43 (2.36–5.27)	0.006
Aortic valve mean gradient, mm Hg	43.0 (37.0–51.0)	43.0 (36.0–51.0)	44.0 (37.5–52.0)	0.027
Aortic valve area, cm^2	0.70 (0.60–0.90)	0.70 (0.60–0.90)	0.70 (0.60–0.83)	0.043
Baseline hemoglobin, g/dL	12.3 (11.1–13.5)	12.2 (10.9–13.4)	12.7 (11.5–13.8)	<0.001
Baseline platelets, ×10^3/qL	217 (177–262)	217 (176–263)	216 (177–261.5)	0.807
Acetylsalicylic acid	1005 (45.1%)	627 (42.9%)	378 (49.4%)	0.003
P2Y$_{12}$ inhibitor	571 (25.6%)	327 (22.4%)	244 (31.9%)	<0.001
Anticoagulation	798 (35.8%)	558 (38.2%)	240 (31.4%)	0.001
Vitamin K antagonist	176 (7.9%)	111 (7.6%)	65 (8.5%)	0.453
Direct oral anticoagulant	622 (27.9%)	446 (30.5%)	176 (23.0%)	<0.001
SAPT	690 (31.0%)	449 (30.7%)	241 (31.5%)	0.701
DAPT	356 (16.0%)	195 (13.3%)	161 (21.0%)	<0.001
SAPT+anticoagulation	192 (8.6%)	126 (8.6%)	66 (8.6%)	0.994
DAPT+anticoagulation	18 (0.8%)	11 (0.8%)	7 (0.9%)	0.684

Values are median (Q1–Q3) or n (%). Group comparisons were performed using the Mann–Whitney *U* test or Student's *t* test for continuous variables and the chi-square test for categorical variables. DAPT indicates dual antiplatelet therapy; SAPT, single antiplatelet therapy; and VARC, Valve Academic Research Consortium.

The incidence of bleeding events has demonstrated a marked decline over recent years in our TAVR program (Figure 2).

Factors Associated With Bleeding Events

As shown in Table 1, VARC-3 bleeding was more frequent in women. The burden of diabetes, arterial hypertension, peripheral artery disease, coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation, and heart failure with reduced ejection fraction was similar in patients with and without bleeding events. In addition, the rates of previous cardiac surgery, previous myocardial infarction or stroke, and New York Heart Association functional class III/IV did not differ. However, chronic kidney disease was more common in the bleeding group (48.8% versus 57.1%, *P*<0.001), and patients with bleeding events were

Table 2. Procedural and Discharge Characteristics, Overall and According to the Presence of VARC-3 Bleeding

Procedural and discharge characteristics	Total (N=2227)	No bleeding (N=1462, 65.6%)	Bleeding (N=765, 34.4%)	*P* value
Procedure urgency				0.116
Elective	1967 (88.3%)	1280 (87.6%)	687 (89.6%)	
Urgent	260 (11.7%)	182 (12.4%)	78 (10.2%)	
Procedure time, min	57 (46–72)	54 (44–66.5)	63 (52–86)	<0.001
Vascular access				<0.001
Transfemoral	2080 (93.4%)	1390 (95.1%)	690 (90.2%)	
Transaxillary	100 (4.5%)	58 (4.0%)	42 (5.5%)	
Transapical	39 (1.8%)	13 (0.9%)	26 (3.4%)	
Transaortic	8 (0.4%)	1 (0.1%)	7 (0.9%)	
Prosthesis type				0.118
Balloon expanding	809 (36.4%)	515 (35.3%)	294 (38.6%)	
Self-expanding	1412 (63.6%)	945 (64.7%)	467 (61.4%)	
Prothesis size	27.35±2.80	27.57±2.74	26.93±2.87	<0.001
Predilatation	1323 (59.4%)	873 (59.7%)	450 (58.8%)	0.685
Postdilatation	326 (14.6%)	211 (14.4%)	115 (15.0%)	0.703
Discharge data				
Admission length, d	7.0 (5.0–10.0)	7.0 (5.0–9.0)	8.0 (6.0–14.0)	<0.001
Intensive care unit admission length, d	2.0 (1.0–3.0)	1.0 (1.0–2.0)	2.0 (1.0–4.0)	<0.001
Paravalvular leak ≥moderate	85 (3.9%)	54 (3.7%)	31 (4.3%)	0.546
Acetylsalicylic acid	1287 (58.8%)	827 (57.1%)	460 (62.2%)	0.022
$P2Y_{12}$ inhibitor	571 (25.6%)	327 (22.4%)	244 (31.9%)	<0.001
Clopidogrel	557 (25.0%)	324 (22.2%)	233 (30.5%)	<0.001
Ticagrelor/Prasugrel	14 (0.6%)	3 (0.2%)	11 (1.4%)	<0.001
Anticoagulation	951 (42.7%)	648 (44.3%)	303 (39.6%)	0.033
Vitamin K antagonist	492 (22.1%)	308 (21.1%)	184 (24.0%)	0.040
Direct oral anticoagulant	459 (20.6%)	340 (23.3%)	119 (15.6%)	<0.001
DAPT	691 (31.0%)	395 (27.0%)	296 (38.7%)	<0.001
SAPT	577 (25.9%)	423 (28.9%)	154 (20.1%)	<0.001
SAPT+anticoagulation	295 (13.2%)	174 (11.9%)	121 (15.8%)	0.010
DAPT+anticoagulation	31 (1.4%)	15 (1.0%)	16 (2.1%)	0.042

Values are median (Q1–Q3) or n (%). Group comparisons were performed using the Mann–Whitney *U* test or Student's *t* test for continuous variables and the chi-square test for categorical variables. DAPT indicates dual antiplatelet therapy; SAPT, single antiplatelet therapy; and VARC, Valve Academic Research Consortium.

associated with higher Society of Thoracic Surgeons scores. Patients in the bleeding group exhibited higher transvalvular mean gradients and smaller aortic valve areas. There was no difference regarding the level of baseline platelets, but baseline hemoglobin was slightly higher in the bleeding group. Patients with bleeding more frequently took acetylsalicylic acid (42.9% versus 49.4%, *P*: 0.003), $P2Y_{12}$ inhibitors (22.4% versus 31.9%, *P*<0.001), and dual antiplatelet therapy (DAPT; 13.3% versus 21.0%, *P*<0.001) before TAVR. Conversely, anticoagulation in general (38.2% versus 31.4%, *P*=0.001) and anticoagulation with direct oral anticoagulants (30.5% versus 23.0%, *P*<0.001) was more frequent in patients without bleeding. Treatment with vitamin K antagonist alone did not differ between the 2 groups.

