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External validation and updating of prediction models of bleeding risk in patients with cancer receiving anticoagulants

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ABSTRACT

Objective Patients with cancer are at increased bleeding risk, and anticoagulants increase this risk even more. Yet, validated bleeding risk models for prediction of bleeding risk in patients with cancer are lacking. The aim of this study is to predict bleeding risk in anticoagulated patients with cancer.

Methods We performed a study using the routine healthcare database of the Julius General Practitioners' Network. Five bleeding risk models were selected for external validation. Patients with a new cancer episode during anticoagulant treatment or those initiating anticoagulation during active cancer were included. The outcome was the composite of major bleeding and clinically relevant non-major (CRNM) bleeding. Next, we internally validated an updated bleeding risk model accounting for the competing risk of death.

Results The validation cohort consisted of 1304 patients with cancer, mean age 74.0±10.9 years, 52.2% males. In total 215 (16.5%) patients developed a first major or CRNM bleeding during a mean follow-up of 1.5 years (incidence rate; 11.0 per 100 person-years (95% CI 9.6 to 12.5)). The c-statistics of all selected bleeding risk models were low, around 0.56. Internal validation of an updated model accounting for death as competing risk showed a slightly improved c-statistic of 0.61 (95% CI 0.54 to 0.70). On updating, only age and a history of bleeding appeared to contribute to the prediction of bleeding risk.

Conclusions Existing bleeding risk models cannot accurately differentiate bleeding risk between patients. Future studies may use our updated model as a starting point for further development of bleeding risk models in patients with cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Bleeding risk is increased in patients with cancer, yet validated models for the prediction of bleeding risk in patients with cancer are lacking.

WHAT THIS STUDY ADDS

⇒ External validation of existing bleeding risk models was performed in routine primary healthcare data. These models cannot accurately predict bleeding in patients with cancer. On updating, only age and history of bleeding contributed to the prediction of bleeding risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Only age and a history of bleeding were shown to have incremental predictive value and could be considered in future prediction models for bleeding in patients with cancer at risk for thromboembolic complications.

INTRODUCTION

Patients with cancer using anticoagulants for treatment of venous thromboembolism (VTE) or prevention of stroke in atrial fibrillation (AF) are at increased risk of thrombosis due to the hypercoagulability state of cancer itself as well as caused by its treatment.[1] However, these patients are also at an increased risk of bleeding.[2] For example, patients with cancer may need to undergo chemotherapy which often causes thrombocytopaenia, drug interactions, periods of reduced renal function and suboptimal nutritional status, which all may increase bleeding risk. Invasive procedures such as surgery, intravenous access lines and biopsies also carry an increased bleeding risk, notably in anticoagulated patients.[2] Finally, the malignant tumour itself may also cause spontaneous bleeding, for example, gastrointestinal, lung or brain tumours.[3–5] Hence, even though often clearly indicated, anticoagulant therapy in patients with cancer with VTE or AF is a complicated clinical endeavour, notably during certain periods of the disease, warranting constantly a vigorous balance between bleeding and thrombosis risk.

Therefore, it is important to identify patients with cancer with an increased risk of bleeding. While on average patients may have a net benefit of anticoagulation, for individualised treatment decisions a bleeding risk

assessment can aid in shared decision-making.[6] A bleeding risk model could be used to monitor the bleeding risk during anticoagulant treatment and to identify individual moments of increased bleeding risk where monitoring or perhaps temporarily reduced dosing may be warranted. Moreover, in patients with advanced cancer and a limited life expectancy, the bleeding risk can outweigh the thrombosis risk reduction, and stopping anticoagulant treatment may perhaps be the preferred option. Knowledge of what then defines and differentiates bleeding risk between patients is paramount.

To assess the risk of bleeding, various risk prediction models have been developed for patients with VTE or AF. These bleeding risk models include various common predictors, for example, age, comorbidities and the concurrent use of medication such as antiplatelet drugs. Some models also include cancer as a predictor to account for the increased bleeding risk in these patients. However, none of the published bleeding risk models has ever been evaluated in a cohort of patients with cancer using healthcare data from primary care including clinically relevant non-major (CRNM) bleeding complications occurring outside the hospital. Therefore, we aimed to externally validate commonly used bleeding risk models in patients with cancer in the primary care setting. We will update and internally validate the best-performing bleeding risk model for use in this vulnerable population.

