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ORIGINAL RESEARCH

VARC-HBR criteria validation in TAVI patients on oral anticoagulation

Daniël C. Overduin[1], MD; Dirk Jan van Ginkel[1], MD; Willem L. Bor[1], MD; Yusuke Kobari[2], MD, PhD; Hugo M. Aarts[3,4], MD; Christophe Dubois[5], MD, PhD; Ole De Backer[2], MD, PhD; Maxim J.P. Rooijakkers[6], MD; Liesbeth Rosseel[7], MD, PhD; Leo Veenstra[8,9], MD; Frank van der Kley[10], MD, PhD; Kees H. van Bergeijk[11], MD; Nicolas M. Van Mieghem[12], MD, PhD; Pierfrancesco Agostoni[13], MD, PhD; Michiel Voskuil[4], MD, PhD; Carl E. Schotborgh[14], MD; Alexander J.J. Ijsselmuiden[8,9], MD, PhD; Jan A.S. Van Der Heyden[15], MD, PhD; Renicus S. Hermanides[16], MD, PhD; Emanuele Barbato[17,18], MD, PhD; Darren Mylotte[19], MD, PhD; Enrico Fabris[20], MD, PhD; Peter Frambach[21], MD; Karl Dujardin[22], MD, PhD; Bert Ferdinande[23], MD; Joyce Peper[1], PhD; Benno J.W.M. Rensing[1], MD, PhD; Leo Timmers[1], MD, PhD; Martin J. Swaans[1], MD, PhD; Jorn Brouwer[1], MD, PhD; Vincent J. Nijenhuis[1,6], MD, PhD; Tom Adriaenssens[5], MD, PhD; Pieter A. Vriesendorp[8,9], MD, PhD; Jose M. Montero-Cabezas[10], MD, PhD; Hicham El Jattari[13], MD; Jonathan Halim[24], MD; Ben J.L. Van den Branden[25], MD, PhD; Remigio Leonora[16], MD; Marc Vanderheyden[7], MD; Michael Lauterbach[22], MD, PhD; Joanna J. Wykrzykowska[11], MD, PhD; Arnoud W.J. van 't Hof[8,9], MD, PhD; Niels van Royen[6], MD, PhD; Jan G.P. Tijssen[3], PhD; Ronak Delewi[3], MD, PhD; Jurriën M. ten Berg[1,8,9]*, MD, PhD

D.C. Overduin and D.J. van Ginkel contributed equally as first authors.

**Corresponding author: Department of Cardiology, St. Antonius Hospital, Koekoekslaan 1, 3435 CM, Nieuwegein, the Netherlands. E-mail: jurtenberg@gmail.com*

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ABSTRACT

BACKGROUND: Bleeding remains a frequent complication after transcatheter aortic valve implantation (TAVI). Recently, the Valve Academic Research Consortium High Bleeding Risk (VARC-HBR) criteria were introduced to identify patients at (very) high risk of bleeding.

AIMS: This study aimed to evaluate the validity of the VARC-HBR criteria for predicting bleeding risk in TAVI patients and to compare its performance with other existing criteria.

METHODS: Data were obtained from the POPular PAUSE TAVI trial, a randomised clinical trial that evaluated the safety and efficacy of continuation versus interruption of oral anticoagulation during TAVI. Major and minor bleeding risk criteria were identified at baseline, and bleeding events were recorded up to 30 days after TAVI. Patients were classified into three groups: those with ≤1 minor criterion (moderate risk), those with 1 major or 2 minor criteria (high risk), and those with ≥2 major or ≥3 minor criteria (very high risk).

RESULTS: A total of 856 patients were included: 332 (39%) were classified at moderate bleeding risk, 337 (39%) at high bleeding risk, and 187 (22%) at very high bleeding risk. Major bleeding occurred in 4.2% of moderate-risk patients, 9.5% in the high-risk group, and 15.0% in the very high-risk group (p<0.001). Receiver operating characteristic analysis showed moderate discriminative performance (area under the curve=0.64, 95% confidence interval: 0.58-0.70). Despite higher-than-expected event rates, the VARC-HBR criteria demonstrated good calibration with observed outcomes.

CONCLUSIONS: The VARC-HBR criteria effectively identified distinct subgroups with a stepwise increase in major bleeding post-TAVI. However, their predictive performance for individual risk was moderate.

KEYWORDS: bleeding risk; high bleeding risk; oral anticoagulation; TAVI; VARC-HBR criteria

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Transcatheter aortic valve implantation (TAVI) is a well-established treatment for patients with symptomatic severe aortic stenosis[1]. Despite numerous technical advancements in recent years, procedure-related bleeding complications remain frequent[2]. This is particularly true in patients with a concomitant indication for oral anticoagulation, who represent about 35% of the current TAVI population[3]. Major bleeding occurs in 3-10% of patients and has been associated with up to a threefold increase in mortality[2,4]. It is also associated with reduced mental and physical quality of life, longer hospitalisation and higher healthcare costs[5]. To anticipate and potentially avoid these events, preprocedural bleeding risk assessment has been recommended to guide preventive strategies[4,6]. As standardised bleeding risk criteria for patients with valvular heart disease were limited, the Valve Academic Research Consortium High Bleeding Risk (VARC-HBR) criteria were recently introduced[7]. Twenty-one clinical, anatomical, and procedural factors were combined, weighted as 15 major and 6 minor criteria. These criteria were developed based on expert consensus; hence, they require empirical validation to substantiate their use in clinical practice. Therefore, we evaluated the VARC-HBR criteria for risk stratification and prediction of 30-day major bleeding risk in patients undergoing TAVI with a concomitant indication for oral anticoagulation.

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Impact on daily practice

The Valve Academic Research Consortium High Bleeding Risk (VARC-HBR) criteria effectively identify three distinct subgroups of patients with a stepwise increase in major bleeding risk after transcatheter aortic valve implantation. Applying these criteria in clinical practice may help select subgroups of patients who could benefit most from precautionary measures for access site management (e.g., radial secondary access, heparin reversal with protamine, and the use of an additional closure device). Given the significant association with bleeding, alternative approaches could be considered for patients with severe calcification or tortuosity of the iliofemoral arteries. For individual risk prediction, the discriminative performance observed in our data was moderate but outperformed other bleeding scores. While moderate, the VARC-HBR performs comparably to other bleeding scores, for example in studies evaluating the Academic Research Consortium High Bleeding Risk criteria in patients undergoing percutaneous coronary intervention.

