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CLINICAL RESEARCH
Thrombosis and antithrombotic treatment

Recurrent venous thromboembolism and bleeding with extended anticoagulation: the VTE-PREDICT risk score

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Abstract

Aims Deciding to stop or continue anticoagulation for venous thromboembolism (VTE) after initial treatment is challenging, as individual risks of recurrence and bleeding are heterogeneous. The present study aimed to develop and externally validate models for predicting 5-year risks of recurrence and bleeding in patients with VTE without cancer who completed at least 3 months of initial treatment, which can be used to estimate individual absolute benefits and harms of extended anticoagulation.

Methods and results Competing risk-adjusted models were derived to predict recurrent VTE and clinically relevant bleeding (non-major and major) using 14 readily available patient characteristics. The models were derived from combined individual patient data from the Bleeding Risk Study, Hokusai-VTE, PREFER-VTE, RE-MEDY, and RE-SONATE ($n = 15{,}141$, 220 recurrences, 189 bleeding events). External validity was assessed in the Danish VTE cohort, EINSTEIN-CHOICE, GARFIELD-VTE, MEGA, and Tromsø studies ($n = 59\,257$, 2283 recurrences, 3335 bleeding events). Absolute treatment effects were estimated by combining the models with hazard ratios from trials and meta-analyses. External validation in different settings showed agreement between predicted and observed risks up to 5 years, with C-statistics ranging from 0.48–0.71 (recurrence) and 0.61–0.68 (bleeding). In the Danish VTE cohort, 5-year risks ranged from 4% to 19% for recurrent VTE and 1% –19% for bleeding.

Conclusion The VTE-PREDICT risk score can be applied to estimate the effect of extended anticoagulant treatment for individual patients with VTE and to support shared decision-making.

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Structured Graphical Abstract

Key Question

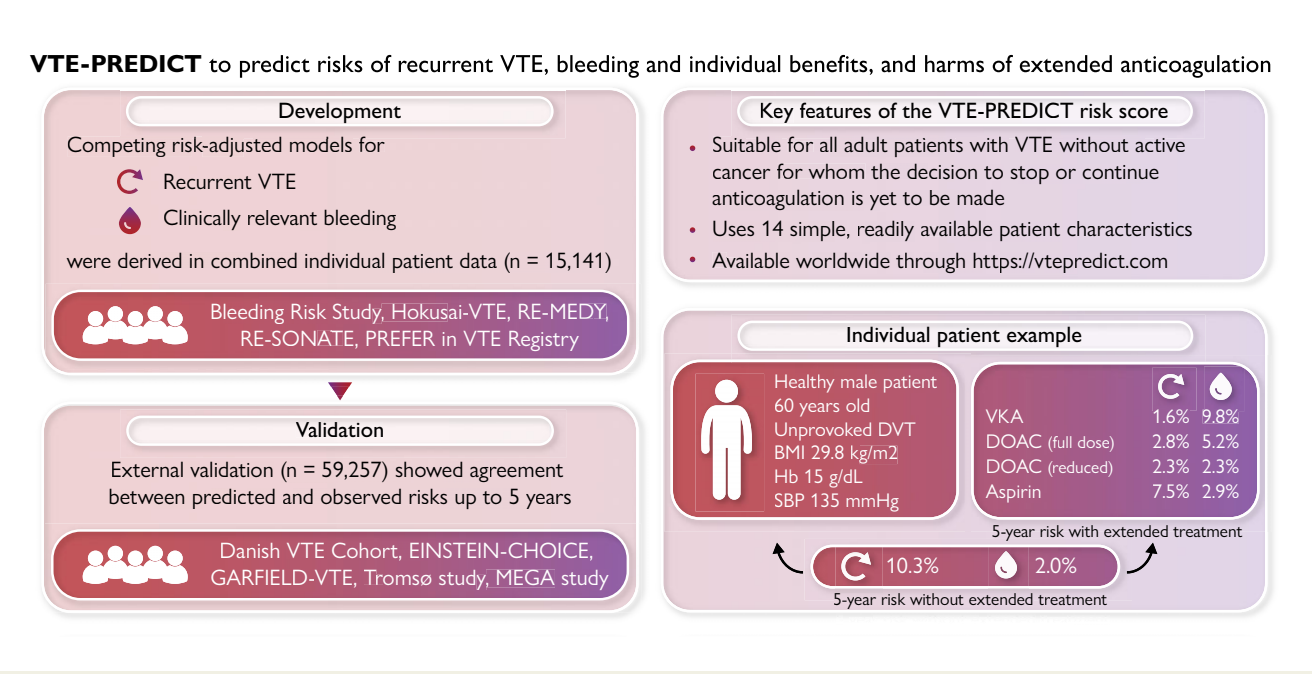
How can we predict risks of recurrence and clinically relevant bleeding in individuals with venous thromboembolism (VTE) without active cancer after initial anticoagulant treatment? How can these models be applied to estimate individual absolute benefits and harms of extended anticoagulation?

Key Finding

The VTE-PREDICT risk score, assessed in data from 15,141 VTE patients, estimated absolute risks of recurrence and clinically relevant bleeding with and without extended anticoagulation. External validation in different clinical settings (n=59,257) showed good calibration up to five years.

Take Home Message

The VTE-PREDICT risk score can be applied to estimate benefits and harms of extended anticoagulant treatment for individual patients with VTE without active cancer. The interactive calculator, available through https://vtepredict.com, facilitates its use and supports shared decision-making in clinical practice.



BMI, body mass index; DOAC, direct oral anticoagulant; DVT, deep venous thrombosis; Hb, haemoglobin; SBP, systolic blood pressure; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Keywords Anticoagulants • Haemorrhage • Prediction model • Recurrence • Risk • Venous thromboembolism

Introduction

The main challenge for treating patients with venous thromboembolism (VTE), comprising pulmonary embolism (PE), and deep venous thrombosis (DVT), is deciding on the duration of anticoagulant therapy. The primary treatment for VTE consists of 3 months of anticoagulation in all patients.[1–3] Primary treatment duration of >3 months but with a limited duration (*e.g.* 9 or 12 months) is not recommended as this simply postpones recurrence until treatment is discontinued (the so-called 'catch-up phenomenon').[4] Therefore, the critical decision is choosing between a short treatment duration of 3 months and an extended treatment without an end-date. Guidelines recommend basing this decision on weighing the risks of recurrent VTE and bleeding. While anticoagulant treatment is effective in reducing recurrence risk, it is associated with a 1%–2% annual risk of major bleeding.[3] Currently, the risk of recurrence is estimated by categorizing patients as having unprovoked VTE or VTE provoked by minor or major transient risk factors, or persistent risk factors.[1–3] The risk of recurrence is low (3% per year or less), if provoked by major transient risk factors (e.g. major surgery), and treatment discontinuation is

recommended after 3 months.[1–3] In the absence of major transient provoking factors, the risk of recurrence is considerably higher.[1–3] For these patients, clinical equipoise exists regarding (dis)continuation of anticoagulant treatment if risk of bleeding is considered low (1.6% per year or less).[2]

Deciding on the anticoagulant treatment duration for individual patients is challenging for multiple reasons. First, the risks of recurrence and bleeding differ between patients, even within the aforementioned groups. For example, there may be patients at high risk of bleeding for whom the benefit of extended treatment still outweighs the bleeding risks because VTE recurrence risk is very high. Second, guidelines do not provide recommendations as to how the risks of recurrent VTE and bleeding should be assessed and weighed. The risks of recurrent VTE and bleeding in the individual patient must be estimated from the results in groups of patients.[1–3] Treatment decisions are currently based primarily on the presence of provoking factors as a way to categorize recurrence risk rather than on the absolute risk of bleeding. However, bleeding may have an important negative impact on quality of life and cause mortality as well.