METHODS

Selection and appraisal of existing bleeding risk models

A priori we selected five existing bleeding risk models based on their common use and the availability of predictors in routine primary healthcare. We selected models developed to predict bleeding in either AF and/or VTE patients receiving anticoagulants. The selected models were as follows: HAS-BLED, ATRIA, ORBIT, VTE-bleed and the AF-bleed.[7–11] The VTE-bleed was developed specifically for the prediction of bleeding in VTE patients, the HAS-BLED, ORBIT and ATRIA for the prediction of bleeding in AF patients. The AF-bleed is an adaptation of the VTE-bleed for the prediction of bleeding in AF patients. The risk of bias was assessed using the PROBAST tool.[12]

Source of the external validation cohort

To validate each bleeding risk model, we used a retrospective, observational cohort from the Julius General Practitioners' Network (JGPN). The JGPN database contains longitudinal routine healthcare data of more than 450 000 individuals from the 1990s of the last century onward, deidentified extracted from the electronic medical files of general practitioners (GPs) in the vicinity of Utrecht in the Netherlands.[13 14] People included in the JGPN database represent the Dutch population, except for nursing home residents who are not represented in this database.

Inclusion and exclusion criteria for the external validation cohort

From May 2000 to January 2022, all patients with a new cancer episode during anticoagulant treatment either with a vitamin K antagonist (VKA), a direct oral anticoagulant (DOAC), low-molecular-weight heparin (LMWH) or heparin indicated for either the treatment of VTE or stroke prevention in AF were included. We only selected patients with a new cancer diagnosis to limit the validation cohort to patients with active cancer. Patients with all types of cancer were eligible for inclusion, except for patients with basal cell carcinoma of the skin. Both patients already using anticoagulants, that is, before the cancer diagnosis (most often for AF), and patients who initiated anticoagulant treatment no longer than 6 months after the index cancer diagnosis were eligible for inclusion. For patient selection, we used the ICPC codes (International Classification of Primary Care) for AF, VTE, and any type of cancer excluding basal cell carcinoma, and ATC (Anatomical Therapeutic Chemical) codes for anticoagulants.[15] For an overview, see online supplemental file 2.

Data collection

For patients already using anticoagulants before the cancer diagnosis, data collection started on the date of the cancer diagnosis (ie, the index date). For patients with active cancer who initiated anticoagulants within 6 months after the cancer diagnosis, the index date is the date of the first prescription of the anticoagulant. We used a maximum of 3 years of follow-up data, after which the disease episode of active cancer was considered dissolved. Because the theoretical end date of a drug prescription often does not correspond with the actual end of anticoagulant treatment (due to, eg, stockpiling or medication non-compliance), we used a 'grace' period of 14 days to extend the anticoagulant treatment period after the date of the last prescription to adjust for this, an approach often applied in the field of bleeding risk analyses.[16] ICPC codes and ATC codes used for predictors and bleeding outcomes are listed in online supplemental file 2.

Outcome definition

The outcome of this study was the composite of major and CRNM bleeding defined as all bleeding events which at least led to face-to-face evaluation by a healthcare professional, based on the criteria of the International Society on Thrombosis and Haemostasis (ISTH).[17] For data on bleeding, both coded data and free-text data were used. For every face-to-face contact registered under any bleeding-related, cancer-related, VTE-related or AF-related ICPC, the free text of the consultation was evaluated to verify that the patient in fact had a (new) bleeding event and to assess the location and type of bleeding. Outcome events were assessed without knowledge of the predictor information.