Methods

STUDY DESIGN

This study is a subanalysis of the POPular PAUSE TAVI (ClinicalTrials.gov: NCT04437303) trial, a randomised clinical trial, conducted at 22 European sites, that evaluated the safety and efficacy of continuing versus interrupting oral anticoagulation during TAVI. Details of the design of the study have been described previously[8]. Briefly, patients were eligible if they were on any oral anticoagulant and scheduled to undergo transfemoral or transsubclavian TAVI. Patients randomised to the continuation strategy maintained oral anticoagulation throughout the periprocedural period, including on the day of the TAVI procedure. Patients randomised to the interruption strategy interrupted oral anticoagulation at least 48 hours before TAVI. Bridging with low-molecular-weight heparin was not recommended. Oral anticoagulation was restarted after TAVI, as soon as deemed safe by the operator and/or treating physician. The TAVI procedures were performed according to the local protocol of each participating study site, including the choice of valve type, whether cerebral embolic protection was used, the amount of periprocedural heparin, the amount of protamine (when administered), and the type of vascular closure device used. Follow-up visits were performed at discharge and 30 days after TAVI. If necessary, the patient's primary care physician and/or treating specialist was contacted for additional information. The trial was approved by the national authorities and ethics committees and by the institutional review board at each participating site.

PATIENTS

Patients planned for transfemoral or transsubclavian TAVI, who were using long-term oral anticoagulation and provided written informed consent, were included. The exclusion criteria were the presence of a mechanical heart valve prosthesis, intracardiac thrombus, venous thromboembolism within 3 months before TAVI or transient ischaemic attack or stroke in patients with atrial fibrillation within 6 months before TAVI.

BLEEDING RISK CRITERIA

Baseline and procedural characteristics, including the VARC-HBR criteria, were registered in standardised electronic case report forms. Slightly modified definitions of severe hepatic disease, prior ischaemic stroke and active malignancy were used. A full list of the criteria and their respective definitions is provided in **Supplementary Table 1**. Patients were classified at moderate risk if no more than one minor criterion was met, at high risk if one major or two minor criteria were met, and at very high risk if at least two major or three minor criteria were met[7]. To compare the VARC-HBR criteria with existing bleeding risk scores, the criteria of the HAS-BLED, ORBIT, DOAC and PREDICT-TAVR bleeding risk scores were also

Abbreviations

BARC	Bleeding Academic Research Consortium	**ROC-AUC**	area under the receiver operating characteristic curve	**VARC**	Valve Academic Research Consortium
CI	confidence interval	**TAVI**	transcatheter aortic valve implantation	**VARC-HBR**	Valve Academic Research Consortium High Bleeding Risk

assessed[9-12]. Full lists of these criteria and their respective definitions, adapted to the current study, are provided in **Supplementary Table 2**.

BLEEDING DEFINITIONS

Bleeding events were collected until 30 days after TAVI and adjudicated by a blinded clinical events committee. Adjudication was based on the Bleeding Academic Research Consortium (BARC) criteria and the Valve Academic Research Consortium (VARC)-3 criteria[13,14]. For this analysis, major bleeding was defined as BARC Type 3-5 bleeding occurring within 30 days after TAVI[7]. The VARC-3-based major bleeding definition (Type 2-4) was used as a sensitivity analysis[14]. BARC and VARC-3 bleeding definitions are detailed in **Supplementary Table 3**.

STATISTICAL ANALYSIS

The analysis population included all patients who had undergone randomisation and subsequent TAVI. Continuous variables are summarised as mean±standard deviation (SD) or as median and interquartile range, as appropriate. Categorical variables are presented as numbers and percentages. Proportions of major bleeding were compared between risk groups using the chi-square test. The discriminative ability of the VARC-HBR criteria, as well as the other bleeding risk scores, was assessed based on the area under the receiver operating characteristic curve (ROC-AUC) with corresponding 95% confidence intervals (CIs). The VARC-HBR criteria were assessed as a three-class risk score (moderate, high, very high risk) and as a point-based score, where minor criteria were given one point and major criteria two points. Calibration was evaluated by comparing predicted probabilities with observed frequencies of major bleeding per risk group. Multivariate logistic regression analysis was performed to assess the relative contribution of each criterion, which is expressed as odds ratios (ORs) with corresponding 95% CIs. Since the main trial did not show non-inferiority of the continued oral anticoagulation strategy, the impact of continuation of oral anticoagulation for the different VARC-HBR risk groups was evaluated. Additional logistic regression analyses were conducted, considering continuation of oral anticoagulation as a major criterion, to evaluate its impact both independently and in combination with other variables. There were no missing data in the evaluated criteria or bleeding outcomes. Statistical analyses were performed using R software, version 4.1 (R Foundation for Statistical Computing).

Results

BASELINE CHARACTERISTICS

Between November 2020 and December 2023, a total of 869 patients were enrolled. Thirteen patients were excluded because TAVI was not initiated or they withdrew informed consent before the procedure. The mean±SD age of the patients was 81.1±5.9 years, and 34.5% were female. The indication for long-term oral anticoagulation was atrial fibrillation in 94.9% of the patients. The majority (81.6%) of patients used a direct oral anticoagulant, of whom 30.4% were on a reduced dose. Out of 856 patients included, 332 (39%) were classified at moderate bleeding risk, 337 (39%) at high bleeding risk, and 187 (22%) at very high bleeding risk. Patients in the higher bleeding risk categories had a greater prevalence of cardiovascular risk factors and comorbidities, consistent with the VARC-HBR criteria. Randomisation to a continued oral anticoagulation strategy was not significantly different between the groups (p=0.43). Baseline and procedural characteristics are detailed in **Table 1** and **Supplementary Table 4**, respectively.

PREVALENCE OF VARC-HBR CRITERIA

The prevalence of VARC-HBR criteria, when present in at least 1% of the patients, is summarised in **Central illustration A.** The most common criterion was severe femoral artery calcification and tortuosity, which was present in 26.8% of the patients. Other prevalent criteria were dual antithrombotic therapy (oral anticoagulation+antiplatelet therapy; 12.5%), history of ischaemic stroke (10.5%), and anaemia (haemoglobin <11 g/dL) at hospital admission (11.6%). The following criteria were rarely observed: non-deferrable major surgery (0.4%), severe hepatic disease (0.7%), history of haemorrhagic stroke (0.9%), dual antiplatelet therapy (meaning triple therapy in this population; 0.5%), conversion to open-heart surgery (0.4%), and spontaneous bleeding >6 and <12 months before TAVI (0.4%). Severe thrombocytopaenia (platelet count <50x10^9/L) at baseline was not observed.

RISK STRATIFICATION

Major bleeding occurred in 4.2% of patients classified at moderate risk, in 9.5% classified at high risk, and 15.0% at very high risk (p<0.001), as shown in **Central illustration B.** Fatal bleeding (BARC Type 5) occurred in 6 patients: 3 (0.9%) in the high-risk group and 3 (1.6%) in the very high-risk group **(Table 2)**. Access site bleeding was the most common bleeding phenotype, which occurred in 4.5% of the moderate-risk group, in 7.1% of the high-risk group and in 10.2% of the very high-risk group. Further details regarding the sites of bleeding across the VARC-HBR subgroups are provided in **Supplementary Table 5**. Major bleeding according to the VARC-3 definition occurred in 6.3% of patients classified at moderate risk, in 10.4% classified at high risk, and 15.5% at very high risk. Bleeding events adjudicated by the VARC-3 criteria are displayed in **Supplementary Table 6**.

