

The OAC³-PAD Risk Score Predicts Major Bleeding Events one Year after Hospitalisation for Peripheral Artery Disease

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WHAT THIS PAPER ADDS

While available risk prediction scores for major bleeding events were developed primarily for patients treated for cardiac disease, there is a paucity of evidence concerning the mid term bleeding risk after treatment of patients with peripheral artery disease. Taking advantage of unselected data from the second largest insurance fund in Germany, a total of 81 930 patients were included in the current retrospective analysis. For the first time, a pragmatic risk score was developed to predict the individual bleeding risk classifying a fifth of the cohort as high risk patients. In total 2.2% of all patients had a major bleeding event after one year.

Objective: There is a paucity of evidence concerning the risk of bleeding after hospitalisation for symptomatic peripheral artery disease (PAD) in everyday clinical practice, as randomised clinical trials commonly exclude patients with heightened risk. The current study aimed to develop a pragmatic risk score that enables prediction of major bleeding during the first year after index discharge.

Methods: Unselected retrospective data from the second largest insurance fund in Germany, BARMER, were used to identify patients with a first hospitalisation for PAD registered between 1 January 2010 and 31 December 2018. Within a separate training cohort, final predictors were selected using penalised Cox regression (least absolute shrinkage and selection operator with ten fold cross validation) with one year major bleeding requiring hospitalisation as outcome. The risk score was internally validated. Four different risk groups were constructed.

Results: A total of 81 930 patients (47.2% female, 72.3 years) underwent hospitalisation for symptomatic PAD. After one year, 1 831 (2.2%) of the patients had a major bleeding event. Independent predictors were previous oral anticoagulation, age over 80, chronic limb threatening ischaemia, congestive heart failure, severe chronic kidney disease, previous bleeding event, anaemia, and dementia. The OAC³-PAD risk score exhibited adequate calibration and discrimination between four risk groups ($c = 0.69$, 95% confidence interval 0.67 – 0.71) from low risk (1.3%) to high risk (6.4%).

Conclusion: A pragmatic risk score was developed to predict the individual major bleeding risk classifying a fifth of the cohort as high risk patients. Individual prediction scores such as the one proposed here may help to inform the risk and benefit of intensified antithrombotic strategies.

Keywords: Antithrombotics, Bleeding, Haemorrhage, Health services research, Outcomes, Peripheral artery disease

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INTRODUCTION

There is growing evidence suggesting that lower limb amputation and death rates can reach between 13% and 50% after five years in peripheral artery disease (PAD) patients with intermittent claudication (IC) and 50% – 90% with chronic limb threatening ischaemia (CLTI).^{1,2} Undoubtedly, antithrombotic therapy may reduce the risk of severe thromboembolic events over time but also significantly increase the risk of major bleeding.^{3–6} Due to the recently published results from COMPASS and VOYAGER PAD, it appears likely that oral anticoagulants will be prescribed more often in this target population, while rates of major bleeding in those trials were similar to earlier trials evaluating full dose anticoagulation, such as ROCKET AF.^{7–9}

Since most randomised controlled trials (RCTs) that compared different antithrombotic strategies have excluded patients with high bleeding risk, it can be challenging to decide the best treatment regimen for patients who have no concomitant indication for oral anticoagulation or intensified antithrombotic therapy.^{9–11} To balance the individual need for an intensified antithrombotic therapy against the increased risk of potentially life threatening bleeding events the treating physician needs to consider the patient's individual risk profile.

However, while both systemic and limb related ischaemic events and their countermeasures were addressed by an increasing number of studies, there is a paucity of evidence regarding the safety of antithrombotic therapies in patients with PAD. Most available risk scores were primarily developed and validated for cardiac disease with unknown applicability to contemporary PAD cohorts. For instance, the HAS-BLED score was developed to assess one year risk of major bleeding in patients with atrial fibrillation from the Euro Heart Survey.¹² The HEMORR2HAGES score used Medicare beneficiaries with atrial fibrillation.¹³ Recently, the ARC-HBR consensus document represented the first pragmatic approach to a consistent definition of high bleeding risk in clinical trials, but these efforts specifically addressed only patients undergoing percutaneous coronary interventions.¹⁴

Those and other scores identified numerous risk factors with wide variation concerning their individual contribution (Supplementary Table S1).