Bleeding events were associated with procedural duration and more frequent use of transaxillary (4.0% versus 5.5%) and thoracotomy (1.0% versus 4.3%) access. The average prosthesis size was smaller in the bleeding group. Overall admission and stay on intensive care were longer in patients with bleeding. At discharge antithrombotic treatment and anticoagulation with vitamin K antagonist were more common in the bleeding group, whereas anticoagulation with direct oral anticoagulants was more frequent in patients who did not experience bleeding.

Variables Associated With Bleeding

Multivariable variables associated with periprocedural VARC-3 bleeding were female sex (OR, 1.25 [95% CI,

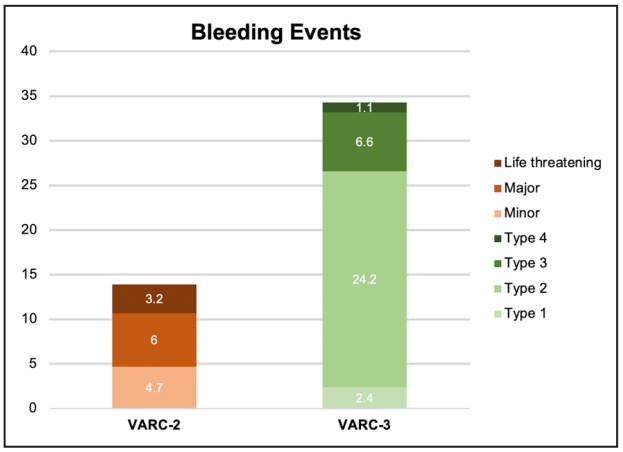

Figure 1. Incidence of bleeding events according to VARC-2 and VARC-3 criteria in percentages.
VARC indicates Valve Academic Research Consortium.

1.03–1.51], *P*=0.023), chronic kidney disease (OR, 1.40 [95% CI, 1.17–1.68], *P*<0.001), the intake of DAPT (OR, 1.61 [95% CI, 1.26–2.05], *P*<0.001), transaxillary access (OR, 1.58 [95% CI, 1.04–2.40], *P*=0.033), thoracotomy (transapical and transaortic) access (OR, 5.20 [95% CI, 2.73–9.89], *P*<0.001), a body mass index (BMI)<18.5 (OR, 2.11 [95% CI, 1.09–4.08], *P*=0.026), and larger sheath sizes of 18 to 19 Fr (OR, 1.85 [95% CI, 1.30–2.62], *P*<0.001) as well as sheath sizes of 20 to 24 Fr (OR, 2.12 [95% CI, 1.43–3.13], *P*<0.001). Patients with a BMI between 35 and 40 also tended to have a higher risk for VARC-3 bleeding, yet this finding was not significant (OR, 1.51 [95% CI, 0.99–2.23], *P*=0.052). Direct oral anticoagulant was protective for VARC-3 bleeding (OR, 0.72 [95% CI, 0.58–0.90], *P*=0.003) (Table 4, Figure 3). When excluding patients with alternative access, this effect was consistent for the transfemoral TAVR cohort (n=2080). Moreover, other variables associated with VARC-3 bleeding also remained the same for the transfemoral cohort (Table 4).

DAPT, thoracotomy access, and chronic kidney disease also remained significant variables associated with VARC-2 bleeding, whereas female sex and transaxillary access showed only borderline significance (Table S1). A low BMI (<18.5) and a larger sheath size did not emerge as an associated variable for VARC-2 bleeding, even in the univariable analysis.

Table 3. Reclassification and Distribution Analysis of Overt VARC-2 Bleedings Based on the Updated VARC-3 Criteria

	Minor	Major	Life threatening	Total
Type 1	52	0	0	52
Type 2	39	84	1	124
Type 3	5	49	47	101
Type 4	0	0	24	24
No bleeding	8	0	0	8
Total	104	133	72	309

VARC indicates Valve Academic Research Consortium.

Bleeding Events and Mortality

In our cohort, a total of 69 patients (3.1%) died at 30 days post TAVR. Patients with VARC-3 bleeding showed progressive increase in 30-day mortality according to severity of bleeding. No patient with type 1 bleeding died within 30 days after TAVR and the impact of type 2 bleeding on 30-day mortality was not significant (HR, 1.00 [95% CI, 0.49–2.03], *P*=0.998). However, type 3 bleeding was strongly associated with mortality (HR, 2.89 [95% CI, 1.35–6.19], *P*=0.006), and type 4 bleeding led to death per definition (Table 5, Figure 4A). When applying VARC-2 criteria, minor bleeding was not associated with 30-day mortality as mortality was zero. Nevertheless, both major (HR, 2.74 [95% CI, 1.26–5.95], *P*=0.011) and life-threatening bleeding (HR, 29.60 [95% CI, 17.42–50.30], *P*<0.001) were strongly associated with increased mortality risk (Table 5, Figure 4B).

A total of 460 patients (20.7%) experienced isolated non-attributable periprocedural blood loss according to the VARC-3 criteria. Non-attributable blood loss between 3 and 5 g/dL, classified as type 2 bleeding, had no impact on 30-day mortality (HR, 0.65 [95% CI, 0.25–1.69], *P*=0.378). However, non-attributable periprocedural blood loss >5 g/dL (type 3 bleeding) was associated with higher mortality risk when compared with patients without periprocedural blood loss (HR, 3.60 [95% CI, 1.09–11.87], *P*=0.035). Considering only patients with transfemoral TAVR, VARC-3 type 3 bleeding was no longer associated with mortality (HR, 1.15 [95% CI, 0.35–3.84], *P*=0.818), whereas both VARC-2 major and life-threatening bleeding still related to increased mortality risk (HR, 2.48 [95% CI, 1.02–6.04], *P*=0.045 and HR, 33.99 [95% CI, 18.88–61.18], *P*<0.001) (Table 5).