To improve clinical decision-making, well-performing models are needed to estimate the absolute risks of VTE recurrence and bleeding on an individual patient basis. Previous studies have shown that medical decision-making can be personalized based on estimates of individualized absolute treatment effects. [5–7] Such estimates can be obtained by combining predicted individual absolute risks with relative treatment effects from trials. The present project extends this methodology to a new patient domain. Personalized risk information is required to facilitate patient involvement and shared decision-making, which will increase patient satisfaction with care and treatment adherence while reducing costs.[8] This may improve the long-term treatment of VTE for individual patients and reduce the worldwide burden of VTE-related morbidity and mortality.

The objective of the present study was to develop and externally validate models for predicting (i) recurrent VTE and (ii) major bleeding and clinically relevant non-major bleeding (CRNMB) within 5 years in patients with VTE without active cancer who completed at least a 3-month primary anticoagulant treatment course. These models may be applied to estimate the absolute benefits and harms of extended anticoagulation for individual patients with VTE in clinical practice.

Methods

Study population

Data sets (trials as well as cohort studies) containing data from adult patients with VTE (i.e. lower extremity DVT and/or PE) without active cancer (i.e. cancer diagnosed or receiving treatment within 6 months prior to the index event or metastatic cancer, excluding non-melanoma skin cancer) who completed primary anticoagulant treatment of at least 3 months with direct oral anticoagulants (DOACs), vitamin K antagonists (VKAs), heparin, or low molecular weight heparin (LMWH), were eligible for inclusion. A definitive selection of data sets was decided on by all authors based on data availability. Data sets were selected for either model development or validation based on reasons related to data availability (i.e. whether data could be combined on the same platform for analysis) and methodologic reasons (e.g. wide range of predictor values, representative population, and possibility to impute systematically missing predictors for model development; different clinical settings for external validation), This is described in more detail in the Supplementary material online, *Expanded Methods*.

Studies for model derivation

Combined individual patient data from three randomized trials and two cohort studies were used for model derivation. The Bleeding Risk Study was a multicentre prospective cohort study that aimed to develop a new prediction tool for major bleeding.[9] Hokusai-VTE was a double-blind, randomized, controlled trial with the aim of assessing the efficacy and safety of edoxaban for treating VTE.[10] PREFER in VTE was a prospective, international observational registry focusing on primary and secondary care.[11] RE-MEDY and RE-SONATE were double-blind, randomized, controlled trials on the efficacy and safety of dabigatran for the extended treatment of VTE.[12]

Studies used for model validation

The models were externally validated in four cohorts and one trial. The population-based Danish VTE cohort was defined from the Danish National Patient Registry, which contains all non-psychiatric discharge diagnoses codes from hospital admissions in Denmark since 1977 and from the emergency department and outpatient clinic visits since 1995.[13] This cohort was linked on an individual level to the Danish Civil Registration System and to the Danish National Prescription Registry. EINSTEIN-CHOICE was a double-blind, randomized, controlled trial comparing two doses of rivaroxaban and aspirin.[14] GARFIELD-VTE was a prospective, international observational registry for long-term follow-up of VTE.[15] The Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis (MEGA) follow-up studies was a population-based prospective cohort study.[16] Finally, the Tromsø population-based cohort included all inhabitants of the Tromsø municipality in Norway, and all VTEs occurring in this cohort were included.

All studies complied with the Declaration of Helsinki. Ethics approval was obtained by the institutional review boards of the participating centres. All patients provided written, informed consent. A more extensive description of the eligibility criteria for the individual studies is provided in Supplementary material online, *Table S1*. Detailed descriptions of the studies have been published elsewhere.[9–13,15–17]

Outcome definitions

Primary outcomes were time-to-first-recurrent VTE (recurrence model) and time-to-first-bleeding event (bleeding model). Recurrent VTE was defined as objectively confirmed, fatal or non-fatal recurrent DVT or PE, or a death to which PE contributed or could not be ruled out. To incorporate all clinically relevant bleeding events, bleeding was defined as a composite of major bleeding and CRNMB according to the International Society on Thrombosis and Haemostasis.[18,19] The definitions used in the individual studies are specified in the Supplementary material online, *Table S2*.

The start of follow-up for the present study was defined as the end of primary treatment (see Supplementary material online, *Figure S1*). Hence, for studies that enrolled patients after a primary treatment of 3 months or longer, the original study start date was retained. For studies that enrolled patients at an earlier stage, follow-up for the present analysis started 3 months after the start of primary treatment in patients who continued anticoagulation for >12 months or on the day of discontinuation of treatment for patients who discontinued primary anticoagulant treatment between 3 and 12 months. Patients were followed until an event of interest (either VTE recurrence or bleeding, depending on the model) or a competing event occurred (i.e. mortality not related to recurrence or bleeding, respectively) or until censoring. Patients were censored after 5 years, when follow-up ended, or when treatment status changed before the occurrence of VTE or bleeding.

Candidate predictors

A list of candidate predictors was constructed prior to model development based on the most recent systematic review of risk scores for recurrence and bleeding after initial treatment for VTE (see Supplementary material online, *Table S3*).[20] Predictors were included in the models if they were (i) included in at least two risk scores, (ii) available in at least two of the

data sets used for model development, and (iii) easily available in clinical practice. A list of predictors and their definitions in the studies used for model development and validation is provided in the Supplementary material online, *Tables S4* and *S5*.

Statistical analysis

Single-level multiple imputations (20 imputed data sets) using predictive mean matching was used for sporadically missing variables in the model derivation data set (for computational reasons). Subsequently, multilevel multiple imputations with predictive mean matching was used to handle systematically missing variables, while allowing for between-study heterogeneity using a random intercept per study. Single imputation using predictive mean matching was used for external validation in the EINSTEIN-CHOICE, MEGA, and Tromsø data sets. For the external validation in the Danish VTE cohort and in the GARFIELD-VTE study, mean imputation was used for sporadically missing values. Systematically missing categorical variables in external validation data sets were assumed to be normal or absent; for continuous variables, the mean of the derivation population was imputed.

Model development

The prognostic model consists of two complementary Fine and Gray competing risk-adjusted models. The baseline hazard was estimated and stratified for each study to account for differences in baseline risks. Transformations on continuous predictors (age, body mass index, haemoglobin, and systolic blood pressure) were applied if this improved model fit was based on Akaike's information criterion. The prognostic models were derived to predict risks within 1 year (bleeding model) or 6 months (recurrent VTE model), depending on the distribution of follow-up time in the individual studies. The model's baseline hazards were recalibrated for the prediction of 5-year risks using the expected/observed ratio as calculated in the MEGA study for the prediction of recurrent VTE and the Danish VTE cohort for the prediction of bleeding events. Data for patients both with and without extended treatment were used for model development and validation. To account for the effects of anticoagulation, offset terms were employed to limit the effects of extended treatment with different DOACs, VKAs, or LMWH to the unbiased causal effects reported in trials and meta-analyses (see Supplementary material online, *Table S6*). Assuming no interactions between treatment effect and predictors on a relative scale, the same relative treatment effect was used for all patients.

Model validation

The predictive performance of the newly derived models in terms of goodness-of-fit and discrimination was assessed separately in each study used for model development (internal validation), as well as in multiple external data sets (external validation). To assess the potential impact of overestimation of model performance in internal validation, in a separate analysis, bootstrapping (1000 samples) was used to obtain C-statistics in the total population for both models. Internal–external cross-validation (IECV) was used to validate the results of internal validation. Similarly, offset terms were used to adjust for the effect of extended anticoagulation. Models were recalibrated to account for differences in the baseline hazard before assessing model performance, as studies reflect different clinical situations. In a sensitivity analysis, the updated models (recalibrated for clinical practice using 1-year and 5-year baseline hazards derived from MEGA and the Danish VTE cohort) were externally validated in the other external validation data sets, without additional recalibration. Furthermore, the performance of the models with updated baseline hazards were also assessed in the combined model development population. In the external validation studies, predictive performance was assessed for up to 5 years of follow-up, depending on the study follow-up duration. Discrimination was examined using Harrell's C-statistics. For goodness-of-fit, predicted risks of recurrent VTE and bleeding were plotted against observed risks in the same time frame (calibration plots), and expected/observed ratios and calibration slopes with 95% confidence intervals (CIs) were estimated.[21]

Comparison with existing risk scores

The performance of the newly derived models was compared with the performance of published risk scores for VTE recurrence and bleeding (see Supplementary material online, *Tables S7* and *S8*) identified from a previous systematic review.[20]

Individual net benefit of extended anticoagulant treatment

To estimate absolute risks with treatment, the models can be combined with hazard ratios (HRs) for recurrent VTE and bleeding from trials and cohorts for different extended treatment strategies (see Supplementary material online, *Table S6*). The individual treatment effect within 5 years was calculated by subtracting absolute risks with extended anticoagulation from the untreated risk using data from the Danish VTE cohort. Subsequently, the net benefit was calculated assuming equal severity of VTE recurrence and bleeding. For all figures in the present paper, pooled estimates for the effect of extended treatment with full dose DOAC and reduced dose DOAC are used (see Supplementary material online, *Table S6*).