Table 1 Characteristics of the 1304 patients with cancer and anticoagulant treatment subdivided in patients with VTE, AF or both

	VTE (N=365)	AF (N=883)	VTE and AF (N=56)	Total (N=1304)
Mean age in years (SD)	66.8 (12.6)	76.8 (8.6)	77.4 (9.3)	74.0 (10.9)
Male sex (n, %)	171 (46.8)	484 (54.8)	26 (46.4)	681 (52.2)
Type of cancer (n, %)				
Gastrointestinal	63 (17.3)	158 (17.9)	7 (12.5)	228 (17.5)
Lung	64 (17.5)	122 (13.8)	8 (14.3)	194 (14.9%)
Breast	44 (12.1)	93 (10.5)	8 (14.3)	145 (11.1%)
Prostate	25 (6.8)	65 (7.4)	2 (3.6)	92 (7.1%)
Urogenital	41 (11.2)	114 (12.9)	9 (16.1)	164 (12.6)
Haematologic	31 (8.5)	61 (6.9)	4 (7.1)	96 (7.4)
Skin	25 (6.8)	171 (19.4)	11 (19.6)	207 (15.9)
Other	72 (19.7)	99 (11.2)	7 (12.5)	178 (13.7)
Type of anticoagulant (n, %)				
VKA	100 (27.4)	528 (59.8)	27 (48.2)	655 (50.2)
Heparin	1 (0.3)	2 (0.2)	0	3 (0.2)
LMWH	182 (49.9)	92 (10.4)	11 (19.6)	285 (21.9)
DOAC	82 (22.5)	261 (29.6)	18 (32.1)	361 (27.7)

AF, atrial fibrillation; DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; VKA, Vitamin K antagonist; VTE, venous thromboembolism.

Predictor definition

Where possible we aimed to use the same definition for each predictor as described in the original validation study of each included risk model. If the exact information was not available, we used the best available approximation. See online supplemental file 3 for an overview of the predictor definitions used in our study. The absence or presence of predictors was assessed without knowledge of the outcome. In absence of an ICPC code or ATC code, the predictor was considered absent. Missing data on predictors were not imputed to reflect daily practice.

Table 2 Bleeding location of major and clinically relevant non-major bleeding for which 215 of the 1304 patients with cancer and anticoagulant treatment contacted the GP during a mean follow-up of 1.5 years

	Total (N=215) (n, %)
Skin	77 (35.8)
Urogenital tract	53 (24.7)
Gastrointestinal tract	27 (12.6)
Ear/nose/throat	22 (10.2)
Other	20 (9.3)
Respiratory tract	10 (4.7)
Intracranial	6 (2.8)

GP, general practitioner.

Data analysis

An incidence rate of the number of bleeds per 100 person-years with a 95% CI for a first CRNM or major bleeding during anticoagulant treatment was calculated. Data analyses were performed in R V.4.0.5.

External validation

To determine the predictive performance of the selected bleeding risk models in our study population, we aimed to assess calibration and discrimination. For discrimination, expressing the proportion in which the bleeding risk model correctly assigns the highest risk to those with a bleed in a random pair of patients (one with a bleed and one without a bleed) we calculated the c-statistic with corresponding 95% CI. For calibration, in absence of the expected risk compared with the observed bleeding risk (O/E ratio) and subsequent calibration plots, we reported the observed bleeding risk in each of the risk categories (as a proxy of the expected risk) where relevant.

Model updating and internal validation

Three Cox proportional hazards models were fitted. First, a simple baseline model was fitted including only the predictors 'age' and 'sex'. Next, this baseline model was updated by including all predictors included in at least two out of four of the existing bleeding risk models selected for external validation. Finally, we added in a third model as a dichotomous variable the cancer types with a high risk of bleeding (ie, mucosal tumours and

Table 3 Characteristics of the 1304 patients with cancer and anticoagulation divided into those with and without bleeding event

	Bleeding (N=215)	No bleeding (N=1089)	Overall (N=1304)
Mean age in years (SD)	75.7 (9.2)	73.7 (11.1)	74.0 (10.9)
Male sex (n, %)	111 (51.6)	570 (52.3)	681 (52.2)
VTE (n, %)	61 (28.4)	360 (33.1)	421 (32.3)
AF (n,%)	163 (75.8)	776 (71.3)	939 (72.0)
History of hypertension (n, %)	132 (61.4)	591 (54.3)	723 (55.4)
History of CVA (n, %)	31 (14.4%)	163 (15.0)	194 (14.9)
History of diabetes (n, %)	42 (19.5)	265 (24.3)	307 (23.5)
History of anaemia	22 (10.2)	123 (11.3)	145 (11.1)
History of renal insufficiency (n, %)	31 (14.4)	125 (11.5)	156 (12.0)