DISCUSSION

The present analysis focuses on incidence, variables associated with bleeding, and impact of periprocedural bleeding according to the VARC-3 definition on 30-day mortality in a contemporary German all comers cohort undergoing mainly transfemoral (93.4%) TAVR between 2018 and 2023. Main findings revealed that (1) bleeding events according to the VARC-3 definition occurred in 34.3% of patients undergoing TAVR compared with 13.9% using VARC-2 criteria; (2) DAPT was associated with a higher risk of bleeding whereas pre-TAVR intake of direct oral anticoagulants was not associated with bleeding; (3) female sex, chronic kidney disease,

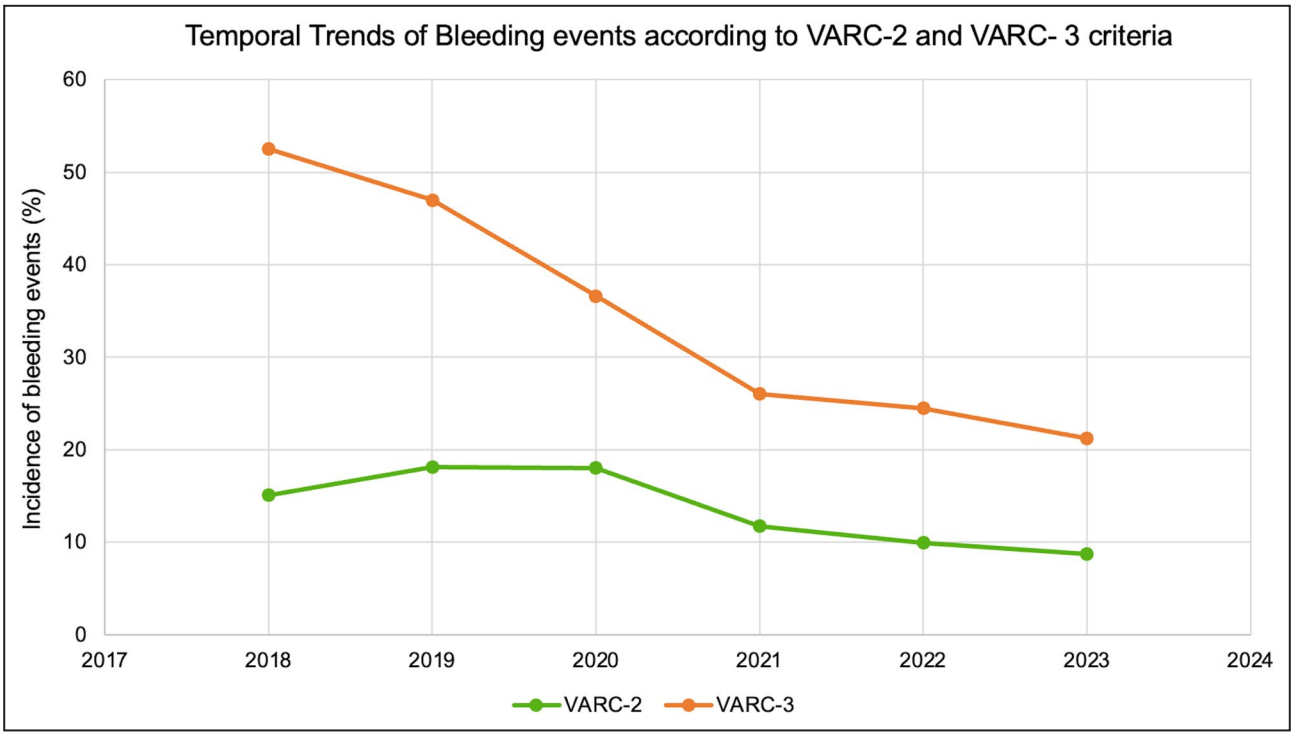

Figure 2. Temporal trends of bleeding events according to VARC-2 and VARC-3 criteria.
VARC indicates Valve Academic Research Consortium.

transaxillary access, thoracotomy access, BMI ≤18.5, and a larger sheath size were independent variables associated with VARC-3 bleeding events after TAVR; (4) both VARC-2 and VARC-3 overall bleeding events were associated with increased 30-day mortality; and (5) non-attributable periprocedural blood loss with a drop in hemoglobin level >5 g/dL (type 3 bleeding) was associated with increased mortality risk, whereas periprocedural blood loss between 3 and 5 g/dL (type 2 bleeding) had no impact on mortality (Graphical Abstract).

Incidence of Bleeding Events

The lower rate of vascular and bleeding complications is considered one of the key advantages of TAVR over conventional surgery.[11] Nevertheless, patients with severe aortic stenosis carry a substantial risk for bleeding complications due to advanced age, high comorbidity burden, and use of antithrombotic medication.[12] Thus, bleeding has been identified as a relevant complication in the TAVR population.[13] We could demonstrate that bleeding events after TAVR occurred in 34.4% of patients when applying the VARC-3 definition, even with advanced transcatheter heart valve technologies of a high-volume center (Figure 1). Using the new VARC-3 definition a substantial augmentation of bleeding events was seen, because periprocedural blood loss is considered as overt bleeding even in the absence of an obvious bleeding source. Isolated non-attributable periprocedural blood loss accounted for nearly two thirds (60.1%) of VARC-3 bleeding events. Conversely, VARC-2 bleeding events, dismissing isolated periprocedural blood loss, occurred in only 13.9% of this patient cohort. These surprising disparities between VARC-2 and VARC-3 bleeding rates need to be acknowledged for every comparison. The reported bleeding rates decreased from 2018 to 2023 every year, likely to be attributed to increasing operator experience, improved valve and sheath technology, larger proportion of low-risk patients, and better strategies for local hemostasis[14] (Figure 2).