A detailed explanation of the methodology can be found in the Supplementary material online, *Expanded Methods*. An overview of relevant model assumptions is provided in Supplementary material online, *Table S9*. All analyses were conducted using R statistical software versions 3.5.2 (model derivation), 4.0.3 (external validation in the Tromsø study and the MEGA study), and version 3.6.3 (external validation in EINSTEIN-CHOICE), and SAS 9.4 (SAS Institute Inc., Cary, NC, USA) for data management in the Danish VTE cohort.

Role of the funding source

This project was funded by ZonMw, the Netherlands Organization for Health Research and Development, as part of their programme 'Goed Gebruik Geneesmiddelen', on the more effective, more efficient, and safer use of medication in day-to-day healthcare, Project Number 848018012. ZonMw had no role in the collection, analysis, and interpretation of data, in the writing of the report, or in the decision to submit the manuscript for publication.

Results

Patient population

Baseline characteristics of the study population are shown in *Table 1*. Flowcharts of patients included in each of the individual studies, follow-up duration, and number of events per study are shown in Supplementary material online, *Figure S2*. Adequate convergence and plausible imputed values were achieved with multiple imputation. In total, 15 141 patients (mean ± standard deviation age 57.1 ± 15.8 years, 41% female, 69% with unprovoked VTE, and 49% receiving extended anticoagulation) were included in the combined data set for model derivation. In this population, 220 recurrences and 169 competing non-VTE-related deaths occurred during the median follow-up of 191 days (interquartile range: [IQR] 44–446 days). Furthermore, during a median follow-up of 189 days (IQR: 42–372 days), 737 bleeding events and 145 competing non-bleeding-related deaths occurred.

Model derivation

Coefficients and sub-distribution HRs of the newly developed VTE-PREDICT risk score are shown in *Table 2*. The underlying formulas are presented in Supplementary material online, *Table S10*. In both models, the strongest predictor was a history of cancer. Calibration plots for each study used for model development as well as for the total

Table 1 Baseline characteristics of the study population for model derivation before imputation stratified by study and overall after imputation

	Bleeding Risk Study		Hokusai-VTE		PREFER in VTE		RE-MEDY		RE-SONATE		Total (after imputation)
	n = 2506	Missing	*n* = 6593	Missing	*n* = 2234	Missing	*n* = 2678	Missing	*n* = 1130	Missing	*n* = 15141
Female sex	904 (36)	0 (0)	2706 (41)	0 (0)	1049 (47)	0 (0)	1040 (39)	0 (0)	494 (44)	0 (0)	6193 (41)
Age (years)	60.2 (14.7)	0 (0)	56.0 (15.8)	0 (0)	60.9 (17.1)	0 (0)	54.5 (15.1)	2 (0)	55.5 (15.4)	0 (0)	57.1 (15.8)
Race		5 (0)		8 (0)	NA	2234 (100)		0 (0)		9 (1)	
Asian	170 (7)		200 (3)				53 (2)		19 (2)		1821 (12)
Black	18 (1)		1464 (22)				218 (8)		86 (8)		660 (4)
Other	2313 (92)		5021 (76)				2407 (90)		1016 (90)		12660 (84)
Medical history											
Prior stroke	81 (3)	0 (0)	193 (3)	0 (0)	85 (4)	2 (0)	66 (3)	0 (0)	19 (2)	0 (0)	444 (3)
History of bleeding	83 (3)	0 (0)	566 (9)	0 (0)	117 (5)	0 (0)	36 (1)	0 (0)	32 (3)	0 (0)	834 (6)
History of VTE	913 (36)	0 (0)	1291 (20)	0 (0)	593 (27)	1 (0)	1430 (53)	0 (0)	167 (15)	0 (0)	4394 (29)
History of cancer	NA	2506 (100)	405 (6)	0 (0)	183 (8)	0 (0)	NA	2678 (100)	NA	1130 (100)	1060 (7)
Atherosclerotic cardiovascular disease	126 (5)	0 (0)	558 (9)	0 (0)	217 (10)	5 (0)	229 (9)	0 (0)	80 (7)	0 (0)	1210 (8)
Hypertension	946 (38)	0 (0)	2554 (39)	0 (0)	947 (42)	2 (0)	1024 (38)	0 (0)	435 (39)	0 (0)	5907 (39)
Diabetes mellitus	273 (11)	0 (0)	665 (10)	2 (0)	221 (10)	1 (0)	234 (9)	0 (0)	89 (8)	0 (0)	1482 (10)
Post-thrombotic syndrome	36 (9)	2120 (85)	45 (1)	1270 (19)	NA	2234 (100)	77 (3)	0 (0)	16 (1)	0 (0)	655 (4)
Liver failure	NA	2506 (100)	0 (0)	2 (0)	26 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
Thrombophilia	602 (24)	0 (0)	371 (6)	9 (0)	138 (6)	0 (0)	411 (15)	0 (0)	84 (7)	0 (0)	1606 (11)
Chronic lung disease	NA	2506 (100)	741 (11)	0 (0)	185 (8)	2 (0)	231 (9)	0 (0)	93 (8)	0 (0)	1427 (9)
Index VTE event											
Distal DVT only	11 (1)	1090 (44)	0 (0)	52 (1)	520 (11)	0 (0)	14 (1)	15 (1)	2 (0)	7 (1)	NA
PE with or without DVT	1204 (48)	0 (0)	2431 (37)	0 (0)	1000 (45)	0 (0)	914 (34)	15 (1)	374 (33)	0 (0)	5930 (39)
Provoked by pregnancy or puerperium	NA	2506 (100)	17 (0)	9 (0)	NA	2234 (100)	NA	2678 (100)	NA	1130 (100)	NA
Provoked by oestrogen therapy	NA	2506 (100)	479 (7)	9 (0)	157 (7)	0 (0)	NA	2678 (100)	NA	1130 (100)	976 (6)
Provoked by surgery, trauma or immobilization	146 (6)	0 (0)	1245 (19)	9 (0)	624 (28)	3 (0)	NA	2678 (100)	NA	1130 (100)	3963 (26)
Physical examination											
BMI (kg/m^2)	31 (7)	7 (0)	28.7 (5.7)	52 (1)	NA	2234 (100)	29.0 (5.5)	6 (0)	28.5 (5.2)	0 (0)	29.3 (5.9)
Systolic blood pressure (mmHg)	NA	2506 (100)	127.7 (14.3)	2 (0)	133.4 (17.6)	118 (5)	129.0 (14.9)	9 (0)	132.0 (15.6)	2 (0)	130.0 (15.6)