To date, the only risk score that predicts serious bleeding in stable outpatients with or at risk of atherothrombotic events was derived from the Reduction of Atherothrombosis for Continued Health (REACH) registry.¹⁵ While this score was an interesting first approach to address outpatients with PAD, certain characteristics and risk profiles of hospitalised cohorts who undergo invasive revascularisation may differ substantially. Further, the score fails to take PAD clinical severity into account.

The aim of the current study was to develop an objective risk score for one year major bleeding in patients

undergoing inpatient treatment of symptomatic PAD using risk factors available during the hospital stay.

MATERIALS AND METHODS

This study used data of Germany's second largest health insurance fund, BARMER, comprising unselected data on approximately nine million German citizens (11% of Germany's population). Information about the German health-care system and the validity of the database have been described elsewhere.^{16,17} Variables were identified according to the German version of the World Health Organisation (WHO) International Classification of Diseases (ICD-10-GM), the Operations and Procedures Codes (OPS), and the international Anatomical Therapeutic Chemical (ATC) Classification (for details see Supplementary Table S2).

Patients ≥ 40 years with index inpatient treatment of symptomatic PAD between 1 January 2010 and 31 December 2018 were included in the analyses. Incident PAD cases were identified using data ranging back to 1 January 2005. Patients dying during index stay, or with length of stay exceeding 100 days and those not continuously insured throughout the prior year were excluded.

Predictors

Several systematic reviews of the literature were conducted for the European Society for Vascular Surgery (ESVS) guidelines on antithrombotic therapy in vascular diseases. The involved writing committee subsequently discussed the clinical relevance of appropriate variables (Supplementary Table S1). For predicting the outcome, the following target variables from the literature were selected: age (grouped in 40 – 60, 61 – 70, 71 – 80, > 80), sex (dichotomised), smoking (any smoking related behavioural disorder), obesity (according to the WHO definition), alcohol or drug abuse (any alcohol related or drug related behavioural disorder), congestive heart failure, hypertension, liver disease, history of stroke or transient ischaemic attack (TIA), history of cancer (excluding skin cancer), anaemia, dementia, severe chronic kidney disease (glomerular filtration rate below 30 mL/min/1.73 m²). For identifying these diseases, the Elixhauser comorbidities classification validated for temporal consistency in the BARMER data set and definitions from other large health claims studies were followed.^{18,19} History of bleeding was defined as transfusion during index hospitalisation, a prior diagnosis of coagulopathy, or a primary diagnosis of major bleeding during the index hospitalisation or the prior year. PAD severity on index hospitalisation was classified according to the Fontaine classification as stage II (intermittent claudication), III (ischaemic rest pain), and IV (ischaemic wound healing disorders, ulcer, gangrene). Also included were relevant prescriptions redeemed at the pharmacy during the year before index hospitalisation classified as antiplatelets, oral anticoagulation, lipid lowering drugs, and non-steroidal anti-inflammatory drugs

(NSAIDs) and whether open surgical repair was performed during the index stay. In total, 23 candidate predictors were made available for model development (see [Supplementary Table S2](#) for details). Few cases containing missing information (442 cases, ~0.5%) were deleted in a listwise manner (complete case analysis).

Outcome

The primary outcome was one year major bleeding, whereby a pre-specified definition specifically developed for claims based research was used. In detail, the definition of the International Society on Thrombosis and Haemostasis (ISTH) adapted by Zhang *et al.*²⁰ to ICD-10 claims data including haemorrhagic stroke and intracranial bleeding, extracranial or unclassified major bleeding in the head or eye, gastrointestinal bleeding, and traumatic intracranial bleeding was followed.²¹ During the time period between one and 365 days after discharge from index hospitalisation, major bleeding was identified as the first primary diagnosis of major bleeding at a subsequent inpatient hospitalisation using data from 1 January 2010 through 31 December 2018. Patients were censored after 365 days of follow up, death, or dropout of the insurance, whichever occurred first.