Variables Associated With Bleeding Events

In our study we were able to identify variables that were significantly associated with increased risk for VARC-3 bleeding events. DAPT before TAVR was an independent risk factor in the multivariable model. As DAPT is mainly prescribed after percutaneous coronary intervention (PCI), our findings add observational evidence to the ongoing debate around timing of PCI and DAPT in the context of TAVR. PCI and DAPT before TAVR should be considered with caution and limited to patients with severe coronary artery disease in proximal vessel segments, especially those with significant symptoms or with acute coronary syndrome.[15] If PCI is not deferable, shortening DAPT to 1 or 3 months may be considered as subsequent $P2Y_{12}$ monotherapy was associated with lower risk for major bleeding compared

Table 4. Multivariable Variables Associated With VARC-3 Bleeding Events for the Entire Patient Cohort and the Transfemoral Cohort Only

Variables associated with VARC-3 bleeding (entire cohort)	Odds ratio (95% CI)	*P* value
Female sex	1.25 (1.03–1.51)	0.023
Chronic kidney disease	1.40 (1.17–1.68)	<0.001
DOAC	0.72 (0.58–0.90)	0.003
DAPT	1.61 (1.26–2.05)	<0.001
Transaxillary access	1.58 (1.04–2.40)	0.033
Thoracotomy access	5.20 (2.73–9.89)	<0.001
BMI<18.5 kg/m^2	2.28 (1.18–4.42)	0.014
BMI 25–30 kg/m^2	1.06 (0.86–1.31)	0.574
BMI 30–35 kg/m^2	0.86 (0.65–1.13)	0.277
BMI 35–40 kg/m^2	1.51 (0.99–2.23)	0.052
BMI>40 kg/m^2	0.80 (0.37–1.71)	0.563
ASA	0.94 (0.73–1.21)	0.629
Anticoagulation	0.95 (0.66–1.38)	0.792
Sheath size: 15–16 Fr	0.96 (0.77–1.19)	0.705
Sheath size: 18–19 Fr	1.85 (1.30–2.62)	<0.001
Sheath size: 20–24 Fr	2.12 (1.43–3.13)	<0.001

Variables associated with VARC-3 bleeding (transfemoral cohort only)	Odds ratio (95% CI)	*P* value
Female sex	1.30 (1.07–1.59)	0.008
Chronic kidney disease	1.47 (1.21–1.78)	<0.001
DOAC	0.71 (0.57–0.89)	0.003
DAPT	1.58 (1.23–2.04)	<0.001
Age 70–80 y	1.58 (0.92–2.71)	0.097
Age 80–90 y	1.51 (0.89–2.56)	0.130
Age>90 y	1.73 (0.89–3.35)	0.104
BMI<18.5 kg/m^2	2.54 (1.24–5.18)	0.011
BMI 25–30 kg/m^2	1.08 (0.87–1.34)	0.477
BMI 30–35 kg/m^2	0.86 (0.65–1.15)	0.311
BMI 35–40 kg/m^2	1.57 (1.03–2.41)	0.037
BMI>40 kg/m^2	0.85 (0.39–1.84)	0.683
ASA	0.96 (0.75–1.22)	0.720
Anticoagulation	0.92 (0.62–1.35)	0.661
Sheath size: 15–16 Fr	0.99 (0.80–1.25)	0.977
Sheath size: 18–19 Fr	1.85 (1.30–2.63)	<0.001
Sheath size: 20–24 Fr	2.12 (1.43–3.13)	<0.001

The reference group for age categories was <70 years of age. The reference group for BMI categories was a BMI between 18.5 and 25.0 kg/m^2. The reference group for sheath size was ≤14 Fr. The blue table represents multivariable variables associated with VARC-3 bleeding for the entire cohort, and the orange table shows multivariable variables associated with VARC-3 bleeding of the transfemoral cohort only. ASA indicates acetylsalicylic acid; BMI, body mass index; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant agent; and VARC, Valve Academic Research Consortium.

with standard DAPT after PCI.[16,17] This approach would allow TAVR 1 month after PCI, although reliable data on optimal timing of PCI in patients before TAVR are scarce.[6] Surprisingly, the use of oral anticoagulation was not associated with an increased risk of bleeding and may be attributable to the periprocedural pausing of anticoagulation and possibly to more attention to access sites in patients on anticoagulation. Moreover, patients without oral anticoagulation more commonly received DAPT, likely explaining the protective effect due to underlying increased bleeding risk in parts of the comparison group. Female sex constitutes an additional risk factor for VARC-3 bleeding, probably explained by smaller and more tortuous iliac vessels and higher age compared with male patients as previously reported.[18,19] Transaxillary access was a significant variable associated with VARC-3 bleeding, which is in line with previous findings.[20] This is likely attributable to the less frequent use of this access route and the lower compressibility of the axillary artery compared with the transfemoral approach. As anticipated, thoracotomy (transapical and transaortic) access was associated with elevated bleeding risk, as a mini-thoracotomy or a surgical cutdown is needed.[21] Any central access route is known for increased mortality risk following TAVR and should be avoided.[22,23] Lastly, both patients with underweight (BMI<18.5) and severe obesity (BMI: 35–40) seem to exhibit an elevated risk of bleeding. The impact of BMI on periprocedural bleeding after TAVR is not clear yet, although the RISPEVA (Registro Italiano GISE sull'Impianto di Valvola Aortica Percutanea) registry confirmed an association of elevated BMI with a higher probability of bleeding and vascular complications.[24,25] Increased rate of bleeding and vascular complications in patients with obesity may be related to complicated vascular access and closure, whereas frailty and small peripheral vessels are contributing factors for access-site bleeding in underweight patients.[24] Finally, a larger sheath size (18–19 Fr and 20–24 Fr) is associated with an increased risk of VARC-3 bleeding, which appears clinically plausible.

Clinical Impact of Bleeding Events After TAVR

TAVR patients comprise older individuals with multiple comorbidities and prevalent antithrombotic treatment, with an inherently elevated risk for bleeding complications. In our cohort, the burden of comorbidities was not different between patients with or without bleeding except for chronic kidney disease at baseline. Therefore, based on our data and in contrast to previously published results, we can hypothesize that clinical outcomes are predominantly influenced by bleeding events rather than by major differences in preexisting comorbidities.[8] Although no patient with type 1 bleeding died and even type 2 bleeding failed to constitute a mortality risk, patients with type 3 bleeding faced an approximately 2.9-fold increase in 30-day