Continued

Table 1 *Continued*

	Bleeding Risk Study		Hokusai-VTE		PREFER in VTE		RE-MEDY		RE-SONATE		Total (after imputation)
	n = 2506	Missing	*n* = 6593	Missing	*n* = 2234	Missing	*n* = 2678	Missing	*n* = 1130	Missing	*n* = 15141
Laboratory values											
Haemoglobin (g/dL)	14.1 (1.6)	36 (1)	13.9 (1.6)	8 (0)	NA	2234 (100)	14.3 (1.4)	19 (1)	14.2 (1.5)	10 (1)	14.0 (1.6)
Platelet count (*10^9/L)	NA	2506 (100)	228.2 (62)	36 (01)	NA	2234 (100)	242.4 (62.2)	30 (1)	238.0 (61.9)	12 (1)	241.7 (67.0)
Creatinine clearance (mmol/L)	84.2 (23.7)	174 (7)	84.2 (23.7)	3 (0)	135.7 (27.1)	2109 (94)	84.2 (19.2)	15 (1)	82.0 (20.2)	11 (1)	89.3 (27.1)
D-dimer during anticoagulation	615.3 (994.7)	1735 (69)	447.7 (524.7)	337 (5)	NA	2234 (100)	NA	2678 (100)	NA	1130 (100)	NA
D-dimer after cessation of anticoagulation	NA	2506 (100)	NA	6593 (100)	NA	2234 (100)	NA	2678 (100)	NA	1130 (100)	NA
Concomitant treatment											
Antiplatelet therapy	84 (24)	0 (0)	1341 (20)	0 (0)	255 (12)	13 (1)	191 (7)	57 (2)	94 (8)	0 (0)	2032 (13)
NSAIDs	92 (4)	0 (0)	1708 (26)	0 (0)	NA	2234 (100)	477 (18)	57 (2)	125 (11)	0 (0)	2646 (18)
Extended treatment											
None or placebo	0 (0)	0 (0)	6133 (93)	0 (0)	1068 (48)	0 (0)	0 (0)	0 (0)	565 (50)	0 (0)	7766 (51)
VKA	2271 (91)	0 (0)	234 (4)	0 (0)	828 (37)	0 (0)	1336 (50)	0 (0)	0 (0)	0 (0)	4669 (31)
DOAC	235 (9)	0 (0)	226 (3)	0 (0)	259 (12)	0 (0)	1342 (50)	0 (0)	565 (50)	0 (0)	2627 (17)
LMWH	0 (0)	0 (0)	0 (0)	0 (0)	79 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	79 (1)

	Danish VTE cohort		EINSTEIN-CHOICE		GARFIELD-VTE		MEGA		Tromsø	
	n = 43367	Missing	*n* = 3276	Missing	*n* = 8181	Missing	*n* = 3980	Missing	*n* = 453	missing
Female sex	21643 (50)	0 (0)	1456 (44)	0 (0)	3983 (49)	0 (0)	2184 (55)	0 (0)	236 (52)	0 (0)
Age (years)	63.4 (17.2)	0 (0)	58.3 (14.7)	6 (0)	57.4 (17.1)	0 (0)	47.9 (12.9)	0 (0)	67.2	0 (0)
Race	NA	43367 (100)		0 (0)		631 (8)		0 (0)	NA	453 (100)
– Caucasian			2286 (70)		5669 (75)		3735 (94)			
– Asian			458 (14)		1155 (15)		45 (1)			
– Black			120 (4)		351 (5)		49 (1)			
– Other			412 (13)		375 (5)		141 (4)			
Medical history										
Prior stroke	3658 (8)	0 (0)	43 (1)	0 (0)	20 (0)	0 (0)	80 (2)	292 (7)	35 (8)	0 (0)
History of bleeding	5159 (12)	0 (0)	54 (2)	0 (0)	451 (6)	0 (0)	NA	3980 (100)	25 (6)	0 (0)
History of VTE	6098 (14)	0 (0)	565 (17)	0 (0)	1345 (16)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
History of cancer	4238 (10)	0 (0)	166 (5)	0 (0)	524 (6)	0 (0)	103 (3)	0 (0)	25 (6)	0 (0)

Continued

Table 1 *Continued*

	Danish VTE cohort		EINSTEIN-CHOICE		GARFIELD-VTE		MEGA		Tromsø	
	n = 43367	Missing	*n* = 3276	Missing	*n* = 8181	Missing	*n* = 3980	Missing	*n* = 453	missing
Atherosclerotic cardiovascular disease	7570 (18)	0 (0)	158 (5)	0 (0)	NA	8181 (100)	180 (5)	261 (9)	76 (17)	0 (0)
Hypertension	10227 (24)	0 (0)	1311 (40)	0 (0)	NA	8181 (100)	NA	3980 (100)	99 (22)	0 (0)
Diabetes mellitus	3605 (8)	0 (0)	326 (10)	0 (0)	NA	8181 (100)	127 (3)	292 (7)	19 (4)	0 (0)
Post-thrombotic syndrome	310 (1)	0 (0)	18 (1)	0 (0)	NA	8181 (100)	1612 (66)	1538 (39)	NA	453 (100)
Thrombophilia	640 (2)	0 (0)	210 (6)	0 (0)	264 (3)	0 (0)	133 (3)	0 (0)	61 (13)	0 (0)
Chronic lung disease	15449 (36)	0 (0)	146 (4)	0 (0)	NA	8181 (100)	214 (6)	261 (9)	10 (2)	0 (0)
Index VTE event										
Distal DVT only	0 (0)	0 (0)	0 (0)	0 (0)	2028 (35)	8181 (100)	934 (23)	0 (0)	91 (20)	0 (0)
PE with or without DVT	18369 (42)	0 (0)	1626 (50)	0 (0)	3249 (40)	0 (0)	1640 (41)	0 (0)	189 (42)	0 (0)
Provoked by pregnancy or puerperium	326 (1)	0 (0)	21 (1)	0 (0)	157 (2)	0 (0)	NA	3980 (100)	NA	453 (100)
Provoked by oestrogen therapy	4560 (11)	0 (0)	171 (5)	0 (0)	598 (7)	0 (0)	1237 (31)	48 (1)	33 (7)	0 (0)
Provoked by surgery, trauma or immobilization	7676 (18)	0 (0)	630 (19)	0 (0)	1769 (22)	0 (0)	1581 (40)	76 (2)	64 (14)	0 (0)
Physical examination										
BMI (kg/m^2)	NA	43367 (100)	28.8 (5.7)	2 (0)	28.7 (5.9)	666 (10)	26.9 (4.8)	342 (9)	27.6 (4.8)	2 (0)
Systolic blood pressure (mmHg)	NA	43367 (100)	NA	3276 (100)	NA	6741 (100)	NA	3980 (100)	145 (25.2)	76 (17)
Laboratory values										
Haemoglobin (g/dL)	13.4 (1.8)	31653 (73)	14.2 (1.6)	2 (0)	13.2 (1.9)	1035 (15)	13.9 (1.4)	2084 (53)	12.8 (2.0)	25 (6)
Platelet count (×10^9/L)	NA	43367 (100)	241 (64.8)	4 (0)	244 (87.8)	991 (15)	NA	3980 (100)	245 (79)	53 (12)
Creatinine clearance (mmol/L)	NA	43367 (100)	80.4 (20.3)	0 (0)	1.1 (0.8)	1068 (16)	77.5 (37)	2056 (52)	81.7 (31.9)	50 (11)
D-dimer during anticoagulation	NA	43367 (100)	NA	3276 (100)	NA	8181 (100)	NA	3980 (100)	NA	453 (100)
D-dimer after cessation of anticoagulation	NA	43367 (100)	NA	3276 (100)	NA	8181 (100)	494.9 (983.0)	1778 (44.7)	NA	453 (100)
Concomitant treatment										
Antiplatelet therapy	14714 (34)	0 (0)	1449 (44)	0 (0)	743 (9)	0 (0)	114 (3)	362 (9)	47 (10)	0 (0)
NSAIDs	2444 (6)	0 (0)	177 (5)	0 (0)	330 (4)	0 (0)	NA	3980 (100)	8 (2)	0 (0)
Extended treatment										
None or placebo	32590 (75)	0 (0)	1095 (33)	0 (0)	2874 (35)	0 (0)	3474 (87)	0 (0)	297 (66)	0 (0)
VKA	9917 (23)	0 (0)	0 (0)	0 (0)	1926 (24)	0 (0)	504 (13)	0 (0)	147 (42)	0 (0)
DOAC	613 (1)	0 (0)	2181 (67)	0 (0)	2914 (36)	0 (0)	0 (0)	0 (0)	2 (0)	0 (0)
LMWH	247 (1)	0 (0)	0 (0)	0 (0)	467 (6)	0 (0)	2 (0)	0 (0)	7 (2)	