AF, atrial fibrillation; CVA, cerebral vascular accident; VTE, venous thromboembolism.

lung tumours) versus all other types of cancer. To account for possible non-linearity of age, a restricted cubic spline with four knots was used. For all three models, Akaike's information criterion (AIC) was determined and likelihood ratio tests (LRT) were performed to compare the fit of the models. A final model was selected based on AIC and LRT. To account for the competing risks of non-bleeding-related death, a cause-specific hazard model was used for internal validation.[18] The model was internally validated using 10-fold cross-validation, and calibration and discrimination were calculated. Finally, as an additional explorative analysis, backward elimination based on AIC was used for model reduction,[19] and the predicted bleeding risk associated with the remaining predictors was plotted. Proportional hazard assumptions were visually checked for the final model by plotting scaled Schoenfeld residuals for every predictor.

RESULTS

Descriptive statistics study population

The validation cohort consisted of 1304 patients with cancer, mean age 74.0±10.9 years, 52.2% male. In total, 365 (28%) patients had a VTE diagnosis, 883 (67.7%) an AF diagnosis and 56 (4.3%) patients had both an AF and VTE diagnosis (table 1). At the index date, 655 (50.2%) patients used a VKA, 361 (27.7%) a DOAC, 285 (21.9%) LMWH and 3 (0.2%) patients heparin.

Bleeding events in the validation cohort

In total 215 (16.5%) patients had at least one major or CRNM bleeding event during a mean follow-up of 1.5 (SD 1.2) years. The incidence rate for a first major or CRNM bleeding was 11.0 per 100 person-years (95% CI 9.6 to 12.5). Tables 2 and 3 provide an overview of the bleeding locations and characteristics of patients with and without bleeding, respectively.

External validation of the existing bleeding risk models

See online supplemental file 1 for the risk of bias assessment of the selected bleeding risk models. In table 4, the c-statistics with 95% CI for each of the existing bleeding risk models are presented. The c-statistics ranged between 0.55 (95% CI 0.51 to 0.59) and 0.56 (95% CI 0.52 to 0.60). Since we were not able to formally assess the calibration of the models, table 5 shows the distribution of patients and bleeding events across the risk strata of each bleeding risk model. Because all patients in our study have cancer, all patients were categorised in the high-risk category in case of the VTE-bleed. For some bleeding risk models, there was a doubling of the observed bleeding risk in the higher risk categories compared with the lower risk categories, for other bleeding risk models this increase was less pronounced.

Model updating and internal validation

Our second model, consisting of the variables age, sex, hypertension, history of bleeding, renal insufficiency, anaemia and use of antiplatelet drugs performed best. For an elaboration, see online supplemental file 4. The adjusted c-statistic of the competing risk model after internal validation was 0.61 (95% CI 0.54 to 0.70). Table 6 demonstrates the HRs, CIs and internal validation performance measures of the competing risk model. In figure 1, the calibration plot of the final model is

Table 4 External validation of five bleeding risk models in the total study population; C-statistics with 95% CI

	VTE-bleed	AF-bleed	HAS-BLED	ATRIA	ORBIT
C-statistic	0.56	0.56	0.56	0.55	0.56
95% CI	0.52 to 0.60	0.51 to 0.60	0.52 to 0.60	0.51 to 0.59	0.52 to 0.60

AF, atrial fibrillation; VTE, venous thromboembolism.