RISK PREDICTION

The ROC-AUC of the VARC-HBR criteria was 0.64 (95% CI: 0.58-0.70) when assessed as a three-class risk score and 0.65 (95% CI: 0.58-0.71) when assessed as a point-based score **(Figure 1)**. The ROC-AUC of the HAS-BLED score was 0.52 (95% CI: 0.45-0.60), the ORBIT score 0.54 (95% CI: 0.48-0.60), the DOAC score 0.55 (95% CI: 0.48-0.62), and the PREDICT-TAVR score 0.54 (95% CI: 0.47-0.61) **(Figure 2)**. Although the observed event rates were slightly higher than predicted, the VARC-HBR criteria showed overall good calibration with observed outcomes **(Central illustration B)**. Based on logistic regression analysis, severe femoral artery calcification and tortuosity (OR 2.5, 95% CI: 1.5-4.3), anaemia at baseline (OR 2.2, 95% CI: 1.1-4.2), and conversion to open-heart surgery (OR 21.2, 95% CI: 1.8-491.5) appeared to be the most influential predictors. The VARC-HBR model, showing the univariate and multivariate

Table 1. Baseline characteristics.

	Moderate bleeding risk (n=332)	High bleeding risk (n=337)	Very high bleeding risk (n=187)
Age, years	80.1±5.6	81.9±5.7	79.2±6.6
Female sex	114 (34.3)	128 (38.0)	53 (28.3)
Body mass index, kg/m^2	27.9±4.6	27.3±4.8	26.6±4.6
EuroSCORE II, %	3.4±3.5	3.9±4.0	4.6±5.0
NYHA Class III or IV	191 (57.5)	209 (62.0)	130 (70.6)
Atrial fibrillation	319 (96.1)	323 (95.8)	176 (94.1)
Paroxysmal	154 (48.7)	135 (41.9)	87 (49.4)
CHA_2DS_2-VASc	4.07±1.3	4.6±1.4	4.9±1.4
Hypertension	256 (77.1)	253 (75.1)	150 (80.2)
Diabetes			
None	243 (73.2)	249 (73.9)	115 (61.5)
Non-insulin dependent	68 (20.5)	60 (17.8)	48 (25.7)
Insulin dependent	21 (6.3)	28 (8.3)	24 (12.8)
Coronary artery disease	128 (38.6)	171 (50.7)	113 (60.4)
History of myocardial infarction	40 (12.0)	56 (16.6)	40 (21.4)
Previous cerebrovascular event	33 (9.9)	79 (23.4)	55 (29.4)
Peripheral artery disease	32 (9.6)	63 (18.7)	68 (36.4)
Chronic obstructive pulmonary disease	51 (15.4)	43 (12.8)	22 (11.8)
Chronic renal insufficiency	151 (45.5)	173 (51.3)	108 (57.8)
Previous heart valve surgery	23 (6.9)	26 (7.7)	15 (8.0)
Previous spontaneous bleeding[$]	15 (4.5)	31 (9.2)	38 (20.3)
Active malignancy[#]	0 (0)	21 (6.2)	26 (13.9)
Type of oral anticoagulation			
Vitamin K antagonist	48 (13.0)	66 (19.6)	45 (24.1)
Direct oral anticoagulant	289 (87.0)	271 (80.4)	142 (75.9)
Randomised to continuation of OAC	168 (50.6)	162 (48.1)	101 (54.0)

Data are presented as mean±SD or n (%). [#]Excluding non-melanoma skin cancer. [$]Requiring hospitalisation or transfusion. EuroSCORE: European System for Cardiac Operative Risk Evaluation; NYHA: New York Heart Association; OAC: oral anticoagulation; SD: standard deviation

associations of the individual criteria with the occurrence of major bleeding, is presented in **Table 3**. Additionally, in **Supplementary Table 7**, the randomised strategy was evaluated as a major criterion and showed no significant interaction in either univariate or multivariate analyses (OR 1.1, 95% CI: 0.7-1.9). Accordingly, multivariate logistic regression models of the other bleeding scores are reported in **Supplementary Table 8**-**Supplementary Table 11**. The sensitivity analysis, in which the VARC-HBR criteria were applied to predict major bleeding based on the VARC-3 definition, yielded similar results (ROC-AUC of 0.64 [95% CI: 0.58-0.70]).

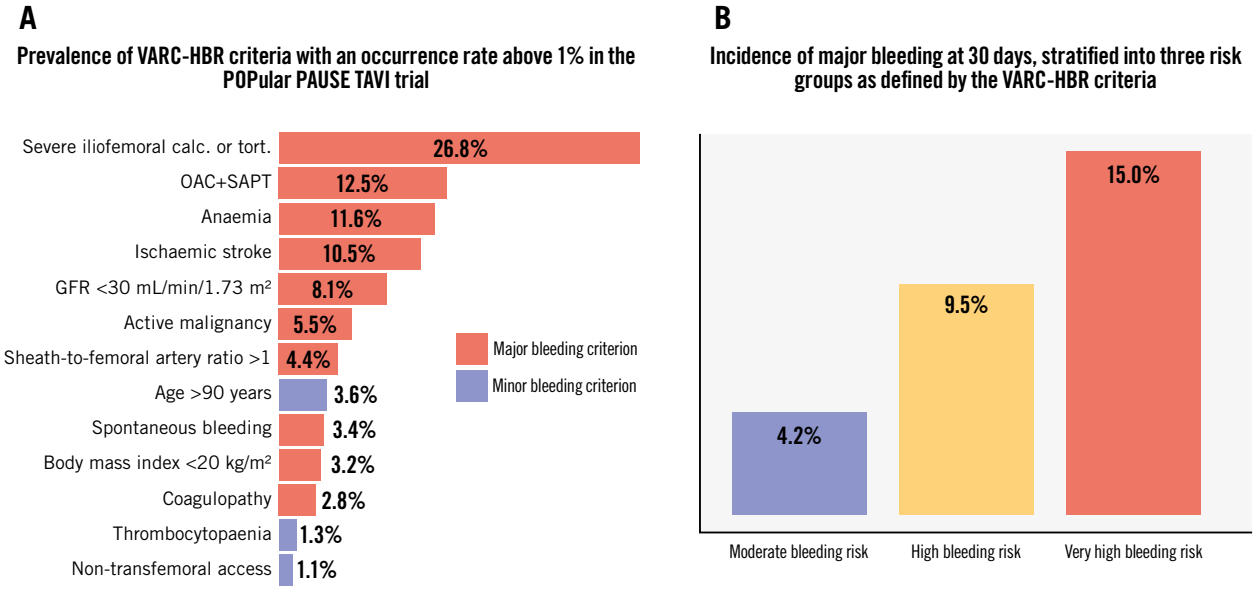
Discussion

In this subanalysis of the POPular PAUSE TAVI trial, we evaluated the VARC-HBR criteria for risk stratification and prediction of 30-day major bleeding risk in patients undergoing TAVI with a concomitant indication for oral anticoagulation. The main findings were as follows: (1) the VARC-HBR criteria effectively identified three well-distributed subgroups, with a stepwise increase in major bleeding risk across the risk categories; (2) for individual risk prediction, the discriminative performance of the VARC-HBR criteria was moderate, yet, it appeared to outperform existing bleeding risk scores in this population; (3) severe femoral artery calcification and tortuosity, anaemia, and conversion to open-heart surgery were identified as the most contributory criteria.