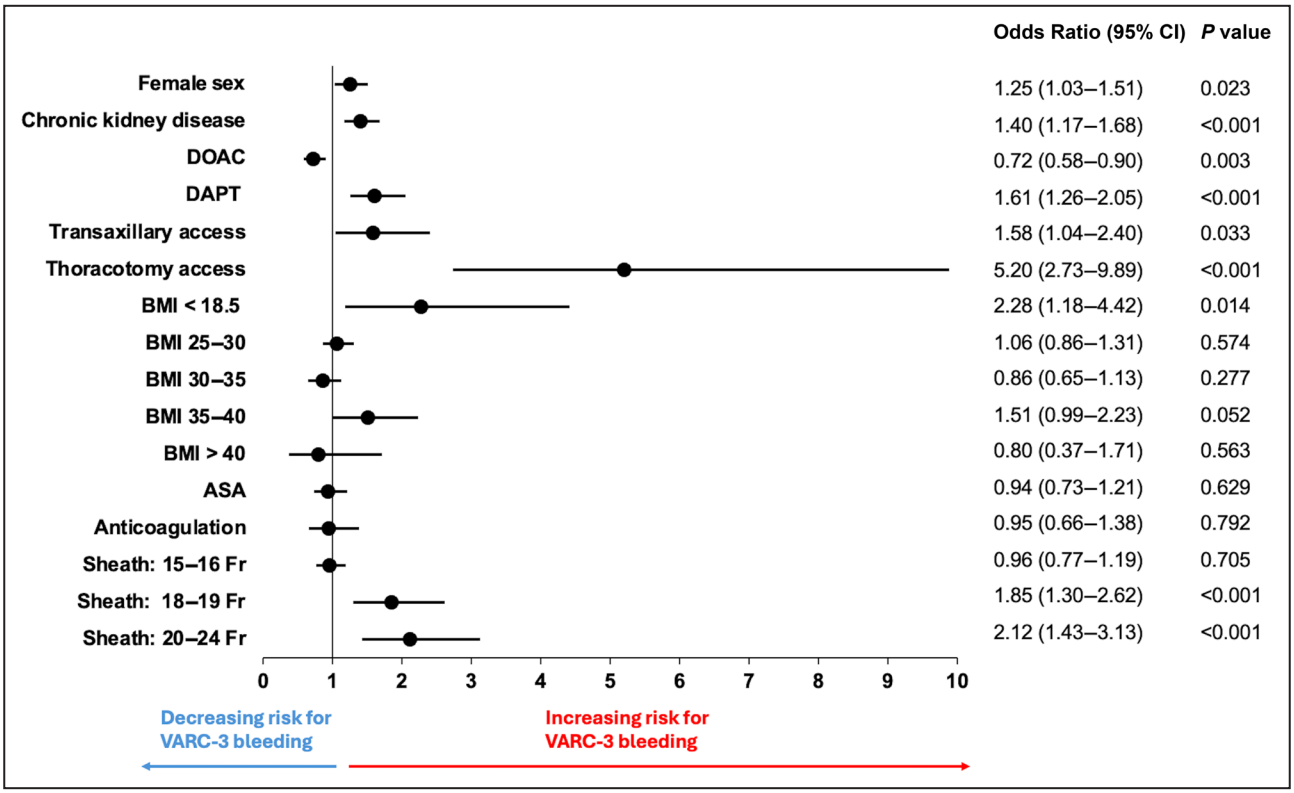

Figure 3. Variables associated with VARC-3 bleeding events.
ASA indicates acetylsalicylic acid; BMI, body mass index; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant agent; and VARC, Valve Academic Research Consortium.

mortality. Type 4 bleeding events were, by definition, all fatal (Figure 4A, Table 5).

The finding that type 2 bleeding is not associated with 30-day mortality contradicts prior data from Avvedimento et al. Notably, the previous cohort had a higher prevalence of major comorbidities, such as chronic obstructive pulmonary disease, peripheral artery disease, and prior myocardial infarction, as well as a greater number of patients with prior cardiac surgeries. Their average Society of Thoracic Surgeons score was 5.2, about 2 points higher than in our cohort.[8] It is doubtful that type 2 bleeding alone, in a cohort with a baseline hemoglobin of ~12 g/dL, significantly affects 30-day mortality post TAVR. It seems more plausible that 30-day mortality was driven by underlying conditions and unreported complications, such as infections. Nevertheless, type 2 bleeding may contribute to mortality in patients with complex comorbidities, potentially explaining why its impact on 30-day mortality is not significant in our less comorbid cohort.

When applying VARC-2 criteria to the same patients, the association of bleeding events and mortality at 30 days was similar. Accordingly, no patient with minor bleeding died within 30 days, whereas major bleeding would have increased the risk of death 2.74 times, and life-threatening bleeding was associated with a 29-fold increased risk of death (Figure 4B, Table 5).

In the light of these findings both the VARC-2 and the VARC-3 criteria exhibit prognostic relevance, but neither one appears to be superior in terms of applicability. Analyzing the transfemoral cohort only, the VARC-3 criteria appear to lose prognostic relevance as type 3 bleedings are not significantly associated with elevated mortality when non-transfemoral access was excluded (HR, 1.15 [95% CI, 0.35–3.84], P=0.805). With more frequent use of transfemoral access the VARC-3 criteria will lose any incremental impact, whereas VARC-2 criteria will not lose validity as shown. Besides mortality, repercussions of bleeding events also affect prolonged intensive care and hospital stay with significant economic burden on the health care system.[26] Regardless of applied criteria, the message is to avoid major bleeding as an anemic environment is associated with increased odds of mortality in similar interventions.[27]

Clinical Implications of VARC-3 Bleeding Events

The new VARC-3 criteria differ from the previous VARC-2 criteria in 2 key aspects. First, the number of

Table 5. Association Between Bleeding Events and 30-Day Mortality According to VARC-3 and VARC-2 Criteria in the Entire Patient Cohort and Transfemoral TAVR Patients Only

VARC-3 bleeding (entire cohort)	Hazard ratio (95% CI)	*P* value
30 d mortality		
No bleeding	…	…
Type 1*	…	…
Type 2	1.00 (0.49–2.03)	0.998
Type 3	2.89 (1.35–6.19)	0.006
Type 4	…	…
VARC-3 bleeding (transfemoral cohort only)	**Hazard ratio (95% CI)**	***P* value**
30 d mortality		
No bleeding	…	…
Type 1*	…	…
Type 2	0.91 (0.42–1.96)	0.805
Type 3	1.15 (0.35–3.84)	0.818
Type 4	…	…
VARC-2 bleeding (entire cohort)	**Hazard ratio (95% CI)**	***P* value**
30 d mortality		
No bleeding	…	…
Minor*	…	…
Major	2.74 (1.26–5.95)	0.011
Life threatening	29.60 (17.42–50.30)	<0.001
VARC-2 bleeding (transfemoral cohort only)	**Hazard ratio (95% CI)**	***P* value**
30 d mortality		
No bleeding	…	…
Minor*	…	…
Major	2.48 (1.02–6.04)	0.045
Life threatening	33.99 (18.88–61.18)	<0.001

VARC indicates Valve Academic Research Consortium.