Data are shown as n (%) or mean (SD) unless otherwise specified.
BMI, body mass index; DVT, deep venous thrombosis; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; PE, pulmonary embolism; NSAIDs, non-steroidal anti-inflammatory drugs; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 2 Prediction models for recurrent VTE and bleeding

	Predictor	Recurrent VTE		Bleeding	
		sHR (95% CI)	χ2 statistic	sHR (95% CI)	χ2 statistic
Demographics and physical examination	Age (per decade)	1.01 (0.97–1.06)	0.20	1.05 (1.03–1.08)	7.95
	Female sex	0.86 (0.75–0.98)	2.38	1.14 (1.05–1.24)	4.87
	BMI (kg/m^2; per 1 unit increase)	1.00 (0.99–1.02)	0.21		
	Systolic blood pressure (per 10 mmHg)			1.07 (1.03–1.10)	14.36
Index event	PE	1.02 (0.89–1.18)	0.05	1.07 (0.98–1.17)	1.47
	Provoked by surgery, trauma or immobilization	0.81 (0.68–0.98)	3.16		
	Provoked by oestrogen therapy	0.68 (0.47–1.00)	2.53		
Medical history	History of cancer	1.53 (1.14–2.06)	6.44	2.48 (2.00–3.07)	128.44
	History of VTE	1.13 (0.97–1.32)	1.10		
	History of bleeding			1.26 (1.11–1.44)	4.57
	Stroke			1.26 (1.08–1.46)	3.72
Lab values	Hb (g/dL; per 1 unit increase)			0.95 (0.93–0.97)	9.69
Co-medication	NSAIDs			1.22 (1.08–1.38)	5.92

BMI, body mass index; CI, confidence interval; Hb, haemoglobin; NSAIDs, non-steroidal anti-inflammatory drugs; PE, pulmonary embolism; sHR, sub distribution hazard ratio; VTE, venous thromboembolism.

population are shown in Supplementary material online, *Figures S3* and *S4*. Internal C-statistics for the recurrent VTE model ranged from 0.51 to 0.79; overall 0.68 (95% CI: 0.65–0.72) (see Supplementary material online, *Figures S3* and *S4*). With bootstrapping, this was 0.68 (95% CI: 0.62 to 0.73). The C-statistic of 0.51 was observed in the RE-MEDY study, in which all patients were on extended anticoagulation and the range of predicted risks was limited. Internal C-statistics for the bleeding model ranged from 0.65 to 0.73; overall, both in the main analysis and with bootstrapping, they were 0.69 (95% CI: 0.67–0.72). Pooled coefficients derived from IECV are similar to coefficients derived in the total population for both models, although CIs with IECV derived using IECV were smaller (see Supplementary material online, *Table S11*). Similarly, C-statistics found in IECV were in the same range as in the total population, although the pooled estimate for the recurrent VTE model was somewhat lower (see Supplementary material online, *Table S11*).

External validation

Calibration plots for both models after recalibration in each of the external validation data sets (total $n = 59\,257$; 2283 VTE recurrences, 3335 bleeding events) are shown in *Figures 1* and *2*. The C-statistics for the recurrent VTE model ranged from 0.48 (0.45–0.52) to 0.71 (0.66–0.77). Calibration plots show agreement between predicted and observed risks for up to five years of follow-up. In GARFIELD-VTE, predicted risks did not correspond to observed risks. For the bleeding risk score, C-statistics ranged from 0.61 (0.54–0.67) to 0.68 (0.65–0.70). For both models, predicted risks were higher than observed risks among patients with higher predicted risks in the Danish VTE cohort, GARFIELD-VTE, and the Tromsø study. The calibration plot for the bleeding risk score in the Tromsø study reflects a very low number of outcome events. When limited to patients without or with extended anticoagulant treatment for recurrent VTE and bleeding, respectively, predicted risks were higher and more homogeneous. Other calibration measures are shown in Supplementary material online, *Table S12*. Performance of the recalibrated models containing baseline hazards to be used in clinical practice is shown in Supplementary material online, *Figures S5* and *S6*, and Supplementary material online, *Table S13*. In cohort studies, the risks of recurrent VTE are somewhat underestimated, whereas in mainly trial populations (i.e. EINSTEIN-CHOICE and the combined model development population), the risks are somewhat overestimated. The recalibrated bleeding model underestimates risks in a trial population.

Comparison with existing risk scores

In the total population, after adjusting for the effect of extended anticoagulation, the discrimination of the VTE-PREDICT risk scores is comparable to the other existing risk scores for recurrent VTE and bleeding (see Supplementary material online, *Figure S7*). When limited to a subset of patients without extended treatment (recurrent VTE) and to patients with extended treatment (bleeding), point estimates of the pooled C-statistics for VTE-PREDICT were highest [0.61 (95% CI: 0.58–0.63) for recurrent VTE; 0.63 (95% CI: 0.61–0.64) for bleeding].

Individual predicted absolute benefit and harm

Absolute risks of recurrent VTE and bleeding within 5 years ranged from 3.8% to 19.1% for recurrent VTE, and 1.3% to 19.0% for bleeding (see Supplementary material online, *Figure S8*). In the Danish VTE cohort, with extended treatment with full dose DOAC, the absolute

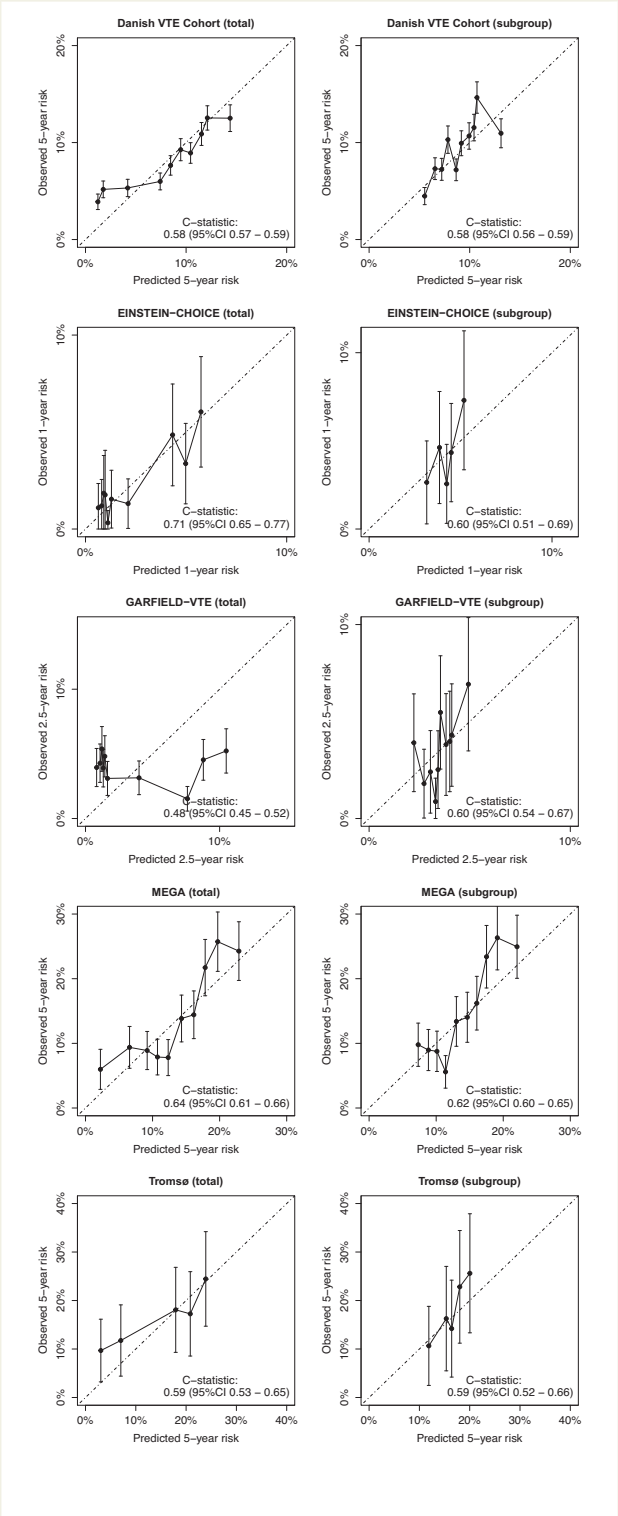


Figure 1 Calibration plots for the VTE-PREDICT model for recurrent venous thromboembolism in external data sets. The study population is divided into 5 or 10 equal groups (depending on population size) based on the predicted risk of recurrent venous thromboembolism according to the VTE-PREDICT risk score and plotted against observed incidences in the same time frame. The longest available follow-up duration is used