In contemporary studies, major bleeding has been reported in 3-10% of patients within 30 days after TAVI[4,15-18]. The observed bleeding rate in our study was slightly higher, which could be attributed to the fact that we evaluated a subgroup of patients receiving oral anticoagulation, half of whom continued their therapy throughout the periprocedural period[8]. These high rates of bleeding emphasise the need for adequate risk assessment[7]. Based on the current findings, the VARC-HBR criteria seem to be a valuable tool for this purpose. The clinical implications of identifying patients at (very) high risk of bleeding may lie in adopting precautionary measures for access site management, since access site bleeding appeared to be the most common bleeding phenotype early after TAVI. For example, the use of the radial artery for secondary vascular access, protamine administration for heparin reversal at the end of the procedure, and the use of an additional vascular closure device may mitigate the bleeding risk in these

EuroIntervention Central Illustration

VARC-HBR criteria and bleeding risk in the POPular PAUSE TAVI trial.



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A) Prevalence of VARC-HBR criteria (occurrence >1%). B) 30-day major bleeding incidence stratified by VARC-HBR risk. calc.: calcification; GFR: glomerular filtration rate; OAC: oral anticoagulation; SAPT: single antiplatelet therapy; TAVI: transcatheter aortic valve implantation; tort.: tortuosity; VARC-HBR: Valve Academic Research Consortium High Bleeding Risk

Table 2. BARC bleeding types stratified according to VARC-HBR risk groups.

Bleeding type	Moderate (n=332)	High (n=337)	Very high (n=187)
Minor bleeding (Type 2)	63 (19.0)	53 (15.7)	40 (21.4)
Major bleeding (Type 3-5)	14 (4.2)	32 (9.5)	28 (15.0)
Type 3a	7 (2.1)	16 (4.8)	19 (10.2)
Type 3b	6 (1.8)	13 (3.9)	6 (3.2)
Type 3c	1 (0.3)	-	-
Type 5a	-	-	-
Type 5b	-	3 (0.9)	3 (1.6)

Data are n (%). BARC: Bleeding Academic Research Consortium; VARC-HBR: Valve Academic Research Consortium High Bleeding Risk

patients[17-19]. Recently, a dedicated stepwise vascular closure algorithm was shown to be associated with a major vascular complication rate (including major bleeding) of less than 1%[20]. This systematic approach may particularly be useful in patients at (very) high risk of bleeding.

Regarding the choice of antithrombotic therapy, the additional value of the VARC-HBR criteria may be limited, particularly in this subpopulation using oral anticoagulation, since interrupting oral anticoagulation before TAVI and restarting oral anticoagulation monotherapy after TAVI seems to be the appropriate strategy in general[8,15]. Dual antiplatelet

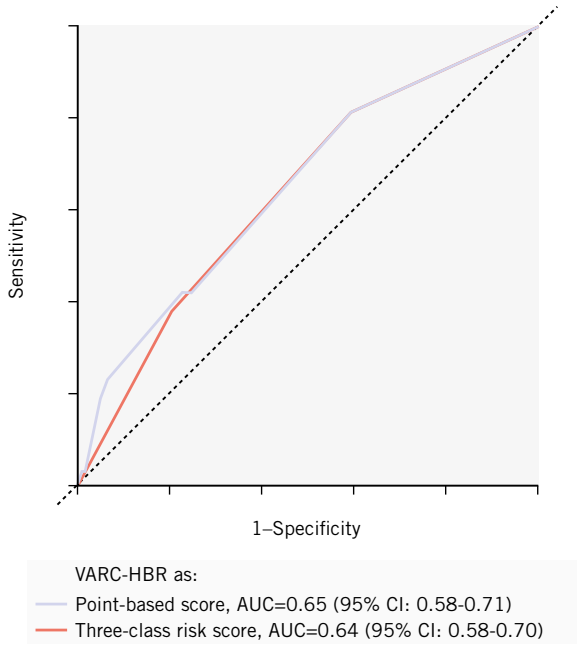

Figure 1. *ROC curves of VARC-HBR criteria. AUC: area under the curve; CI: confidence interval; ROC: receiver operating characteristic; VARC-HBR: Valve Academic Research Consortium High Bleeding Risk*

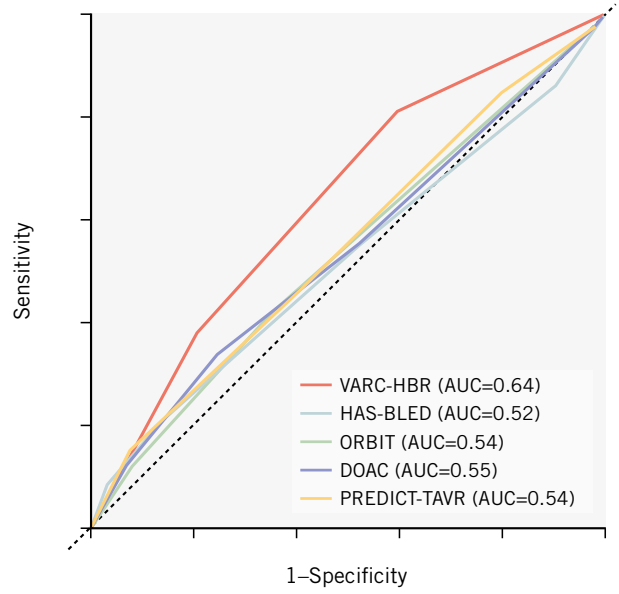

Figure 2. *Performance of the VARC-HBR criteria compared to other bleeding risk scores. AUC: area under the curve; VARC-HBR: Valve Academic Research Consortium High Bleeding Risk*

therapy in addition to oral anticoagulation (triple therapy) is discouraged based on current literature. Our dataset showed that it was potentially an important predictor (OR 3.8, 95% CI: 0.17-34.62). Switching from a vitamin K antagonist to a direct oral anticoagulant after TAVI may be best avoided in (very) high-risk patients, as this has been associated with an increased risk of major bleeding[21]. Interestingly, in patients without a concomitant indication for oral anticoagulation or antiplatelet therapy, the need for lifelong single antiplatelet therapy has recently been questioned in high bleeding risk patients[22]. However, randomised controlled trials are needed before omitting antiplatelet therapy can be recommended. The ongoing Non-antithrombotic Therapy After TAVI Trial (NAPT; ClinicalTrials.gov: NCT06007222) and the Personalized, CT-guided Antithrombotic Therapy Versus Lifelong Single Antiplatelet Therapy to Reduce Thromboembolic and Bleeding Events in Non-atrial Fibrillation Patients After TAVI trial (POPular ATLANTIS; ClinicalTrials.gov: NCT06168370) are expected to provide further evidence on this topic[23].