Table 5 Distribution of patients and bleeding events across the risk categories of each bleeding risk model

Risk category	VTE-bleed			AF-bleed			HAS-BLED			ATRIA			ORBIT		
	Distribution of points	n/total	IR with 95% CI	Distribution of points	n/total	IR with 95% CI	Distribution of points	n/total	IR with 95% CI	Distribution of points	n/total	IR with 95% CI	Distribution of points	n/total	IR with 95% CI
Low	≤1 points	–	–	≤2 points	36/298	8.1 (5.7 to 11.2)	0 points	10/106	7.6 (3.7 to 14.0)	0–3 points	81/584	8.9 (7.1 to 11.1)	≤2 points	130/892	9.4 (7.9 to 11.2)
Medium	N/A	N/A	N/A	N/A	N/A	N/A	1–2 points	126/837	9.5 (7.9 to 11.3)	4 points	26/194	8.7 (5.7 to 12.8)	3 points	48/243	13.6 (10.1 to 18.1)
High	≥2 points	215/1304	11.0 (9.6 to 12.5)	≥3 points	179/1006	11.8 (10.2 to 13.7)	≥3 points	79/361	15.7 (12.4 to 19.5)	≥5 points	108/526	14.3 (11.7 to 17.3)	≥4 points	37/169	16.4 [11.5 to 22.6)
Total		215/1304	11.0 (9.6 to 12.5)		215/1304	11.0 (9.6 to 12.5)		215/1304	11.0 (9.6 to 12.5)		215/1304	11.0 (9.6 to 12.5)		215/1304	11.0 (9.6 to 12.5)

AF, atrial fibrillation; IR, incidence rate; N/A, not applicable; n/total, number of bleeding events/ total number of patients in the corresponding risk category; VTE, venous thromboembolism.

Table 6 Internal validation of the competing risk model

	HR	95% CI
Age	1.0	1.0 to 1.1
Age'	0.9	0.8 to 1.0
Age"	1.4	0.8 to 2.5
Sex	0.9	0.7 to 1.3
Anaemia	1.0	0.7 to 1.4
Renal insufficiency	1.1	0.7 to 1.6
Antiplatelet use	1.5	0.9 to 2.5
History of hypertension	1.1	0.9 to 1.5
History of bleeding	1.5	1.1 to 2.0
C-statistic	0.61	0.54 to 0.70
R^2	0.018	
Brier score	0.13	0.12 to 0.15

A cubic spline with four knots was used to account for non-linearity of the variable age. The variable age is, therefore, divided into three groups depicted as age, age' and age".

shown. Based on backward selection using model 2, only the predictors 'age' and 'history of bleeding' remained in the model. See figure 2 for the association between the expected bleeding risk and the predictors 'age' and 'history of bleeding'.

DISCUSSION

Our study shows that while bleeding is common in patients with cancer receiving anticoagulants (11 per 100 patient-years), existing and updated bleeding risk models with commonly available predictor variables

Figure 1 Calibration plot final model.

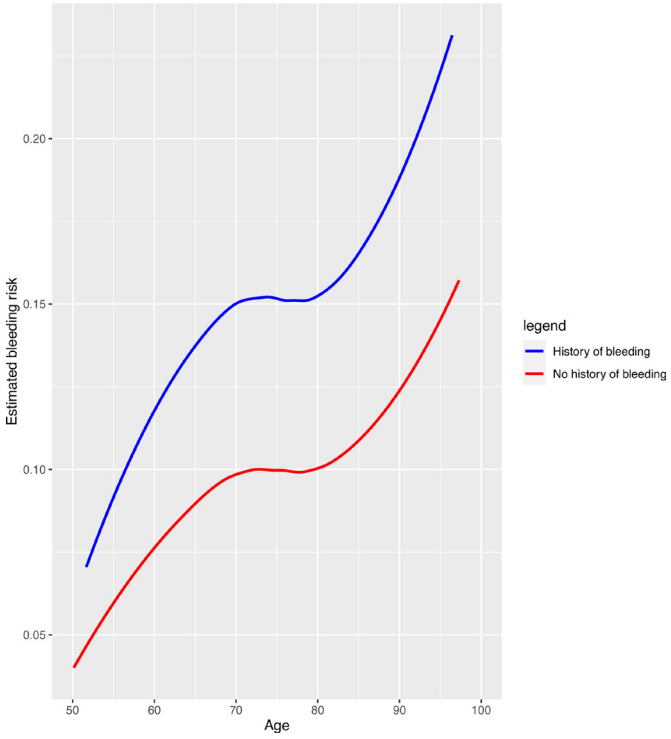

Figure 2 Relation between estimated bleeding risk, age and history of bleeding.

were unable to differentiate the risk of bleeding in this population. Only age and a history of bleeding appeared to be relevant to estimate bleeding risk in our primary care dataset.