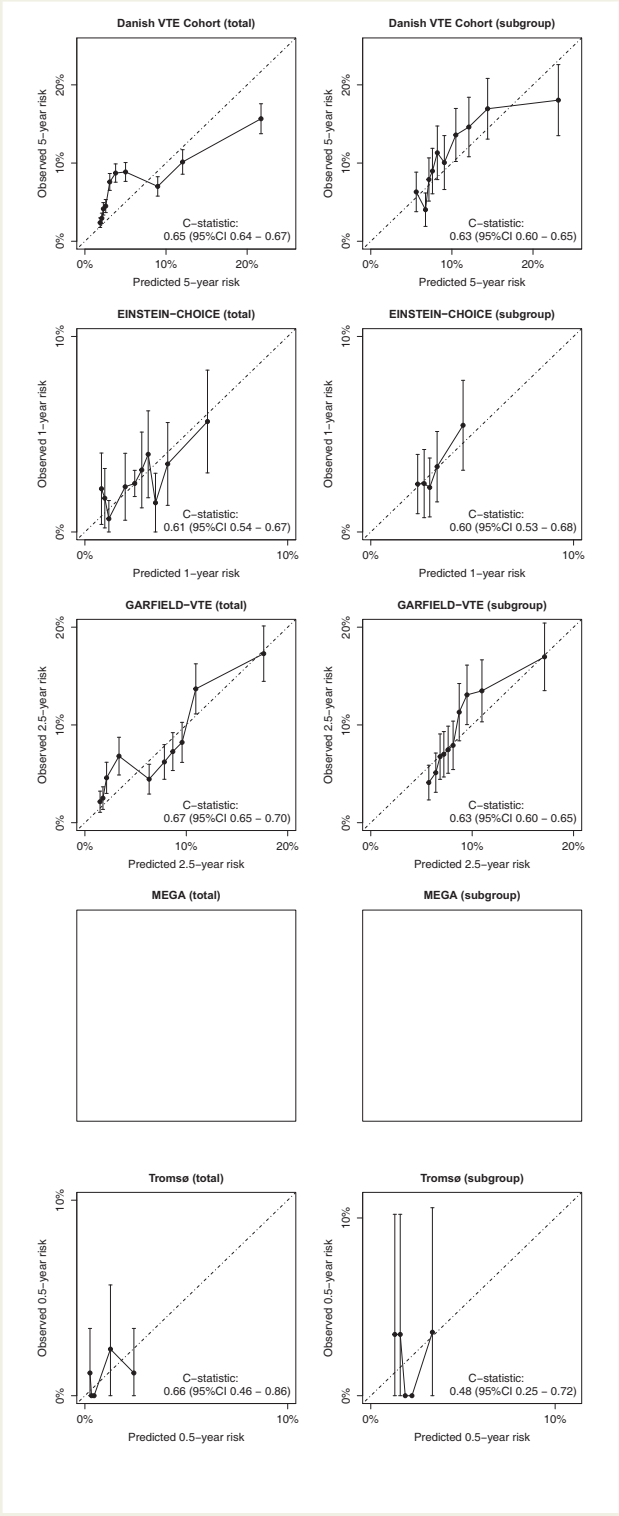


Figure 2 Calibration plots for the VTE-PREDICT model for bleeding in external data sets. The study population is divided into 5 or 10 equal groups (depending on population size) based on predicted risk of bleeding according to the VTE-PREDICT risk score and plotted against observed incidences in the same time frame. The longest available follow-up duration is used

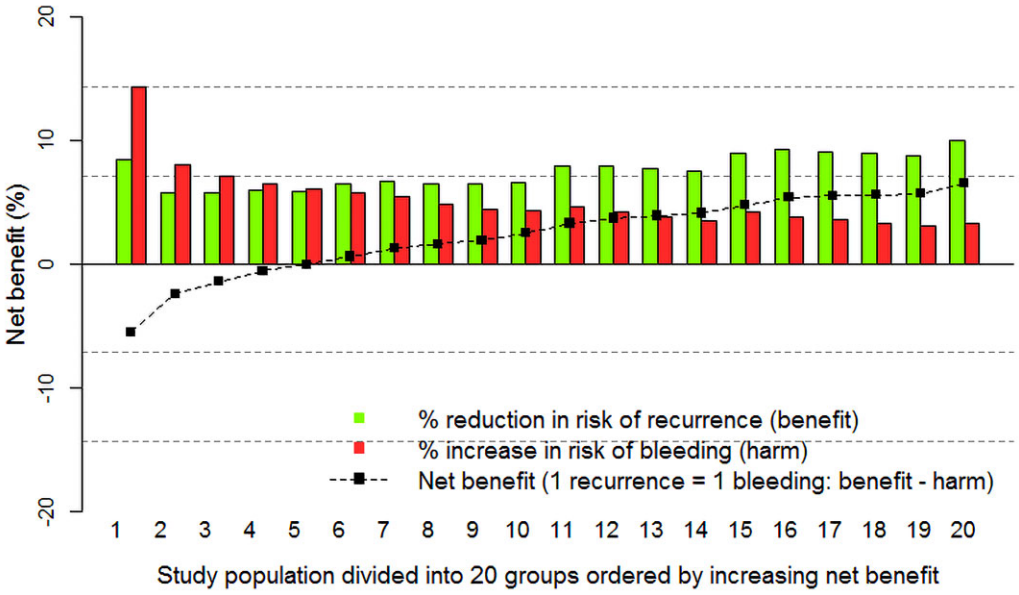


Figure 3 Individual absolute recurrence risk reduction and increase in risk of bleeding with extended anticoagulation. If recurrent venous thromboembolism is considered to be as severe as clinically relevant bleeding, the benefit of extended anticoagulation with the full dose of a direct oral anticoagulant outweighs the harm for 77.2% of patients