To the best of our knowledge, PREDICT-TAVR is the only other bleeding risk score specifically developed for patients undergoing TAVI[12]. Previous external validation showed a much better predictive performance than our data. This may be due to our evaluation of the version of the model without serum iron and our assessment of the common femoral artery diameter as a binary variable (<6 mm or not) instead of the original per-millimetre variable. The HAS-BLED, ORBIT and DOAC scores were specifically designed for patients on oral anticoagulation, but independent of the need for TAVI[9-11]. Their limited predictive performance in this setting is likely due to the fact that these scores were developed to predict spontaneous bleeding rather than procedure-related bleeding, which involves different risk factors. The VARC-HBR criteria

Table 3. Logistic regression analysis.

VARC-HBR criteria*	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Minor criteria				
Age >90 years	1.14 (0.27-3.31)	0.84	1.40 (0.32-4.27)	0.60
Dual antiplatelet therapy (besides OAC)	3.56 (0.17-28.18)	0.27	3.79 (0.17-34.62)	0.28
Non-transfemoral access	1.33 (0.07-7.37)	0.79	0.79 (0.04-4.72)	0.83
Major criteria				
BMI <20 kg/m²	1.33 (0.31-3.94)	0.64	1.37 (0.31-4.32)	0.63
Chronic kidney disease (eGFR <30 mL/min/1.73 m²)	1.43 (0.61-2.96)	0.37	1.05 (0.40-2.40)	0.91
Active malignancy	1.94 (0.77-4.24)	0.12	1.80 (0.67-4.23)	0.20
Anaemia (Hb <11 g/dL)	2.11 (1.11-3.80)	0.02	2.16 (1.06-4.21)	0.03
Previous ischaemic stroke	1.37 (0.64-2.66)	0.38	1.37 (0.61-2.80)	0.42
Chronic bleeding diathesis	1.53 (0.36-4.58)	0.50	1.60 (0.34-5.48)	0.49
Spontaneous bleeding#	1.73 (0.50-4.62)	0.32	1.19 (0.29-3.83)	0.79
Dual antithrombotic therapy (OAC+SAPT)	1.91 (1.01-3.42)	0.04	1.53 (0.74-2.96)	0.22
Non-deferrable major surgery	5.34 (0.25-56.40)	0.17	3.60 (0.15-44.46)	0.33
SFAR >1	1.64 (0.55-4.00)	0.32	1.21 (0.38-3.19)	0.72
Severely calcified and tortuous iliofemoral arteries	2.26 (1.38-3.68)	0.001	2.50 (1.46-4.29)	0.001
Immediate conversion to open-heart surgery	21.69 (2.05-470.18)	0.012	21.20 (1.77-491.47)	0.02

*Due to limited occurrence, associations for the following variables could not be estimated: moderate thrombocytopaenia, first spontaneous bleeding >6 and <12 months before TAVI, severe hepatic disease, severe thrombocytopaenia, previous intracranial haemorrhage, and oral anticoagulation (applied to everyone). #Defined as spontaneous (non-intracranial) bleeding requiring hospitalisation or transfusion in the previous 6 months (or at any time if recurrent). BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; OAC: oral anticoagulation; OR: odds ratio; SAPT: single antiplatelet therapy; SFAR: sheath-to-femoral artery ratio; VARC-HBR: Valve Academic Research Consortium High Bleeding Risk

provide a more comprehensive approach, distinguishing factors that impact periprocedural and non-periprocedural bleeding, or both. Still, the discriminative performance observed in our data was only moderate, quite similar to what has been reported in studies evaluating the ARC-HBR criteria in patients undergoing percutaneous coronary intervention[24,25]. In a large-scale observational study, the ROC-AUC of the ARC-HBR criteria was 0.64 (95% CI: 0.61-0.66) when assessed as a two-class variable, which increased to 0.68 (95% CI: 0.65-0.71) when assessed as a point-based variable[25]. Such an improvement was not observed in our analysis. This may be related to the fact that the VARC-HBR definition was designed as a three-class instead of a two-class system, thus providing a more granular approach. Upon exploration of our data, we observed that the point-based scores were clustered in three groups (1 point, 3 points, and 5 points), indicating that the three-class risk score appropriately described the degree of variation in our data.

Severe iliofemoral calcification and tortuosity are widely recognised risk factors for major bleeding[26,27]. However, the VARC-HBR document provides no specific guidance on how this criterion should be determined. Considering its prevalence and contributory value, a more specific definition may improve the predictive value of the VARC-HBR criteria. Previous studies have shown that ventral (or anterior) common femoral artery calcification seems to be more relevant than overall iliofemoral calcification[28]. Also, the degree of longitudinal and especially circumferential extent of calcification appears to be associated with major bleeding risk[29]. Finally, considering severe femoral tortuosity as an independent criterion, given its distinct aetiology, may further enhance predictive performance[26,27].

Limitations

Our findings should be interpreted considering the following limitations. Although all 21 VARC-HBR criteria were included in the dataset, three variables had to be slightly modified because of data availability. Second, due to the limited sample size, the predictive value of uncommon criteria could not be assessed. Additionally, for a few variables, this resulted in wide confidence intervals, which should be interpreted with caution. Third, follow-up was limited to 30 days after TAVI, which resulted in access-related bleeding being more prominent compared to the 1-year major bleeding defined by VARC-HBR. Finally, almost all patients were treated using the transfemoral approach, so the results should not be generalised to other access site approaches for TAVI. The same applies to patients not using oral anticoagulation.

Conclusions

Among patients with a concomitant indication for oral anticoagulation, the VARC-HBR criteria identified three well-distributed subgroups, with a stepwise increase in major bleeding risk within 30 days after TAVI. However, for individual risk prediction, the discriminative performance of the VARC-HBR criteria were moderate but appeared to outperform existing bleeding risk scores in this population. Severe femoral artery calcification and tortuosity, anaemia, and conversion to open-heart surgery were identified as the most contributory criteria.