Comparison with literature

The incidence rate of a first major or CRNM bleeding event in our study was 11.0 per 100 person-years, which was higher than in previous studies in AF[8–11] and in VTE patients.[7] Because we selectively focused on patients with cancer and could include CRNM bleedings only seen by the GP and not necessarily by specialists, our incidence rate indeed is much higher. In a recently published study performed in patients with cancer-associated thrombosis who were included in a randomised trial, an incidence of major and CRNM bleeding of 14.2% was found during a follow-up period of 12 months,[20] which is more comparable to what we found. Such a high bleeding risk certainly calls for a careful and shared decision on anticoagulant treatment based on an individually predicted bleeding risk.

Performance of existing bleeding risk models including an updated competing risk model

This study showed that predicting bleeding risk in patients with cancer is difficult with existing bleeding risk models. The c-statistics of 0.56 for all existing models indicate that in two individual patients with cancer on anticoagulant treatment, one experiencing bleeding and the other not, the probability that the patient experiencing the bleeding event receives a higher estimated bleeding risk from available models is 'only' 56%, thus almost similar as to flipping a coin. Model updating using state-of-the-art methodology only slightly improved model performance, yet this still would be considered poor performance against current standards. Moreover, this updated model did not yield sufficient calibration, likely due to insufficient sample size.

Likely other predictors, not included in the valuated prediction models, may be predictive of bleeding in patients with cancer. Identifying these predictors and incorporating these in prediction models for bleeding should be the focus of further studies. The recently developed CAT-BLEED model (developed in patients with cancer-associated thrombosis) includes cancer-related factors such as cancer subtypes and associated chemotherapy.[20] Although detailed information on chemotherapy was not available in our dataset, we were not able to confirm that cancer subtypes provide reliable incremental prognostic information with relation to bleeding risk. We did, however, observe that age and a prior history of bleeding are useful, and these predictors are 'ready at hand'.

Clinical implications and future considerations

For patients with active cancer using anticoagulants, a clinically relevant or major bleed may be an impactful event that perhaps could influence further anticoagulant treatment decisions. Our analyses demonstrate that such bleeding events indeed occur frequently in anticoagulated patients with cancer, highlighting the need for shared decision-making with respect to anticoagulant treatment. To support such decisions, for example, (temporarily) withholding anticoagulation, reducing the dose or switching between anticoagulants, an accurately predicted risk of bleeding for balancing against the benefits of anticoagulation is an important necessity. There are several steps to be taken to improve prediction in future research. First, to improve the value of known predictors, reporting on bleeding risk models and the modelling itself need improvement. All models included in our study had a high risk of bias according to the PROBAST guideline due to the lack of relevant information on, for example, predictor selection or predictor assessment, not handling missing data appropriately, or not accounting for competing risk. This in fact is a more general call for better reporting on bleeding risk models, not only for the subgroup of patients with cancer. Second, further research is needed to identify future cancer-specific risk factors for bleeding and to include these in bleeding risk models. Ultimately, though, after accurate prediction, randomized controlled trials are needed that evaluate clinically relevant outcomes when anticoagulation is reduced with the aim to mitigate bleeding risk in high-risk individuals. Thus, not only identifying those who may experience a bleed but also what to employ in order to prevent these bleeds. Finally, future developments in anticoagulants with lower risk of bleeding, such as with factor XIa inhibitors are promising. These drugs are currently

tested in phase II and III trials, and they may also reduce bleeding risk in patients with cancer as they do in patients without cancer.[21 22]