Statistical analysis

Step 1: sample split in training and validation data set. The full data were partitioned randomly into a training (60%) and validation cohort (40%) and descriptive statistics of both cohorts were expressed as absolute numbers and percentages or means with standard deviation, as appropriate. The risk score was developed using solely the training data and was thereafter finally validated and calibrated for its ability to discriminate patients using the validation cohort.

Step 2: selection of target variables. A time to event framework was applied to account for right censoring. For selecting the most important predictors among all 23 identified candidate variables, penalised Cox regression models were estimated using the least absolute shrinkage and selection operator (LASSO) procedure with ten fold cross validation for choosing the optimal regularisation parameter lambda within one standard deviation from the minimum.²² The LASSO is a regularisation technique that enables automatic selection of a sparse set of predictors with the largest effects on the bleeding outcome.

Step 3: construction of the bleeding risk score. The final model was estimated via non-penalised Cox regression with only the selected predictors in the data whereby the validity of assuming proportional hazards was assessed using the test suggested by Grambsch and Therneau.²³ The variables identified via LASSO were finally ranked by importance for predicting the outcome in the validation cohort using the permutation algorithm suggested by Breiman.²⁴ Hazard ratios with 95% confidence intervals (CIs) were computed for assessing the excess risk associated with each variable. For constructing the risk score, the beta coefficients of the final

model were multiplied by 10 and rounded to the nearest integers.

Step 4: risk groups. Based on the quartiles in the validation cohort, patients were grouped into four categories low risk, low moderate risk, high moderate risk, and high risk. Kaplan-Meier survival functions with 95% CIs were plotted for the risk groups to assess whether they were well separated. Expected bleeding risks were derived from the group specific probabilities predicted by the final Cox model.

Step 5: model performance (discrimination). Based on the point scores associated with each predictor variable, model performance was assessed in the validation set. The discrimination of the score was measured using Harrell's C index.²⁵

Step 6: model performance (calibration). Calibration of the model was assessed by comparing the observed rate of major bleeding using the Kaplan-Meier function with the expected rate based on the risk model equation, separately by each point score and by the four risk groups.

Software

SAS version 9.04 (SAS Institute, Cary, NC, USA) was used for data management. Descriptive, plots, penalised and non-

Table 1. Characteristics of 81 930 patients with symptomatic peripheral artery disease of the training and validation cohort to evaluate one year major bleeding requiring hospitalisation in Germany

	Training cohort n = 49 158	Validation cohort n = 32 772
Age – y	72.3 ± 11.2	72.3 ± 11.1
Female sex	23 201 (47.2)	15 460 (47.2)
PAD, Fontaine stage II	27 882 (56.7)	18 393 (56.1)
PAD, Fontaine stage III	5 618 (11.4)	3 688 (11.3)
PAD, Fontaine stage IV	15 658 (31.8)	10 691 (32.6)
Open surgical repair	11 388 (23.2)	7 427 (22.7)
<i>Comorbidities, prior year</i>		
History of major bleeding	5 706 (11.6)	3 814 (11.6)
Congestive heart failure	8 651 (17.6)	5 739 (17.5)
Hypertension	35 542 (72.3)	23 676 (72.2)
Liver disease	1 046 (2.1)	701 (2.1)
Obesity	4 259 (8.7)	2 805 (8.6)
History of stroke or TIA	1 616 (3.3)	1 158 (3.5)
Smoking	6 598 (13.4)	4 358 (13.3)
Alcohol or drug abuse	1 633 (3.3)	1 031 (3.1)
Dementia	2 916 (5.9)	1 992 (6.1)
Chronic kidney disease, severe	2 915 (5.9)	2 000 (6.1)
Anaemia	5 201 (10.6)	3 490 (10.6)
Cancer	1 545 (3.1)	1 083 (3.3)
<i>Medication, prior year</i>		
NSAIDs	18 663 (38.0)	12 642 (38.6)
Antiplatelet drugs	16 330 (33.2)	10 731 (32.7)
Oral anticoagulation	7 633 (15.5)	5 058 (15.4)
Lipid lowering drugs	22 944 (46.7)	15 334 (46.8)

Data are presented as n (%) or mean ± standard deviation. PAD = peripheral artery disease; TIA = transient ischaemic attack; NSAIDs = non-steroidal anti-inflammatory drugs.

penalised Cox regressions, and model diagnostics were performed in R version 4.0.3 (*ggplot2*, *survival*, *glmnet*, *Hmisc*, *tableone* package; R Foundation for Statistical Computing, Vienna, Austria).