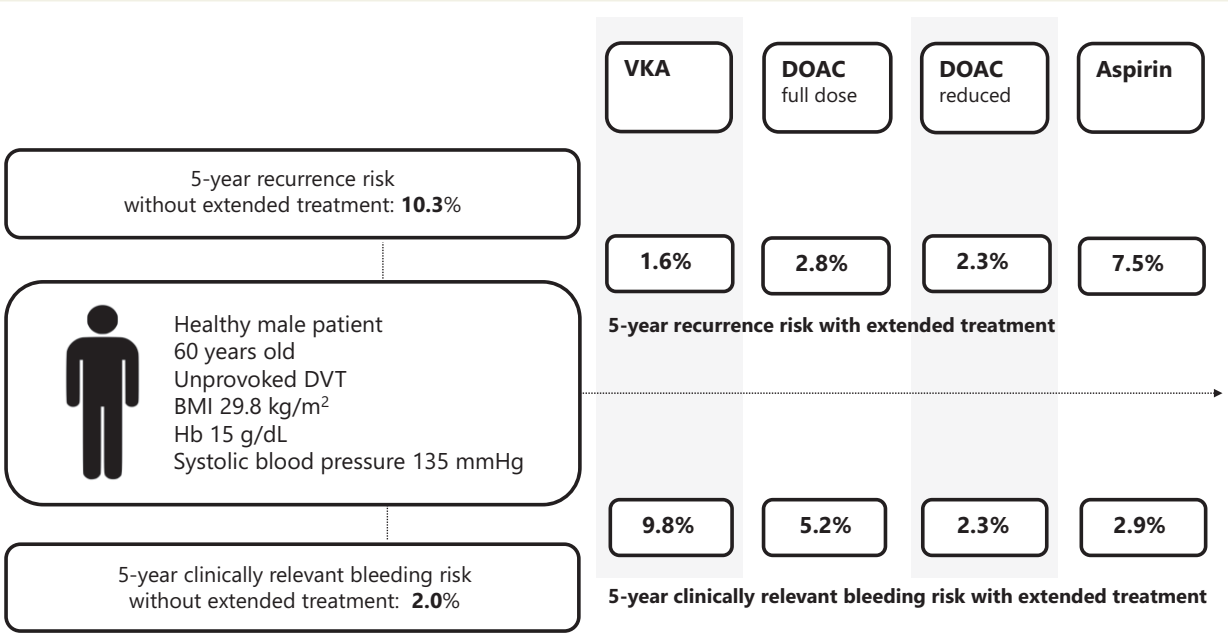


Figure 4 An individual patient example of the VTE-PREDICT risk score to predict the treatment effects of various extended antithrombotic treatment strategies. Estimates for reduced dose direct oral anticoagulants should be interpreted with caution as the pooled treatment effect is partly based on a comparison between reduced-dose direct oral anticoagulants and aspirin rather than reduced dose direct oral anticoagulants vs. placebo alone (see Supplementary material online, *Table S6*)

predicted reduction in risk of recurrent VTE is higher than the increase in risk of bleeding for 77% of patients (*Figure 3*). *Figures 4* and *5* and Supplementary material online, *Figure S8* show examples of how the VTE-PREDICT risk score can be used in clinical practice and as an online calculator.

Discussion

The VTE-PREDICT risk score, developed and validated in data from 74 398 patients, estimates absolute risks of recurrence and clinically relevant bleeding for patients with VTE without active cancer after

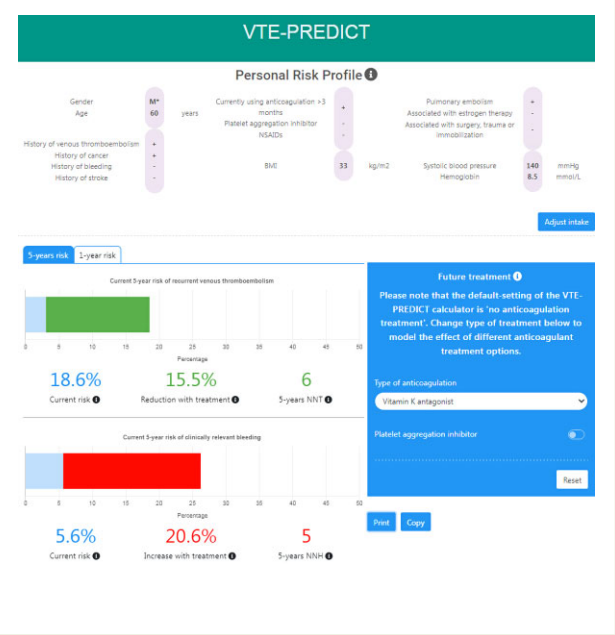


Figure 5 Screenshot of the VTE-PREDICT calculator. *Screenshot from* https://vtepredict.com

initial anticoagulant treatment. The risk score is suitable for all patients for whom the decision to stop or continue anticoagulation remains uncertain. With simple, readily available patient characteristics absolute recurrence risk reduction and increase in bleeding can be estimated real-time for the individual patient. An interactive calculator, worldwide available for free through https://vtepredict.com/, facilitates the use of these models to individualize treatment decisions and improve shared decision-making in clinical practice (*Structured Graphical Abstract*).

In multiple external data sets, the performance of VTE-PREDICT is comparable with published risk scores. However, VTE-PREDICT has added practical and methodological benefits, including the use of easily available predictors, extensive external validation, the prediction of absolute risks and treatment effects, and the availability of models for recurrent VTE and bleeding in one calculator. This is highly important, given that both physicians and patients have a tendency to focus on recurrent VTE rather than bleeding.[22,23] Before applying the model, no strict distinction between unprovoked and provoked VTE needs to be made. Moving away from dichotomizing VTE as provoked or unprovoked has been advocated.[24] The number of patients with distal DVT in the model development population is limited, but in the GARFIELD-VTE and MEGA studies, a higher proportion of patients had distal DVT only. Therefore, with some caution, the VTE-PREDICT score can also be used for patients with distal DVT. By using data from patients with and without extended anticoagulation for model development, we aimed to achieve maximum variation in patient characteristics. Therefore, the model may be used for all patients in whom treatment duration is yet to be decided.

Overall, the C-statistics for VTE-PREDICT and other risk scores for recurrent VTE and bleeding evaluated in this study are modest, with values generally between 0.50 and 0.70. Similar findings are reported in other studies on risk scores for patients with VTE.[20] The maximum C-statistic that can be achieved with a model varies with the distribution of risks in the population. If there is little spread, the C-statistics may be low even if a model is perfectly calibrated.[25] Furthermore, differences in eligibility criteria, study population, setting, and predictor substitutions, compared with the model development population, may be responsible for the reduced discrimination in external validation studies.[26] In treated or untreated subgroups, the range of predicted risks may be even smaller due to treatment duration being decided based on a patient's risk profile. Furthermore, antithrombotic treatment has a profound impact on predicted risks. These differences in study characteristics, along with differences in treatment patterns, are also reflected by differences in the events occur between the studies. Results of the external validation of recalibrated models should be interpreted in light of differences between studies. For example, overestimation of recurrence risks in cohort studies may reflect a lower positive predictive value of the diagnosis of recurrent VTE in those cohorts.[27] Underestimation of risks in trial populations suggests a healthier population, better registration of diagnoses, or better treatment adherence. The latter can also be the underlying mechanism for bleeding risks being higher than predicted in trial patients. Notably, finding good discrimination for a prognostic model is highly challenging. For a diagnostic model, C-statistics of 0.90 and higher are desirable and plausible, as the aim is to discriminate between patients with and without a disease at the time that the model is used. However, the outcome of interest for prognostic models lies in the future. Hence, C-statistics are often below 0.70. This is especially true when predicting outcomes in a population of patients who all share the same disease, because these populations are more homogenous. Lastly, discrimination is of most interest when classification into groups is the purpose of a score.[25] However, since the goal of VTE-PREDICT is to estimate absolute risks and treatment effects, agreement between predicted and observed risks is considered more important when assessing the model's clinical value.[21] Alternatively, transient and/or unmeasured risk factors may affect model performance. Both recurrent VTE and bleeding are influenced by a multitude of transient risk factors (e.g. accidents, surgery, or blood pressure variation) occurring post initial assessment, which may complicate risk prediction. However, our results show agreement between predicted and observed risks for up to 5 years of follow-up after initial treatment in different clinical settings.

Variation in predicted risks and model discrimination appeared lower for high-risk subgroups (i.e. untreated patients for recurrent VTE and patients with extended treatment for bleeding). Patient characteristics in these subgroups are likely less varied, as treatment duration depends on the context of routine clinical care in most studies. Additionally, extended anticoagulation has a large impact on the range of predicted risks compared with other predictors. This can be specifically appreciated from the calibration plot of the recurrent VTE model in RE-MEDY, in which all patients were on extended treatment and had very low risks of recurrent VTE. While discrimination in this population was poor, it stemmed from the absence of variation in risks. In the cohort studies used for external validation of VTE-PREDICT, predicted risks in the low-risk groups were underestimated. This was most notable for the bleeding. Hence, in cohort studies, patients without extended anticoagulation are at a higher risk of bleeding than expected. A possible explanation for this counterintuitive finding may be that physicians refrain from prescribing extended anticoagulation to patients with strong risk factors for bleeding, which are not captured in the VTE-PREDICT risk score. Alternatively, data on treatment status may not have been precise.