Strengths and limitations

A strength of this study is that the dataset consisted of a large and representative sample of anticoagulated patients with cancer with VTE and/or AF, managed in the community (with data extracted from a longitudinal primary care database), encompassing all patients with cancer, also those only seen by the GP for bleeding complications. All clinically relevant bleeding outcomes could be included, also CRNM bleeding only reported by patients to the GP, including, for example, so-called 'nuisance' bleeds' (euphemistically), which are not always reported or registered in hospital datasets. Also, clinically relevant bleeding which occurred in the hospital setting was registered in our database as well, and thus included in our analysis. For model updating, we used state-of-the-art methodology including a cause-specific Cox-proportional hazard model, which is a recommended method for analysis of time-to-event data in the presence of competing risk (ie, non-bleeding related death).[18] Not accounting for competing risks can lead to an overestimation of the bleeding risk, certainly in a population of patients with cancer.[23] A limitation of this study is that both misclassification of the outcome and of predictors could have occurred. Regarding the predictors, most predictor definitions used in our validation closely resembled the definitions used in the development studies, however, some minor differences could not be avoided. We relied on data from routine care, and while we were able to assess free text for all patients, a distinction between major and CRNM was not possible. Last, due to a lack of power we were not able to study the predictive performance of the models in subgroups (eg, for AF and VTE patients separately, type of cancer or type of anticoagulant).

CONCLUSIONS

Bleeding in patients with cancer could not be accurately predicted using commonly used existing bleeding risk models. Only age and a history of bleeding were shown to have incremental predictive value and should be considered in future prediction models for bleeding in patients with cancer at risk for thromboembolic complications.

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Patient consent for publication Not applicable.

Ethics approval The study was conducted in accordance with the General Data Protection Regulation (GDPR) and other regulations, acts and guidelines. The Medical Research Ethics Committee (MREC) of the UMC Utrecht confirmed that the Dutch law on Medical Research Involving Human Subjects Act (WMO) does not apply to this study and that official approval of this study by the MREC was not required under Dutch legislation. For this study, only deidentified data were used, meaning data cannot be directly traced back to the patient.

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Supplement 1. Risk of bias assessment of the five evaluated bleeding models

	Domain: Participants	**Domain: Predictors**	**Domain: Outcome**	**Domain: Data analysis**	
Model	**Risk of bias introduced by selection of participants**	**Risk of bias introduced by predictors or their assessment**	**Risk of bias introduced by the outcome or its determination**	**Risk of bias introduced by the analysis**	**Overall judgement**
ATRIA	Unclear	Low	Unclear	High	High
HAS-BLED	Low	High	Unclear	High	High
ORBIT	Low	Low	Unclear	High	High
VTE-bleed	Low	Low	Unclear	High	High
AF-bleed	Low	Low	Unclear	High	High

For each selected model, two authors (ETR, SvD) independently assessed the risk of bias using the PROBAST checklist. (23) *All twenty signaling questions in four domains were answered, to derive at an overall judgment of the model's risk of bias (high, low, unclear).*

Supplement 2. ICPC and ATC codes used for patient selection and used for extraction of outcome and predictor information from the JPGN database

ICPC and ATC codes used for patient selection

ICPC code atrial fibrillation/flutter: K78

ICPC codes venous thromboembolism: K93, K94, K94.01, K94.02

ATC codes anticoagulants: B01AA, B01AE, B01AF, B01AB

ICPC codes malignancy:, A79, B72, B72.01, B72.02, B73, B74, B74.01, D74, D75, D76, D77, D77.01, D77.02, D77.03, D77.04, F74.01, H75.01, K72.01, L71.01, N74, R84, R85, S77, S77.02, S77.03 , S77.04, T71 , U75 , U76, U77, X75, X76, X76.01, X77, X77.01, X77.02, Y77, Y78, Y78.01, Y78.02, Y78.03

ICPC codes used for extraction of outcome information

ICPC codes bleeding events: A10, F75.01, F75.02, U80.01, S16.01, D16, K90.01, K90.02, R06, D14, D15, F75.01, N80.01, N80.02, N80.03, R24, U06, X06, X08, X08.01, X12, X13, W17

ICPC code atrial fibrillation/flutter: K78

ICPC codes venous thromboembolism: K93, K94, K94.01, K94.02

ICPC codes malignancy:, A79, B72, B72.01, B72.02, B73, B74, B74.01, D74, D75, D76, D77, D77.01, D77.02, D77.03, D77.04, F74.01, H75.01, K72.01, L71.01, N74, R84, R85, S77, S77.02, S77.03 , S77.04, T71 , U75 , U76, U77, X75, X76, X76.01, X77, X77.01, X77.02, Y77, Y78, Y78.01, Y78.02, Y78.03