Reporting guidelines

The TRIPOD statement was adhered to, and all analyses were performed to minimise the potential risk of bias, following the PROBAST consensus statement.^{26,27}

Sensitivity analysis

The discrimination of the score was also assessed for major bleeding at three years after discharge from index hospitalisation and was separately tested in patients with and without prior antiplatelet therapy, with or without prior oral anticoagulation, and was also tested separately by sex. Excluding all patients with a follow up duration of less than three months, the impact of post-discharge antithrombotic medication within three months after discharge on the prediction of bleeding risk was assessed in detail. Thereby, the strength of the association of the use of antithrombotics before and after index stay was measured using chi squared tests and the Phi coefficient. After adding prescription of antiplatelets and oral anticoagulation to the list of candidate variables, variable selection (step 2 above) and construction of the risk score (step 3 above) was replicated.

RESULTS

Between 1 January 2010 and 31 December 2018, a total of 81 930 patients (47.2% female, 72.3 ± 11.1 years) underwent inpatient treatment for symptomatic PAD. Thereof,

23.0% underwent open surgery, 55.8% underwent peripheral endovascular intervention, 7.1% underwent lower extremity amputation, and 14.1% were treated non-invasively during the index stay.

Within one year after index discharge, 1 831 (2.2%) of the patients required an inpatient treatment for major bleeding (including 8.4% who had a non-traumatic intracranial bleeding event, 6.7% a traumatic intracranial bleeding event, 25.6% an extracranial or unclassified head bleeding event, and 59.4% a gastrointestinal bleeding event).

The training cohort and validation cohort contained 49 158 and 32 772 patients with 1 102 (2.2%) and 729 (2.2%) major bleeding events, respectively (Table 1 and Fig. 1). Thus, for each of the 23 tested variables, 49 and 32 events were available in the two cohorts, respectively. During the first year after discharge, 10 273 (20.9%) and 7 103 (21.7%) patients were censored due to death, end of study, or change to another health insurance plan in the training and validation cohorts, respectively. Median follow up was 365 days in both cohorts.

OAC³-PAD bleeding risk score

The OAC³-PAD bleeding score comprised the following eight independent predictors Oral anticoagulation therapy (5 points), Age above 80 (2 points), Chronic limb threatening ischaemia (4 points), Congestive heart failure (3 points), severe Chronic kidney disease (3 points), Prior bleeding event (5 points), Anaemia (8 points), Dementia (3 points).

Thereby, exposure to any of these risk factors was associated with a hazard ratio between 1.26 (95% CI 1.10 – 1.44) for age above 80 and 2.15 (95% CI 1.85 – 2.51) for anaemia (Table 2).

The OAC³-PAD bleeding risk score exhibited adequate discrimination in the validation cohort ($c = 0.69$, 95% CI