*Cox regression analysis was not applicable for type 1 and minor bleeding due to the absence of 30-day mortality in patients with these bleeding types. The blue tables represent results for the entire cohort, and the orange tables show results of the transfemoral cohort only.

bleeding categories has been expanded from 3 (minor, major, and life-threatening bleeding) to 4 (types 1–4). Type 4 bleeding has been introduced as a new category to specifically classify bleeding events that result in death. Second, the VARC-3 authors specify all procedural blood loss as overt bleeding, even without an identifiable source. This classification implicates that blood loss resulting in a hemoglobin drop of 3 to 5 g/dL is categorized as type 2 bleeding, and a hemoglobin drop of >5 g/dL qualifies as type 3 bleeding and inevitably resulted in an increase of bleeding events in our cohort.[7] There is ongoing controversy regarding the clinical significance of periprocedural, non-attributable blood loss and its impact on patient outcomes. The initial study evaluating periprocedural blood loss reported that non-attributable bleeding resulted in increased mortality at 30 days and 1 year.[28] A more recent study found no significant differences between patients with non-attributable blood loss and those without any bleeding events.[8] Importantly, in both analyses a substantial portion of patients underwent TAVR using more traumatic access routes (e.g. transapical, transcarotid), rendering a comparison to our contemporary TAVR population difficult with almost exclusive percutaneous transfemoral access and modern closure devices.[8,28] In our study, we determined that non-attributable blood loss between 3 and 5 g/dL (type 2 bleeding) did not affect mortality (HR, 0.65 [95% CI, 0.25–1.69], *P*=0.378), whereas blood loss >5 g/dL (type 3 bleeding) was associated with increased risk for 30-day mortality (HR, 3.60 [95% CI, 1.09–11.87], *P*=0.035). Our findings suggest that only substantial non-attributable blood loss (>5 g/dL), in a contemporary TAVR cohort with mostly transfemoral TAVR access, has significant implications. Conversely, non-attributable blood loss resulting in a hemoglobin drop <5 g/dL does not appear to influence mortality and rather overestimates bleeding events. Future studies with multicenter patient cohorts may further decode the impact of non-attributable blood loss.

Limitations

With the observational nature, inherent study limitations such as unrecorded confounders may not be fully excluded. Data were collected in a single center and therefore do not reflecting worldwide TAVR patients in different health care systems. Moreover, the event adjudication committee was multidisciplinary but local. Furthermore, we expect an underreporting of type 1 bleeding events, as they may remain undetected in clinical practice. Lastly, another limitation is the relatively small number of patients with life-threatening (VARC-2) as well as type 3 and type 4 bleeding (VARC-3). This inevitably results in relatively wide CIs, and the HRs should be interpreted with caution.

CONCLUSIONS

The updated VARC-3 criteria provide a refined classification system for bleeding, demonstrating prognostic relevance, as higher-grade bleeding is associated with an increased risk of 30-day mortality. However, it is noteworthy that the VARC-2 bleeding classification remains clinically meaningful, as it correlates with progressive mortality risk in proportion to the extent of bleeding as well. Importantly, the VARC-3 criteria have a lower prognostic relevance when analyzing the transfemoral cohort only, whereas VARC-2 criteria do not lose prognostic relevance. The adoption of