Authors' affiliations

1. Department of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands; 2. The Heart Center, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; 3. Department of Cardiology, Amsterdam UMC, Amsterdam, the Netherlands; 4. Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands; 5. Department of Cardiovascular Medicine, University Hospital Leuven, Leuven, Belgium; 6. Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands; 7. Department of Cardiology, Hartcentrum Aalst, Aalst, Belgium; 8. Department of Cardiology, Maastricht University Medical Center, Maastricht, the Netherlands; 9. Cardiovascular Research Institute Maastricht (CARIM), Maastricht, the Netherlands; 10. Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; 11. Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands; 12. Department of Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands; 13. Department of Cardiology, Hospital Aan de Stroom (ZAS) Middelheim, Antwerp, Belgium; 14. Department of Cardiology, Haga Hospital, The Hague, the Netherlands; 15. Department of Cardiology, Sint-Jan Hospital, Brugge, Belgium; 16. Department of Cardiology, Isala Hospital, Zwolle, the Netherlands; 17. Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy; 18. Department of Cardiology, Sant'Andrea University Hospital, Rome, Italy; 19. Department of Cardiology, University Hospital Galway, Galway, Ireland; 20. Cardiothoracovascular Department, University of Trieste, Trieste, Italy; 21. Department of Cardiology, Institut National de Chirurgie Cardiaque et de Cardiologie Interventionnelle, Luxembourg, Luxembourg; 22. Department of Cardiology, AZ Delta, Roeselare, Belgium; 23. Department of Cardiology, Hospital Oost-Limburg, Genk, Belgium; 24. Department of Cardiology, Elisabeth-Tweesteden Hospital, Tilburg, the Netherlands; 25. Department of Cardiology, Amphia Hospital, Breda, the Netherlands

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Supplementary data

Supplementary Table 1. VARC-HBR definitions.
Supplementary Table 2. HAS-BLED, ORBIT, DOAC and PREDICT-TAVR definitions.
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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-01066

Supplementary data

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Supplementary Table 1. VARC-HBR definitions.

VARC-HBR criteria[7]	Current study if modified	Category	Comments
Age >90 years		Minor	Identical
BMI <20, cachexia (except for Asian patients)		Major	Identical
End-stage CKD (eGFR <30 mL/min), dialysis		Major	Identical
Liver cirrhosis with portal hypertension	Severe hepatic disease[I]	Major	Modified
Active stage III and IV malignancies	Active malignancy (excluding non-melanoma skin cancer)[II]	Major	Modified
Haemoglobin <11 g/dL		Major	Identical
Moderate baseline thrombocytopaenia (platelet count ≥50 and <100×109/L)		Minor	Identical
Severe baseline thrombocytopaenia (platelet count <50×109/L)		Major	Identical
Previous intracranial haemorrhage		Major	Identical
Moderate or severe ischaemic stroke (National Institutes of Health Stroke Scale score ≥5 on presentation) in the past 6 months	Previous ischemic stroke	Major	Modified
Chronic bleeding diathesis, coagulopathy, Heyde's syndrome		Major	Identical
First spontaneous (non-intracranial) bleed requiring hospitalisation or transfusion >6 and <12 months before TAVI		Minor	Identical
Spontaneous (non-intracranial) bleeding requiring hospitalisation or transfusion in the past 6 months (or at any time if recurrent)		Major	Identical
Need for long-term OAC		Minor	Identical
Need for long-term OAC combined with at least one antiplatelet agent		Major	Identical
Need for DAPT/concurrent PCI		Minor	Identical
Non-deferrable major surgery		Major	Identical
Sheath-to-femoral artery ratio >1		Major	Identical
Severe calcifications and tortuous iliac and/or femoral arteries (peripheral artery disease)		Major	Identical
Non-transfemoral access		Minor	Identical
Immediate conversion to open heart surgery		Major	Identical

[I] Any of the following: (i) Child-Pugh class C; (ii) MELD score >10; (iii) Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt; (iv) Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction

[II] Active malignancy is defined as diagnosis within the previous 12 months or ongoing active cancer treatment (surgery, radiotherapy, chemotherapy, or immunotherapy). Cancer that is considered to be in complete remission or requires only maintenance therapy (e.g., tamoxifen for breast cancer) is not considered active.

Supplementary Table 2. HAS-BLED, ORBIT, DOAC and PREDICT-TAVR definitions.

HAS-BLED[9]	**Current study**	**Comments**
Hypertension		Identical
Abnormal renal function: chronic dialysis, renal transplantation, or serum creatinine > 200 mmol/L	Chronic dialysis, serum creatinine > 200 mmol/L	Modified
Abnormal liver function: chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement	Severe hepatic disease[I]	Modified
Stroke		Identical
Bleeding history or predisposition (anemia)		Identical
Labile INR: therapeutic time in range < 60%		Identical
Elderly: >65 years		Identical
Drugs: other antiplatelet agents or NSAIDS		Identical
Drugs: >8 units alcohol per week		Identical
ORBIT bleeding score[10]	**Current study**	**Comments**
Older than 74		Identical
Anemia (<13 mg/dL for males and <12 mg/dL for females) or hematocrit (<40% for males and <36% for females)		Identical
Bleeding history		Identical
Insufficient kidney function [<60 ml/min/1.73 meters2]		Identical
Treatment with Antiplatelet		Identical
DOAC Score[11]	**Current study**	**Comments**
Age		Identical
Creatinine clearance/estimated glomerular filtration rate (mL/min)		Identical
Underweight (body mass index <18.5 kg/m2)		Identical
Stroke/transient ischemic attack/embolism history	Stroke/transient ischemic attack history	Modified
Diabetes		Identical
Hypertension		Identical
Antiplatelet use; aspirin or DAPT		Identical
Nonsteroidal anti-inflammatory (NSAID) use		Identical
Bleeding history		Identical
Liver disease defined as AST, ALT, ALP ≥3X upper limit of normal, ALP ≥2X upper limit of normal, or cirrhosis.	Severe hepatic disease[I]	Modified
PREDICT TAVR (score without serum iron)[12]	**Current study**	**Comments**
Oral anticoagulant		Identical
Hemoglobin		Identical
Common femoral artery diameter, scale	Common femoral artery diameter <6mm, yes/no	Modified
Dual antiplatelet therapy	Combination of oral anticoagulant with at least one antiplatelet agent	Modified
Creatinine clearance		Identical

[I] Any of the following: (i) Child-Pugh class C; (ii) MELD score >10; (iii) Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt; (iv) Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction

Supplementary Table 3. BARC and VARC-3 bleeding definitions.

BARC definition[13]
Type 0
No bleeding
• **Type 1**
Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
• **Type 2**
Any overt, actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:
o requiring nonsurgical, medical intervention by a healthcare professional,
o leading to hospitalization or increased level of care, or
o prompting evaluation
• **Type 3**
o **Type 3a**
- Overt bleeding plus haemoglobin drop of 3 to <5 g/dL* (provided haemoglobin drop is related to bleed)
- Any transfusion with overt bleeding
o **Type 3b**
- Overt bleeding plus haemoglobin drop ≥5 g/dL* (provided haemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/ nasal/ skin/ haemorrhoid)
- Bleeding requiring intravenous vasoactive agents
o **Type 3c**
- Intracranial haemorrhage (does not include micro bleeds or haemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision
• **Type 4**
CABG-related bleeding
- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period
Cell saver products are not counted.
- Chest tube output ≥2L within a 24-h period
• **Type 5**
Fatal bleeding
- **Type 5a**
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
- **Type 5b**
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood = 1g/dL haemoglobin).
CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.