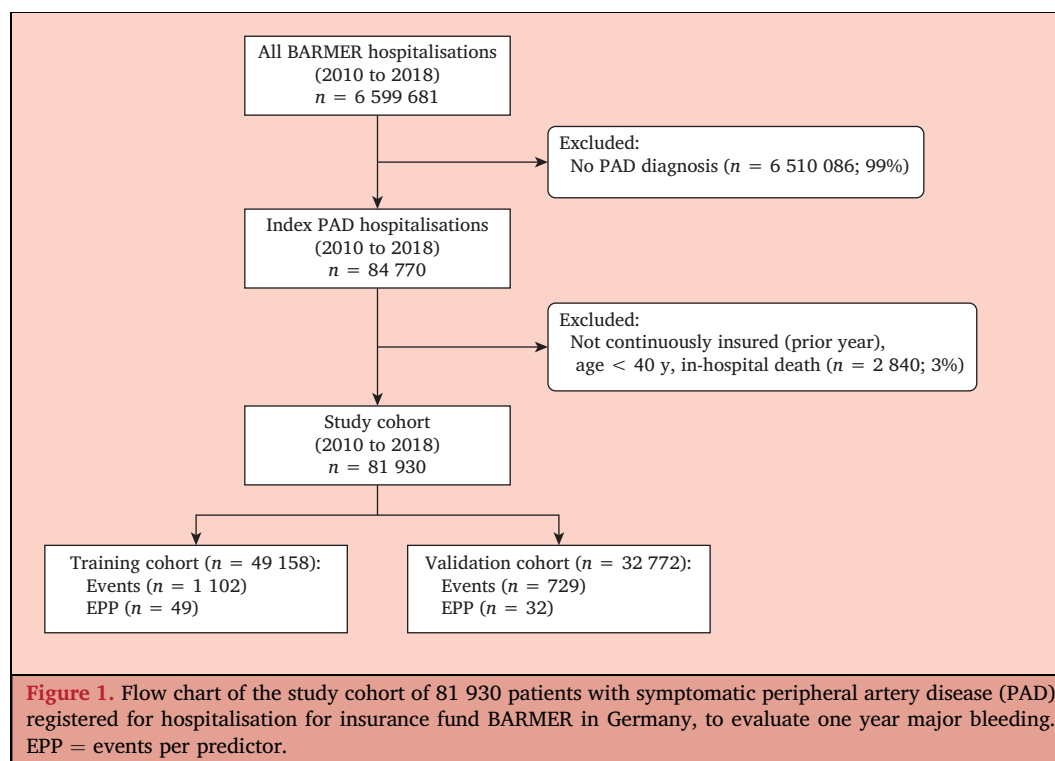


Table 2. Predictors of one year major bleeding, hazard ratios (HR) including 95% confidence intervals (CIs) variable importance, and point score in the validation cohort of 32 772 patients with symptomatic peripheral artery disease

Variables	HR (95% CI)	Importance*	Points
Oral anticoagulation before index hospitalisation	1.72 (1.50–1.97)	0.52	5
Age above 80	1.26 (1.10–1.44)	0.34	2
Chronic limb threatening ischaemia	1.46 (1.27–1.67)	1.00	4
Congestive heart failure	1.36 (1.18–1.56)	0.11	3
Chronic kidney disease, severe	1.29 (1.07–1.57)	0.10	3
Prior bleeding	1.59 (1.37–1.85)	0.53	5
Anaemia	2.15 (1.85–2.51)	0.81	8
Dementia	1.41 (1.15–1.74)	0.19	3

PAD = peripheral artery disease.

* Breiman importance as proportion scaled to the most important variable.

0.67 – 0.71). The summarised point score ranged from 0 to 33 points corresponding to a range of approximately 0% – 20% major bleeding risk, and expected rates were broadly in line with observed rates (Supplementary Figure S1).

The final four risk groups were (1) a low risk group with 0 points ($n = 12\,515$), (2) a low to moderate risk group with 1 – 4 points ($n = 6\,618$), (3) a moderate to high risk group with 5 – 9 points ($n = 7\,062$), and (4) a high risk group with 10 – 33 points ($n = 6\,577$) associated with an estimated risk of 1.28%, 1.79%, 2.62 %, and 6.42%, respectively. For these groups, the model appeared to be sufficiently calibrated with expected values slightly underestimating the moderate to high risk group and slightly overestimating the high risk group (Fig. 2). Likewise, the risk groups allowed discrimination of the different long term courses during the follow up to incident major bleeding adequately with non-overlapping 95% CIs at one year after discharge from index hospitalisation (Fig. 3).