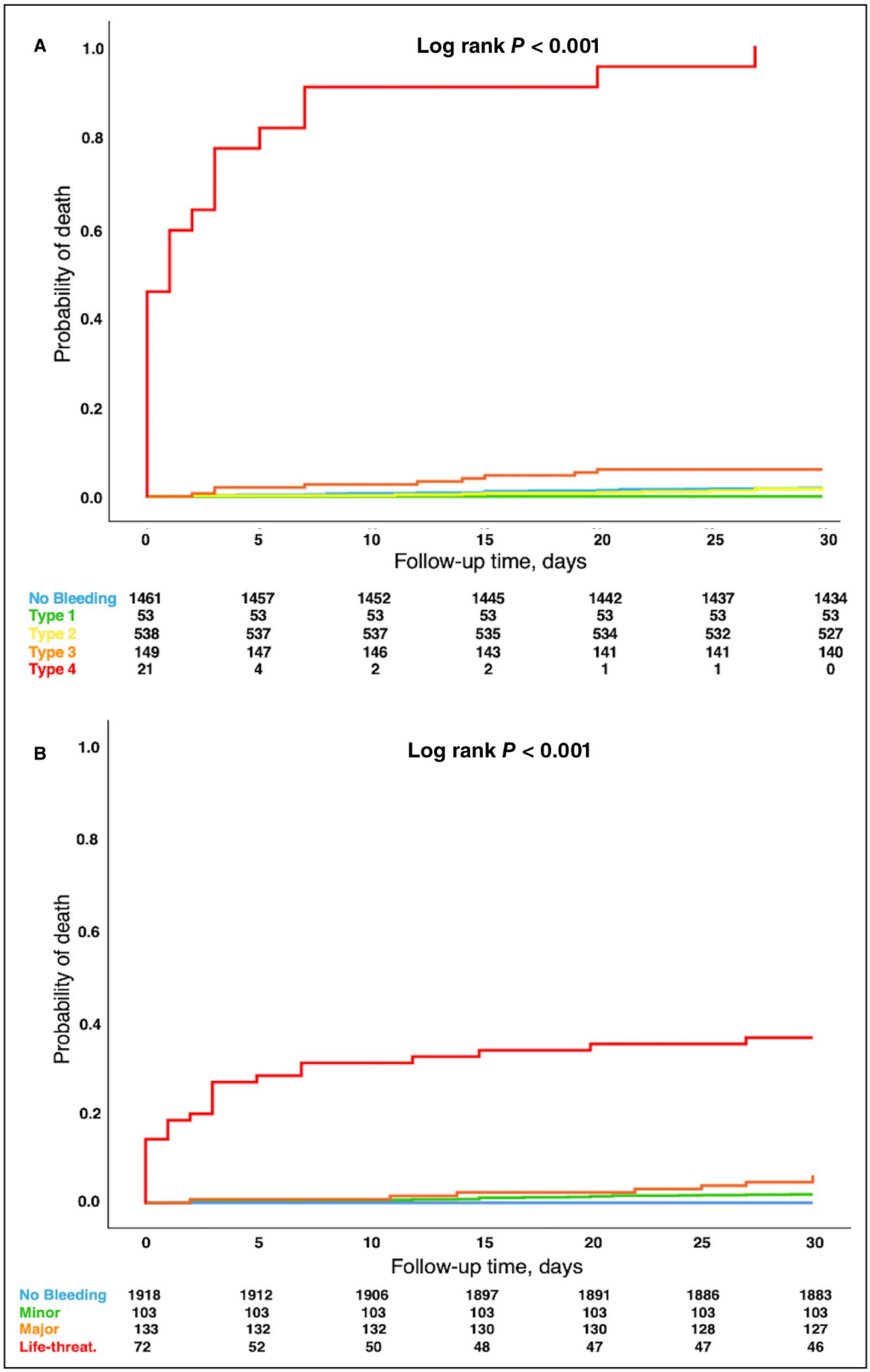

Figure 4. Kaplan–Meier estimates of 30-day mortality.
A, Kaplan–Meier estimates for 30-day mortality according to the presence and severity of VARC-3 bleeding events. **B**, Kaplan–Meier estimates for 30-day mortality according to the presence and severity of VARC-2 bleeding events. VARC indicates Valve Academic Research Consortium.

VARC-3 bleeding definition induces a substantial increase in bleeding events when applied to the same set of patients. These findings require further validation with similar or even larger patient cohorts.

ARTICLE INFORMATION

Received October 15, 2024; accepted June 4, 2025.

Affiliations

Department of Cardiology, Heart Center Cologne, Faculty of Medicine and University Hospital, University of Cologne, Cologne, Germany (S.N., J.H., M.M., V.M., S.L., J.C., R.N., J.D., S.B., H.W., M.A.); Department for Cardiology III—Angiology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany (M.M.); Department of Cardiothoracic Surgery, Heart Center Cologne, Faculty of Medicine and University Hospital, University of Cologne, Cologne, Germany (E.K., K.E.); and Department of Cardiac Surgery, University Hospital Bonn, Bonn, Germany (K.E.).

Acknowledgments

We thank all nurses and staff of the TAVR program and express our gratitude to colleagues for background support regarding this article.

Sources of Funding

The authors received no financial support for the research, authorship, and publication of this article.

Disclosures

J. Curio has received research grant support from Boston Scientific. H. Wienemann has received travel grants from JenaValve. M. Adam has received personal fees from Medtronic and personal fees from JenaValve, Edwards Lifesciences, Meril Life Sciences, and Boston Scientific. S. Baldus received research grants and lecture honoraria from Edwards Lifesciences, Abbott Vascular, Boston Scientific and JenaValve. The other authors have no conflicts of interest to declare.