VARC-3 definition[14]
Overt bleeding[b] that fulfils one of the following criteria:
Type 1
• Overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention by a health care professional, leading to hospitalization, an increased level of care, or medical evaluation (BARC 2)
• Overt bleeding that requires a transfusion of 1 unit of whole blood/red blood cells[c] (BARC 3a)
Type 2
• Overt bleeding that requires a transfusion of 2–4 units of whole blood/red blood cells[c] (BARC 3a)
• Overt bleeding associated with a haemoglobin drop of >3 g/dL (>1.86 mmol/L) but <5 g/d (<3.1 mmol/L) (BARC 3a)
Type 3
• Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial (associated with haemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome (BARC 3b, BARC 3c)
• Overt bleeding causing hypovolemic shock or severe hypotension (systolic blood pressure <90 mmHg lasting >30 min and not responding to volume resuscitation) or requiring vasopressors or surgery (BARC 3b)
• Overt bleeding requiring reoperation, surgical exploration, or re-intervention for the purpose of controlling *bleeding (BARC* 3b, BARC 4*)*
• Post-thoracotomy chest tube output ≥ 2 L within a 24-h period (BARC 4)
• Overt bleeding requiring a transfusion of ≥ 5 units of whole blood/red blood cells (BARC 3a)[c]
• Overt bleeding associated with a haemoglobin drop ≥ 5 g/dL (>_3.1 mmol/L) (BARC 3b).
Type 4
• Overt *bleeding* leading to death. Should be classified as:
o Probable: Clinical suspicion *(BARC* 5a)
o Definite: Confirmed by autopsy *or* imaging (BARC 5b)
[a] *The timing, indication, and number of transfused blood products should be collected and reported specifically during the index procedure, during the entire index hospitalization, and during follow-up after discharge, whether or not overt bleeding is identified.*
[b] *Overt bleeding is defined as any clinically obvious source of bleeding or bleeding source identified after appropriate investigation and diagnostic testing (e.g. imaging). Any procedural blood loss should be considered overt bleeding.*

[c] *Total number of transfusions should be reported separately for (i) within 48 h of the index procedure, (ii) the total duration of the index procedure hospitalization, and (iii) during any subsequent repeat hospitalization.*

Supplementary Table 4. Procedural characteristics.

Characteristic	Moderate bleeding risk (n=332)	High bleeding risk (n=337)	Very high bleeding risk (n=187)
Primary approach – no.(%)			
Transfemoral	332 (100)	328 (97.3)	187 (100)
Transsubclavian	0	9 (2.7)	0
Type of anaesthesia – no.(%)			
General	36 (10.8)	41 (12.2)	28 (15.0)
Conscious sedation	94 (28.3)	74 (22.0)	42 (22.5)
Local	202 (60.8)	222 (65.9)	117 (62.6)
Ultrasound guided vascular access – no.(%)	233 (70.2)	231 (68.5)	133 (71.1)
Additional arterial access site – no.(%)			
Transfemoral	227 (68.6)	222 (65.9)	138 (74.6)
Transradial	73 (22.1)	65 (19.3)	34 (18.4)
Both	31 (9.4)	50 (14.8)	13 (7.0)
Implanted device – no.(%)			
Sapien (3 / 3 Ultra)	107 (32.2)	75 (22.7)	58 (31.7)
CoreValve Evolut (R, Pro, Pro+, FX)	156 (47.0)	162 (48.9)	73 (39.9)
Accurate Neo (2)	31 (9.3)	41 (12.4)	26 (14.2)
Meril Myval	17 (5.1)	25 (7.6)	18 (9.8)
Other	21 (6.3)	28 (8.5)	8 (4.4)
Predilation – no.(%)	161 (48.5)	194 (57.6)	96 (51.6)
Postdilation – no.(%)	55 (16.6)	62 (18.4)	40 (21.5)
Usage of cerebral embolic protection – no.(%)	33 (9.9)	36 (10.7)	16 (8.6)
Parenteral anticoagulation (proportion heparin usage) – no.(%)	331 (99.7)	336 (99.7)	185 (98.9)
Heparin dose – IU	7748.9 (2832.5)	7669.3 (2646.4)	7408.8 (2451.6)
Protamine administration – no.(%)	260 (78.3)	260 (77.2)	138 (75.0)
Protamine dose – IU	6620.4 (3076.8)	6186.5 (2690.0)	6340.7 (2715.5)
Methods used for vascular closure primary access site – no.(%)			
Pressure bandage	93 (28.0)	105 (31.2)	77 (41.2)
Perclose ProGlide / ProStyle	253 (76.2)	254 (75.4)	145 (77.5)
MANTA Vascular Closure Device	60 (18.1)	62 (18.4)	29 (15.5)
Angio-Seal	93 (28.0)	87 (25.8)	33 (17.6)
Covered stent	9 (2.7)	11 (3.3)	4 (2.1)
Surgical repair	19 (5.7)	20 (5.9)	11 (5.9)
Methods used for vascular closure secondary access site(s) – no.(%)			
Pressure bandage (including TR band)	128 (38.6)	137 (40.7)	79 (42.2)
Perlose ProGlide / ProStyle	25 (7.5)	21 (6.2)	9 (4.8)
MANTA Vascular Closure Device	0 (0.0)	1 (0.3)	1 (0.5)
Angio-Seal	233 (70.2)	236 (70.0)	127 (67.9)

Supplementary Table 5. Major bleeding sites.

	Moderate bleeding risk (n=332)	High bleeding risk (n=337)	Very high bleeding risk (n=187)
Access site bleeding	15 (4.5)	24 (7.1)	19 (10.2)
Pericardial bleeding (acute cardiac tamponade)	0 (0.0)	4 (1.2)	3 (1.6)
Intrathoracal bleeding	1 (0.3)	1 (0.3)	0 (0.0)
Intra-abdominal bleeding	1 (0.3)	1 (0.3)	1 (0.5)
Retroperitoneal bleeding	3 (0.9)	4 (1.2)	3 (1.6)
Gastro-intestinal bleeding	0 (0.0)	0 (0.0)	1 (0.5)
Urogenital bleeding	1 (0.3)	0 (0.0)	1 (0.5)
Intracranial bleeding	1 (0.3)	0 (0.0)	1 (0.5)
Skin or muscle hematoma requiring medical attention	0 (0.0)	3 (0.9)	0 (0.0)
ICD or pacemaker pocket bleeding	1 (0.3)	1 (0.3)	1 (0.5)
Other bleeding	0 (0.0)	1 (0.3)	0 (0.0)

Supplementary Table 6. VARC bleeding types stratified according to VARC-HBR risk groups.