Sensitivity analysis

After three years 1 506 (4.46%) patients had a major bleeding event in the validation cohort. For these patients, the discrimination of the OAC³-PAD bleeding risk was only marginally smaller ($c = 0.67$, 95% CI 0.66 – 0.68) (Table 3). At the same time, the long term courses to incident major bleeding among the risk groups are clearly distinguishable (Supplementary Figure S2). Assessing discrimination for different subgroups of the validation cohort resulted in c indices ranging between 0.62 (95% CI 0.60 – 0.64) for patients with prior use of oral anticoagulation and 0.69 (95% CI 0.67 – 0.71) for males (Table 3). In the subgroup of patients with a follow up duration of at least three months, there was a significant association between antiplatelets use ($p < .001$, Phi = 0.22) and oral anticoagulation use ($p < .001$, Phi = 0.52) one year before and three months after

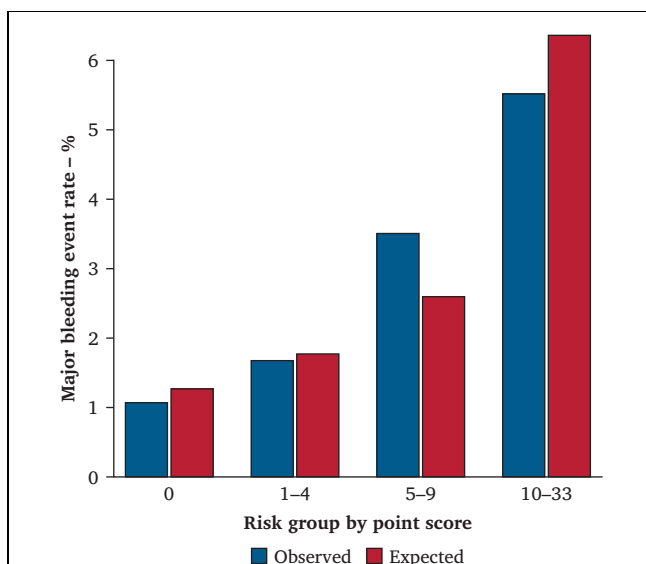


Figure 2. Model calibration comparing expected (dark) and observed (light) one year risk of major bleeding event for each risk quantile by point score in the validation cohort of 32 772 patients with symptomatic peripheral arterial disease requiring hospitalisation.

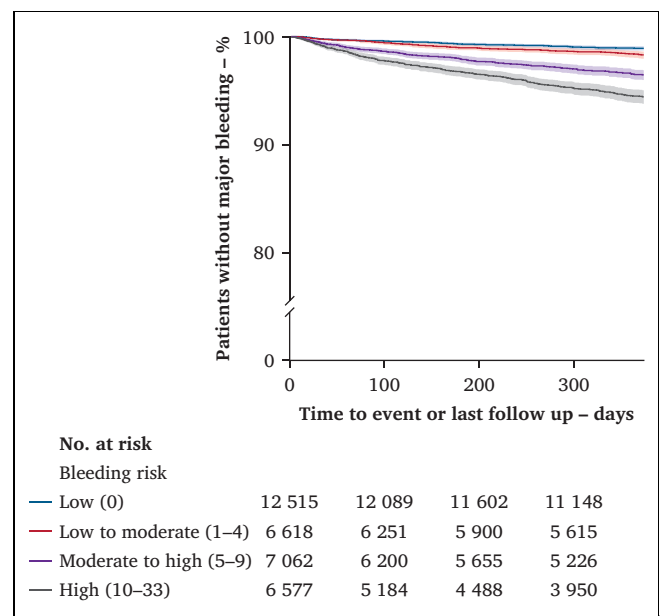


Figure 3. Cumulative Kaplan-Meier estimate of observed freedom from major bleeding events after discharge for each risk quantile from low risk to high risk in the validation cohort of 32 772 patients with symptomatic peripheral arterial disease requiring hospitalisation. Note the adapted y axis scale.