Estimated risks of recurrence, bleeding, and treatment effects may be used to facilitate shared decision-making. Patient involvement in the decision to stop or continue anticoagulation may lead to better treatment adherence, as treatment decisions are tailored to their needs. When

discussing estimates of the risks of recurrent VTE and bleeding with an individual patient, it is essential to also consider associated morbidity and mortality, the impact on quality of life, and the patient's preferences. In *Figure 3*, net benefit is calculated by assuming equal severity of recurrent VTE and clinically relevant bleeding. However, this approach does not capture all relevant factors. The actual optimal ratio between recurrence risk reduction and an increase in the risk of bleeding may be different from 1. Therefore, the calculator will not provide advice on whether to stop or continue anticoagulant treatment based only on estimated risks. Future studies should focus on how to weigh risks to better guide treatment decisions. Also, ways to better communicate risks to patients to further stimulate and improve shared decision-making need to be developed. Furthermore, the impact of the VTE-PREDICT risk score on clinical shared decision-making needs to be studied.

By allowing for the estimation of real-time risks of recurrent VTE and bleeding for individual patients, VTE-PREDICT provides an important step further towards personalizing anticoagulant treatment. However, some important limitations must be acknowledged. First, variation in definitions of predictors and outcomes among the individual studies used for model development may have attenuated associations between predictors and outcomes, thereby reducing the models' predictive performance. At the same time, using combined individual patient data from different studies increases power, enhances the model's potential generalizability, and provides the option to include variables that are not available in all data sets, resulting in a more complete model. Second, while the performance of the bleeding risk model was consistent in all external validation studies, the predictive performance of the recurrent VTE model varied. In GARFIELD-VTE, C-statistics of all evaluated recurrence risk scores were close to 0.50, except for the VTE-PREDICT model in patients without extended treatment. Potential explanations could be a low incidence of the strongest predictors in patients with extended treatment, or lower treatment adherence in non-trial patients.[28] Third, in most studies used for model development or validation, deaths in which PE could not be ruled out were included as recurrent VTE events. The proportion of these events among VTE recurrences is unknown. This may have led to misclassification, thereby reducing model performance. Fourth, we assumed relative treatment effects to be constant over time, across studies and settings, and homogenous among all patients. However, no long-term data on DOACs exist. Absolute effects may be different from those presented in *Figures 2* and *3* when applying the treatment effects of individual DOACs rather than a pooled estimate. For *Figure 3*, pooled estimates for the effect of full dose DOAC were used only, as robust pooled estimates for reduced dose DOAC are currently unavailable. As no head-to-head comparison has been made among DOACs, the treatment effects of different types of DOACs should not be directly compared. Therefore, we recommend that decisions about the type of anticoagulant first be based on clinical characteristics, preferences, and local availability, before assessing risks. Fifth, antiplatelet therapy status was registered only at the end of the initial treatment, or, if unavailable, at the index event. Therefore, the offset term for antiplatelet therapy may differ from the actual effect of antiplatelet therapy in the study. Point estimates of the effect of treatment were used with the offset terms, although trials and meta-analyses generally provide CIs. However, we did not introduce variance for the sake of simplicity.[29] To be able to adjust for the effect of treatment, patients could be either on or off extended anticoagulation. As our study population consisted of patients after initial treatment, not all follow-up data could be used from studies that included patients during the index event. Furthermore, the model is constructed using baseline risks rather than time-varying risks in a dynamic model that simulates clinical practice.

Conclusion

The VTE-PREDICT risk score estimates the risks of recurrent VTE and bleeding in patients with VTE who do not have active cancer and who have completed initial anticoagulant treatment. The VTE-PREDICT risk score can be applied to estimate the absolute benefits and harms of extended anticoagulation for individual patients and support shared decision-making.

Contributors statement

M.A. de Winter, M. Nijkeuter, J.A.N. Dorresteijn and F.L.J. Visseren were responsible for study conception and design. M.A. de Winter drafted the manuscript in close collaboration with J.A.N. Dorresteijn, and M. Nijkeuter. The present study is based on an analysis of existing data of multiple cohorts and trials. Underlying data were verified by the authors of the original studies. Analysis of data for model development and for external validation in EINSTEIN-CHOICE, the MEGA study and the Tromsø study for the present study was performed by M.A. de Winter and verified by J.A.N. Dorresteijn and M. Nijkeuter. Analysis for external validation in the Danish VTE cohort were performed by E. Horváth-Puhó. Analysis for external validation in the GARFIELD-VTE data were performed by A. Farjat and S. Virdone; U. Maheswari provided programming support. Other VTE-PREDICT study group members were responsible for data collection. All authors contributed to interpretation of the results, critically revised the manuscript, and were responsible for and approved its final version.

Supplementary data

Supplementary data is available at *European Heart Journal* online.

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AstraZeneca. All fees were paid to his company. Alfredo Farjat was a full-time employee at Thrombosis Research Institute when he collaborated with this study. Akos Ference Pap is an employee of Bayer AG. Samuel Goldhaber reports grants or contracts from Bayer, Boston Scientific BTG EKOS, NHLBI, BMS, Janssen and Pfizer, consulting fees from Agile, Pfizer, Bayer, speaker fees from Lankenau Grand Rounds in Medicine, Bakken Symposium -University of Minnesota, The Brigham Board Review in Critical Care 'Virtual Studio/Distance Learning', New York Cardiovascular Symposium, Latin American Anticoagulation Series Conference, Jeresaty Symposium—Trinity Health of New England, Rutgers New Jersey Medical School Grand Rounds, SBACV Symposium—Brazil Society of Angiology and Vascular Medicine, Brigham-Sheba Collaboration on Thrombosis and Vascular Medicine and Philippine Society of Vascular Medicine Annual Convention. Michael Grosso is an employee of Daiichi Sankyo. Ajay Kakkar reports grants from Bayer AG, Sanofi SA, personal fees from Anthos Therapeutics, Bayer AG, Sanofi S.A. Karen Pieper reports consulting fees from Cryolife, J&J Pharmaceuticals, Artivion and Element Science. Gary Raskob reports consultancy fees or honoraria from AMAG Pharma, Anylam, Anthos Therapeutics, Bayer HealthCare Pharmaceuticals Inc., Bristol-Myers Squibb, Daiichi Sankyo Inc., Janssen Global Services LLC, Pfizer, and XaTrek; honoraria from BMS, Pfizer, Daiichi Sankyo; DSMB or advisory board membership from Anthos Therapetuics, Janssen, Bristol-Myers Squibb and Pfizer, leadership or fiduciary role in other board, society, committee or advocacy group of OU Health, stock or stock option ownership for AbbVie, Inc., Gilead Sciences Inc, GlaxoSmithKline, LLC., LLY, MRK, and Pfizer. Sam Schulman reports research grants, paid to his institution, from Octopharma, and consulting fees from Alexion, Bayer, Boehringer–Ingelheim, Sanofi, Daiichi Sankyo and Octopharma. Minggao Shi is an employee of Daiichi Sankyo. Phillip Wells reports grants and speaker fees from BMS/Pfizer, consulting fees from Anthos and speaker fees and consulting fees from Bayer Healthcare. All fees are paid to his institution. The other authors have nothing to declare.

Data availability

Data used for the current study are available upon reasonable request and approval of the individual cohorts or collaborative groups; please contact the individual cohorts and trials used for the current study for details. Study protocol and statistical analysis plan of the present study will be available on request from the authors, and will be made available through Vivli after publication (http://vivli.org). R scripts for calculation of the VTE-PREDICT algorithms are available on request from authors.

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