Supplemental Material

Table S1

REFERENCES

1. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, Capodanno D, Conradi L, De Bonis M, De Paulis R, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease: developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;43:561–632. doi: 10.1093/eurheartj/ehab395
2. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2021;143:e72–e227. doi: 10.1161/CIR.0000000000000923
3. Forrest JK, Deeb GM, Yakubov SJ, Gada H, Mumtaz MA, Ramlawi B, Bajwa T, Teirstein PS, DeFrain M, Muppala M, et al. 3-year outcomes after transcatheter or surgical aortic valve replacement in low-risk patients with aortic stenosis. *J Am Coll Cardiol*. 2023;81:1663–1674. doi: 10.1016/j.jacc.2023.02.017
4. Mack MJ, Leon MB, Thourani VH, Pibarot P, Hahn RT, Genereux P, Kodali SK, Kapadia SR, Cohen DJ, Pocock SJ, et al. Transcatheter aortic-valve replacement in low-risk patients at five years. *N Engl J Med*. 2023;389:1949–1960. doi: 10.1056/NEJMoa2307447
5. Siontis GCM, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, Søndergaard L, Jüni P, Windecker S. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. *Eur Heart J*. 2016;37:3503–3512. doi: 10.1093/eurheartj/ehw225
6. van Nieuwkerk AC, Aarts HM, Hemelrijk KI, Cantón T, Tchétché D, de Brito FS, Barbanti M, Kornowski R, Latib A, D'Onofrio A, et al. Bleeding in patients undergoing transfemoral transcatheter aortic valve replacement: incidence, trends, clinical outcomes, and predictors. *JACC Cardiovasc Interv*. 2023;16:2951–2962. doi: 10.1016/j.jain.2023.10.011
7. Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, Bax JJ, Leipsic JA, Blanke P, Blackstone EH. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol*. 2021;77:2717–2746. doi: 10.1016/j.jacc.2021.02.038
8. Avvedimento M, Real C, Nuche J, Farjat-Pasos J, Galhardo A, Trinh KH, Robichaud M, Delarochellière R, Paradis JM, Poulin A, et al. Incidence, predictors, and prognostic impact of bleeding events after TAVR according to VARC-3 criteria. *J Am Coll Cardiol Intv*. 2023;16:2262–2274. doi: 10.1016/j.jacc.2021.02.038
9. ten Berg J, Sibbing D, Rocca B, van Belle E, Chevalier B, Collet JP, Dudek D, Gilard M, Gorog DA, Grapsa J, et al. Management of antithrombotic therapy in patients undergoing transcatheter aortic valve implantation: a consensus document of the ESC working group on thrombosis and the European Association of Percutaneous Cardiovascular Interventions (EAPCI), in collaboration with the ESC Council on Valvular Heart Disease. *Eur Heart J*. 2021;42:2265–2269. doi: 10.1093/eurheartj/ehab196
10. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem N, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es G, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg*. 2012;42:S45–S60. doi: 10.1093/ejcts/ezs533
11. Forrest JK, Deeb GM, Yakubov SJ, Rovin JD, Mumtaz M, Gada H, O'Hair D, Bajwa T, Sorajja P, Heiser JC, et al. 2-year outcomes after transcatheter versus surgical aortic valve replacement in low-risk patients. *J Am Coll Cardiol*. 2022;79:882–896. doi: 10.1016/j.jacc.2021.11.062
12. Avvedimento M, Nuche J, Farjat-Pasos JI, Rodés-Cabau J. Bleeding events after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2023;81:684–702. doi: 10.1016/j.jacc.2022.11.050
13. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, Pilgrim T, Petrinic T, Nikolakopoulou A, Salanti G, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J*. 2019;40:3143–3153. doi: 10.1093/eurheartj/ehz275
14. Arnold SV, Manandhar P, Vemulapalli S, Vekstein AM, Kosinski AS, Carroll JD, Thourani VH, Mack MJ, Cohen DJ. Mediators of improvement in TAVR outcomes over time: insights from the STS-ACC TVT registry. *Circ Cardiovasc Interv*. 2023;16:e013080. doi: 10.1161/CIRCINTERVENTIONS.123.013080
15. Tarantini G, Tang G, Nai Fovino L, Blackman D, van Mieghem N, Kim WK, Karam N, Carrilho-Ferreira P, Fournier S, Pręgowski J, et al. Management of coronary artery disease in patients undergoing transcatheter aortic valve implantation. A clinical consensus statement from the European Association of Percutaneous Cardiovascular Interventions in collaboration with the ESC working group on Cardiovascular surgery. *EuroIntervention*. 2023;19:37–52. doi: 10.4244/EIJ-D-22-00958
16. Gragnano F, Mehran R, Branca M, Franzone A, Baber U, Jang Y, Kimura T, Hahn JY, Zhao Q, Windecker S, et al. P2Y12 inhibitor monotherapy or dual antiplatelet therapy after complex percutaneous coronary interventions. *J Am Coll Cardiol*. 2023;81:537–552. doi: 10.1016/j.jacc.2022.11.041
17. Calabrò P, Gragnano F. Bleeding in patients undergoing PCI and TAVR. *JACC Cardiovasc Interv*. 2023;16:2165–2168. doi: 10.1016/j.jcin.2023.07.036
18. Vlastra W, Chandrasekhar J, García del Blanco B, Tchétché D, de Brito FS Jr, Barbanti M, Kornowski R, Latib A, D'Onofrio A, Ribichini F, et al. Sex differences in transfemoral transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2019;74:2758–2767. doi: 10.1016/j.jacc.2019.09.015
19. Amgai B, Chakraborty S, Bandyopadhyay D, Gupta M, Patel N, Hajra A, Dey AK, Koirala S, Ghosh RK, Aronow WS, et al. Sex differences in in-hospital outcomes of transcatheter aortic valve replacement. *Curr Probl Cardiol*. 2021;46:100694. doi: 10.1016/j.cpcardiol.2020.100694
20. Lederman RJ, Babaliaros VC, Lisko JC, Rogers T, Mahoney P, Foerst JR, Depta JP, Muhammad KI, McCabe JM, Pop A, et al. Transcaval versus Transaxillary TAVR in contemporary practice: a propensity-weighted analysis. *JACC Cardiovasc Interv*. 2022;15:965–975. doi: 10.1016/j.jcin.2022.03.014
21. Kodali S, Thourani VH, White J, Malaisrie SC, Lim S, Greason KL, Williams M, Guerrero M, Eisenhauer AC, Kapadia S, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter

aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J*. 2016;37:2252–2262. doi: 10.1093/eurheartj/ehw112

22. Daniel PO, Bajwa TK, Popma JJ, Watson DR, Yakubov SJ, Adams DH, Sharma S, Robinson N, Petrossian G, Caskey M, et al. Direct aortic access for transcatheter aortic valve replacement using a self-expanding device. *Ann Thorac Surg*. 2018;105:484–490. doi: 10.1016/j.athoracsur.2017.07.051
23. Kaneko T, Hirji SA, Yazdchi F, Sun YP, Nyman C, Shook D, Cohen DJ, Stebbins A, Zeitouni M, Vemulapalli S, et al. Association between peripheral versus central access for alternative access transcatheter aortic valve replacement and mortality and stroke: a report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *Circ Cardiovasc Interv*. 2022;15:e011756. doi: 10.1161/CIRCINTERVENTIONS.121.011756
24. Berti S, Bartorelli AL, Koni E, Giordano A, Petronio AS, Iadanza A, Bedogni F, Reimers B, Spaccarotella C, Trani C, et al. Impact of high body mass index on vascular and bleeding complications after transcatheter aortic valve implantation. *Am J Cardiol*. 2021;155:86–95. doi: 10.1016/j.amjcard.2021.06.015
25. Lv W, Li S, Liao Y, Zhao Z, Che G, Chen M, Feng Y. The 'obesity paradox' does exist in patients undergoing transcatheter aortic valve implantation for aortic stenosis: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. 2017;25:633–642. doi: 10.1093/icvts/ivx191
26. Arnold SV, Lei Y, Reynolds MR, Magnuson EA, Suri RM, Tuzcu EM, Petersen JL, Douglas PS, Svensson LG, Gada H, et al. Costs of periprocedural complications in patients treated with transcatheter aortic valve replacement. *Circ Cardiovasc Interv*. 2014;7:829–836. doi: 10.1161/circinterventions.114.001395
27. Yin K, Willie-Permor D, Zarrintan S, Dakour-Aridi H, Ramirez JL, Iannuzzi JC, Naazie I, Malas MB. Anemia is associated with higher mortality and morbidity after thoracic endovascular aortic repair. *J Vasc Surg*. 2023;77:357–365.e1. doi: 10.1016/j.jvs.2022.08.037
28. Stortecky S, Stefanini GG, Pilgrim T, Heg D, Praz F, Luterbacher F, Piccolo R, Khattab AA, Räber L, Langhammer B, et al. Validation of the valve academic research consortium bleeding definition in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *J Am Heart Assoc*. 2015;4:e002135. doi: 10.1161/JAHA.115.002135