Table 3. Discriminative ability of the OAC³-PAD bleeding risk score in different subgroups of the validation cohort of 32 772 patients with symptomatic peripheral artery disease and for three year major bleeding as outcome

Subgroup	Patients – n	Events – n	C index (95% CI)
No prior use of oral anticoagulation	27 164	550	0.68 (0.66–0.70)
Prior use of oral anticoagulation	4 879	179	0.62 (0.60–0.64)
No prior use of antiplatelets	21 572	469	0.69 (0.67–0.71)
Prior use of antiplatelets	10 471	260	0.68 (0.66–0.70)
Females	15 117	343	0.68 (0.66–0.70)
Males	16 926	386	0.69 (0.67–0.71)
Outcome, three year major bleeding	32 774	1 506	0.67 (0.66–0.68)

index stay. The penalised Cox regression in this subgroup, that included variables for post-discharge medication, selected also oral anticoagulation but not antiplatelet use after discharge. Yet, the additional information hardly affected the point score assigned to each variable measured at baseline and did not improve the discriminative performance of the risk score ($c = 0.68$, 95% CI 0.65 – 0.71).

DISCUSSION

This health insurance claims analysis identified eight independent predictors of major bleeding events after inpatient treatment of symptomatic PAD. Between 1.3% of patients with low and 6.4% with high risk profile required inpatient treatment for major bleeding during one year after index discharge, emphasising differences between cohorts included in clinical trials and everyday clinical practice. The OAC³-PAD score can help to inform the individual risk of major adverse cardiovascular and limb events against major bleeding risk to decide on the optimal antithrombotic treatment strategy taking into account both benefits and risks associated with the treatment. As far as known, this is the first pragmatic bleeding risk score for patients with PAD also considering disease severity to which many other scores are limited. It is applicable for patients undergoing both endovascular and open surgical revascularisations. For its convenient use in everyday clinical or outpatient practice, a pocket score card (Fig. 4) as well as a responsive website for mobile devices are provided (<https://score.germanvasc.de>).

There is a paucity of evidence concerning bleeding events in patients who undergo invasive revascularisation for PAD. Besides the fact that many observational studies did not consistently report bleeding as an outcome in the longer term, several varying definitions and classification systems have been used that makes it challenging to compare available results directly. This lack of uniformity has also been emphasised recently in clinical trials on coronary disease.²⁸ In an attempt to further harmonise global peripheral arterial revascularisation registries, the VASCUNET and International Consortium of Vascular Registries recently recommended reporting bleeding as an outcome.^{29,30} Unfortunately, no specific definitions were included in those consensus recommendations. In the current study, the ISTH definition of major bleeding was followed and ICD codes specifically developed for the purpose of measuring bleeding rates related to antithrombotic medication were

used. Those were successfully applied in various large European observational studies before.^{31,32}

In the field of peripheral vascular interventions, the available comparative effectiveness evidence concerning different antithrombotic strategies primarily stems from RCTs that largely excluded patients at substantial risk of bleeding. In turn, this might have introduced selection bias that may lead to an overestimation of the net clinical benefit of the treatment under study when applied in