ICPC codes and ATC codes used for extraction of predictor information

ICPC codes malignancy:, A79, B72, B72.01, B72.02, B73, B74, B74.01, D74, D75, D76, D77, D77.01, D77.02, D77.03, D77.04, F74.01, H75.01, K72.01, L71.01, N74, R84, R85, S77, S77.02, S77.03 , S77.04, T71 , U75 , U76, U77, X75, X76, X76.01, X77, X77.01, X77.02, Y77, Y78, Y78.01, Y78.02, Y78.03

ICPC code atrial fibrillation/flutter: K78

ICPC codes venous thromboembolism: K93, K94, K94.01, K94.02

ICPC codes (abnormal) alcohol use: P16, P15, P15.01, P15.02, P15.03, P15.05, P15.06

ICPC codes hypertension: K85, K86, K87

ICPC codes anaemia: B78, B78.01, B78.02, B78.03, B80, B81, B81.01, B81.02, B82

ICPC code reduced kidney function: U99.01

ICPC code liver disease: D97

ICPC codes stroke: K90, K90.00, K90.01, K90.02, K90.03

ICPC codes history of bleeding: A10, F75.01, F75.02, U80.01, S16.01, D16, K90.01, K90.02, R06, D14, D15, F75.01, N80.01, N80.02, N80.03, R24, U06, X06, X08, X08.01, X12, X13, W17

ATC code antiplatelet therapy: B01AC

Supplement 3. Overview of the predictor definition used in the current study for each of the bleeding risk models

	VTE-bleed(7)	**AF-bleed**(18)	**HAS-BLED**(8)	**ATRIA**(9)	**ORBIT**(11)
Age	Age ≥ 60 years	Age ≥ 75 years	Age > 65 years	Age ≥ 75 years	Age ≥ 75 years
Sex	Male with history of hypertension	Male with history of hypertension			
Hypertension			History of hypertension	History of hypertension	
History of bleeding	History of bleeding	History of bleeding	History of bleeding	History of bleeding	History of bleeding
Anemia	ICPC anemia OR Hemoglobin <8 mmol/l in men and <7.5 mmol/l in women around index date (+/- 30 days)	ICPC anemia OR Hemoglobin <8 mmol/l in men and <7.5 mmol/l in women around index date (+/- 30 days)		History of anemia	Hemoglobin <8 mmol/l in men and <7.5 mmol/l in women around index date (+/- 30 days)
Malignancy	New cancer diagnosis	New cancer diagnosis			
Abnormal renal/liver function	eGFR 30-60 ml/min around index date (+/- 30 days)	eGFR 30-60 ml/min around index date (+/- 30 days)	- Bilirubin > 2x upper limit & ASAT/ALAT/AF > 3x upper limit around index date (+/- 30 days) - Creatinine ≥ 200 umol/l around index date (+/- 30 days)	eGFR < 30 ml/min around index date (+/- 30 days)	eGFR < 60 ml/min around index date (+/- 30 days)
Drugs (antiplatelet/NSAID) /alcohol concomitantly			Treatment with antiplatelet around index date (+/- 30 days) / ICPC code alcohol (ab)use		
Stroke			History of stroke		
Labile international normalized ratio			INR <1 or > 4 around index date (+/- 30 days)		
Antiplatelet treatment					Treatment with antiplatelet around index date (+/- 30 days)

Supplement 4. Elaboration model selection

The AIC of the models were 2721.4 (first model, only including age plus sex), 2719.1 (second model with age, sex, hypertension, history of bleeding, renal insufficiency, anaemia and use of antiplatelet drugs), and 2721.0 (third model with age, sex, history of hypertension, history of bleeding, renal insufficiency, anaemia and use of antiplatelet drugs plus cancer type). The second model performed significantly better than the first model based on LRT (χ^2= 12.3, df=5, p<0.031). The third model did not perform significantly better than the second model (χ^2= 0.2, df=1, p≈0.68). Based on both AIC and LRT, the second model had the best fit and was internally validated.