Bleeding type – no. %	Moderate (n=332)	High (n=337)	Very high (n=187)
Minor bleeding (Type 1)	59 (17.8)	51 (15.1)	38 (20.3)
Major bleeding (Type 2-4)	21 (6.3)	35 (10.4)	29 (15.5)
Type 2	5 (1.5)	9 (2.7)	6 (3.2)
Type 3	16 (4.8)	23 (6.8)	20 (10.7)
Type 4	-	3 (0.9)	3 (1.6)

Supplementary Table 7. Logistic regression analysis including randomised strategy.

VARC-HBR criteria*	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Randomization to continued OAC strategy	1.04 (0.65-1.69)	0.86	1.14 (0.68-1.92)	0.61
Minor criteria				
Age > 90 years			1.40 (0.32-4.27)	0.60
Dual antiplatelet therapy (besides OAC)			3.79 (0.17-3.46)	0.28
Non-transfemoral access			0.79 (0.04-4.72)	0.83
Major criteria				
BMI <20			1.33 (0.30-4.24)	0.66
Chronic kidney disease (eGFR <30)			1.04 (0.40-2.39)	0.92
Active malignancy			1.82 (0.68-4.27)	0.20
Anemia (Hb <11 g/dL)			2.16 (1.06-4.20)	0.03
Previous ischemic stroke			1.38 (0.61-2.83)	0.41
Chronic bleeding diathesis			1.62 (0.34-5.55)	0.49
Spontaneous bleeding[#]			1.20 (0.29-3.87)	0.78
Dual antithrombotic therapy (OAC + SAPT)			1.53 (0.74-2.95)	0.23
Non-deferrable major surgery			3.60 (0.15-4.45)	0.33
SFAR >1			1.18 (0.37-3.13)	0.76
Severely calcified and tortuous iliofemoral arteries			2.52 (1.46-4.32)	0.001
Immediate conversion to open heart surgery			20.78 (1.74-480.03)	0.02

OAC denotes oral anticoagulation, BMI body mass index, eGFR estimated glomerular filtration rate, SAPT single antiplatelet therapy, SFAR sheath to femoral artery ratio

*Due to limited occurrence, associations for the following variables could not be estimated: moderate thrombocytopenia, first spontaneous bleeding > 6 and < 12 months before TAVI, severe hepatic disease, severe thrombocytopenia, previous intracranial haemorrhage, oral anticoagulation (applied to everyone)

#Defined as spontaneous (non-intracranial) bleeding requiring hospitalisation or transfusion in the past 6 months (or at any time if recurrent)

Supplementary Table 8. Prevalence and logistic regression: HAS-BLED criteria.

HAS-BLED criteria	Prevalence	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Hypertension	659 (77.0)	0.85 (0.50-1.51)	0.57	0.82 (0.48-1.47)	0.49
Renal dysfunction	39 (4.6)	2.00 (0.74-4.63)	0.13	1.98 (0.69-4.87)	0.16
Liver disease	6 (0.7)	Prevalence too low			
Stroke	167 (19.5)	0.96 (0.50-1.71)	0.89	1.01 (0.53-1.82)	0.98
Bleeding / anemia	227 (26.5)	1.57 (0.93-2.57)	0.08	1.48 (0.87-2.46)	0.14
Labile INR	10 (1.2)	Prevalence too low			
Age	847 (98.9)	0.75 (0.14-14.09)	0.79	1.55 (0.24-30.97)	0.70
APT or NSAIDS	115 (13.4)	1.73 (0.92-3.1)	0.07	1.71 (0.89-3.09)	0.09
Alcohol	114 (13.3)	0.77 (0.33-1.57)	0.51	0.77 (0.33-1.57)	0.50

INR denotes International normalized ratio, APT antiplatelet therapy, NSAIDS non-steroidal anti-inflammatory drugs

Supplementary Table 9. Prevalence and logistic regression: ORBIT criteria.

ORBIT criteria	Prevalence	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Age >74	764 (89.3)	1.73 (0.75-5.03)	0.25	1.68 (0.71-4.93)	0.29
Anemia	417 (48.7)	1.14 (0.70-1.88)	0.61	1.16 (0.69-1.96)	0.59
Bleeding history	90 (10.5)	0.88 (0.36-1.86)	0.76	0.87 (0.34-1.93)	0.74
Renal dysfunction	454 (53.0)	0.93 (0.58-1.50)	0.76	0.90 (0.54-1.48)	0.66
Antiplatelets	107 (12.5)	1.91 (1.01-3.42)	0.04	2.01 (1.05-3.63)	0.03

Supplementary Table 10. Prevalence and logistic regression: DOAC criteria.

DOAC criteria	Prevalence	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Age		1.09 (0.84-1.48)	0.54	1.11 (0.85-1.51)	0.49
≥65	22 (2.6)				
≥70	83 (9.7)				
≥75	226 (26.3)				
≥80	516 (60.2)				
Creatinine clearance		1.12 (0.76-1.65)	0.55	1.12 (0.76-1.66)	0.56
30-60	452 (52.7)				
<30	69 (8.0)				
Underweight	4 (0.5)	Prevalence too low			
Stroke/TIA	167 (19.5)	0.96 (0.50-1.71	0.89	0.94 (0.49-1.7))	0.85
Diabetes	249 (29.1)	1.07 (1.07-2.85)	0.03	1.81 (1.09-2.99)	0.02
Hypertension	659 (77.0)	0.85 (0.50-1.51)	0.57	0.72 (0.42-1.29)	0.25
Antiplatelet use		1.38 (1.01-1.83)	0.03	1.35 (0.98-1.80)	0.05
SAPT	103 (12.0)				
DAPT	4 (0.5)				
NSAID use	8 (0.9)	Prevalence too low			
Bleeding history	84 (9.8)	0.99 (0.73-1.26)	0.915	1.00 (0.74-1.29)	0.99
Liver disease	6 (0.7)	Prevalence too low			

Supplementary Table 11. Prevalence and logistic regression: PREDICT-TAVR criteria.

	Prevalence	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
Oral anticoagulant	858 (100)	Present in all patients			
Hemoglobin	Continuous variable	1.14 (1.01-1.29)	0.036	1.14 (1.00-1.29)	0.05
Common femoral artery diameter < 6 mm	90 (10.5)	1.10 (0.87-1.36)	0.381	1.10 (0.86-1.35)	0.42
Dual antiplatelet therapy	107 (12.5)	0.71 (0.52-1.00)	0.037	0.72 (0.53-1.00)	0.04
Creatinine clearance	Continuous variable	1.12 (0.74-1.73)	0.598	1.01 (0.67-1.58)	0.95