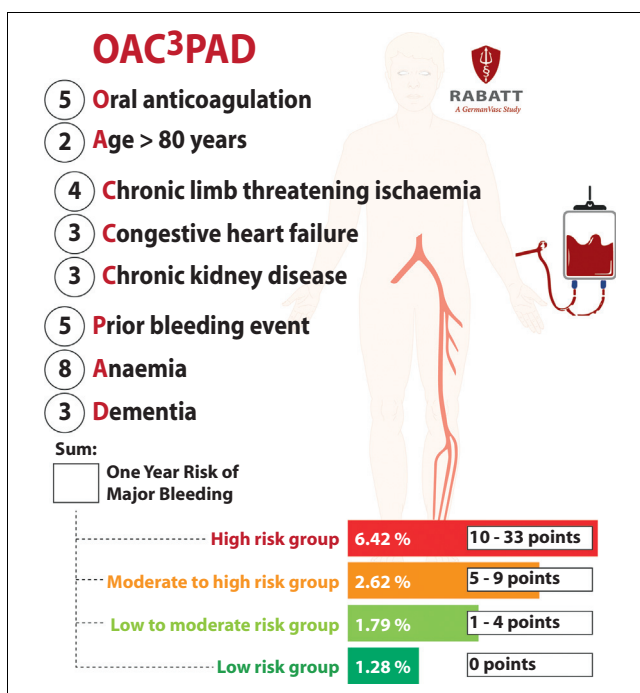


Figure 4. Summary sheet for the OAC³-PAD bleeding risk score including the four risk groups: low; low to moderate; moderate to high; and high risk. The numbers before the risk factors are the point scores to be summarised for the presence of this risk factor. Oral anticoagulation: prior use of direct thrombin inhibitors, vitamin K antagonists or direct factor Xa inhibitors. Chronic limb threatening ischaemia: peripheral artery disease at Fontaine stage III (ischaemic rest pain) and IV (ischaemic wound healing disorders, ulcer, gangrene). Prior bleeding event: transfusion during index hospitalisation or a prior diagnosis of coagulopathy or a prior primary diagnosis of major bleeding. Anaemia: presence of blood loss anaemia or deficiency anaemia or anti-anaemic medication. Dementia: presence of vascular or unspecified dementia or antidementia medication. For further codings and definitions see Supplementary Table S2.

everyday clinical practice. For instance, the VOYAGER PAD trial used major bleeding as safety outcome, defined according to the Thrombolysis in Myocardial Infarction (TIMI) classification. Patients were excluded if they were at a heightened risk of bleeding. In that trial, TIMI major bleeding during three years of follow up occurred in 2.65% of the intervention group with intensified antithrombotic therapy vs. 1.87% in controls (HR 1.43, 95% CI 0.97 – 2.10). Using the secondary safety outcome of ISTH major bleeding, 5.94% vs. 4.06% exhibited an event (HR 1.42, 95% CI 1.10 – 1.84), respectively. The latter classification was rather comparable to the current study, while similar event rates in the TIMI classification after one year were observed only in the low risk groups, while approximately 20% of the cohort were included in high risk groups (Supplementary Table S3).

The current study has limitations. Firstly, retrospective observational study design can only reveal associations. However, the challenge of residual confounding remains a major challenge, and no causality can be drawn from observational research. Specifically, as the same as for comparable risk scores, medical treatments after discharge from index hospital stay were not taken into account. Yet, the sensitivity analysis indicated that medication use before and after index stay were highly correlated and that adding post-discharge medication did not improve the prediction of bleeding risk. As recently proposed, future studies may combine information from clinical prediction models and randomised clinical trials to further improve causal prediction. Secondly, variables were categorised for the purpose of usability in the clinical setting accepting a certain loss of predictive performance. Thirdly, although competing risks were not explicitly modelled, censoring was accounted for, e.g., due to death or end of study period, using a sound survival analysis framework. Lastly, although model optimism was accounted for using a random split sample approach (60:40), external validation can reveal a general applicability of the score and the suitability of measured risk factors in other healthcare systems. The moderate discriminative performance of the score must be viewed against the background that available bleeding risk scores on cardiac disease rarely achieve *c* indices higher than 0.70 (Supplementary Table S1). For example, the recently published PRAISE score for one year bleeding in patients with acute coronary syndrome reported a similar *c* index of 0.70 for validation albeit extensive model selection by using various complex machine learning classifiers.³³ All choices during the development state concerning design and statistical modelling were discussed in an interdisciplinary team involving the ESVS guidelines writing committee on antithrombotics in vascular diseases. Thereby, simplicity and practicability were prioritised, as these aspects were deemed most relevant for the widespread implementation of a bleeding score in clinical practice.³⁴ It appears possible that the major bleeding rates are even higher than observed due to a non-presentation bias (e.g., due to fatal events). However, this bias affects all observational and randomised studies, and the low rate of autopsy studies make it challenging to address these events.

Broad awareness of major bleeding, and a meticulous consideration of the individual risk profile appears reasonable before an established antithrombotic therapy is intensified.

Conclusion

In the current study, a pragmatic risk score comprising eight independent predictors was developed. Individual prediction scores may help to inform the risk and benefit assessment of intensified antithrombotic strategies.

CONFLICTS OF INTEREST

J.N. reports honoraria from Bayer, BD, and Medtronic. V.A. reports honoraria and institutional funding from AstraZeneca, Bayer, Boehringer-Ingelheim/Lilly Alliance, BMS/Pfizer Alliance, NovoNordisk, and Vifor. The other authors declare no conflict related to the current study.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2021.12.019>.

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