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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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Background

- Deciding to stop or continue anticoagulation for venous thromboembolism (VTE) after initial treatment is challenging, as individual risks of recurrence and bleeding are heterogeneous.
- While anticoagulant treatment is effective in reducing recurrence risk, it is associated with a 1%–2% annual risk of major bleeding.
- International guidelines do not provide recommendations as to how the risks of recurrent VTE and bleeding should be assessed and weighed.
- 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.

AIM of the study

- 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.

Methods

- Data sets (trials as well as cohort studies) containing data from adult patients with VTE without active 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.
- The models were externally validated in four cohorts and one trial.
- 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.

Results (I)

- 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).
- During a median follow-up of 189 days (IQR: 42–372 days), 737 bleeding events and 145 competing non-bleeding-related deaths occurred.

Results (II)

- Internal C-statistics for the recurrent VTE model ranged from 0.51 to 0.79; overall 0.68 (95% CI: 0.65–0.72).
- Internal C-statistics for the bleeding model ranged from 0.65 to 0.73; overall 0.69 (95% CI: 0.67–0.72).
- After external validation, the C-statistics for the recurrent VTE model ranged from 0.48 (0.45–0.52) to 0.71 (0.66–0.77); For the bleeding risk score, C-statistics ranged from 0.61 (0.54–0.67) to 0.68 (0.65–0.70).
- 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.
- 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.

Table 2 Prediction models for recurrent VTE and bleeding

	Predictor	Recurrent VTE		Bleeding	
		sHR (95% CI)	$\chi 2$ statistic	sHR (95% CI)	$\chi 2$ 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.

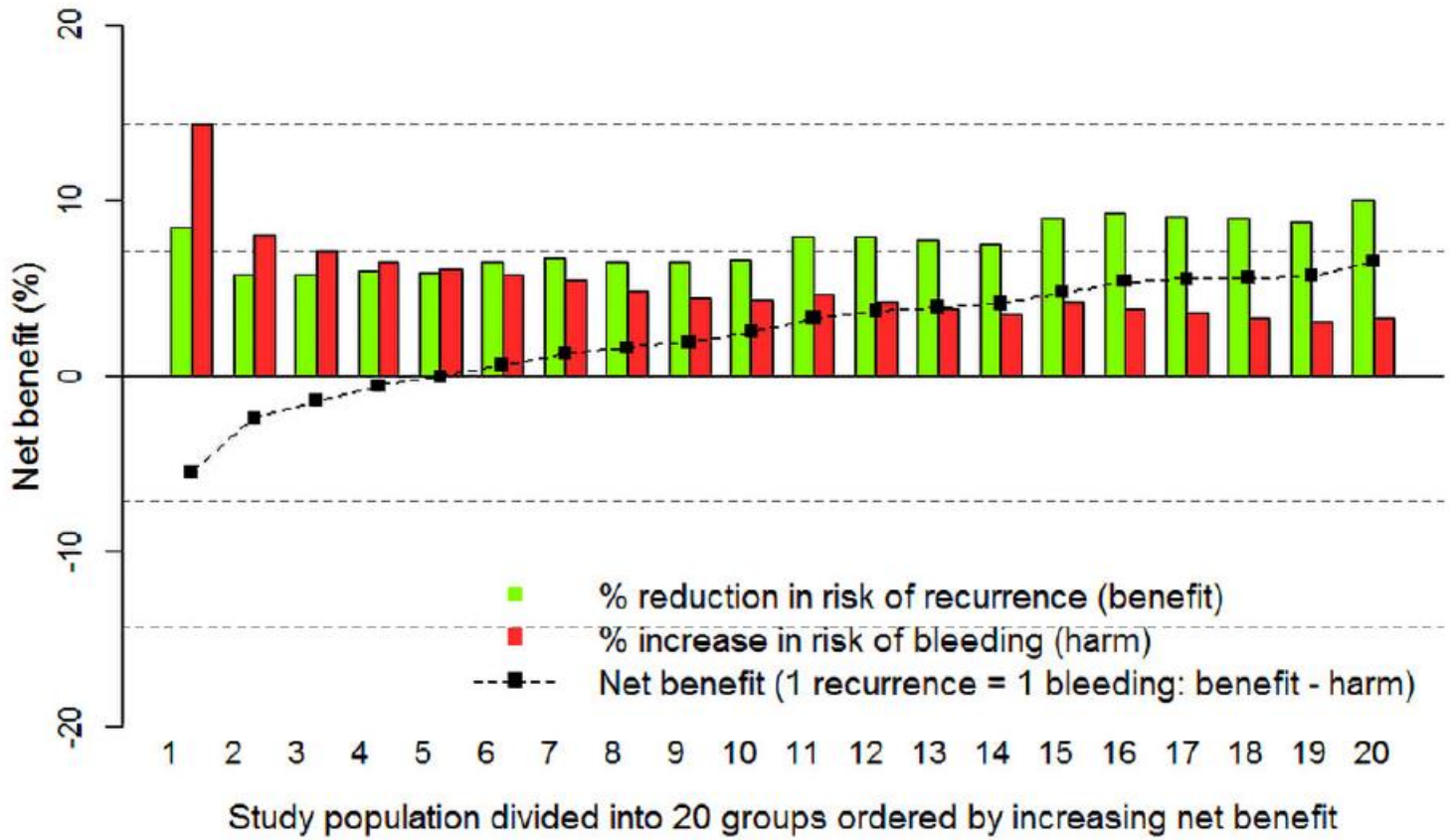

Figure 3 Individual absolute recurrence risk reduction and increase in risk of bleeding with extended anticoagulation. If recurrent venous thromboembolism is considered to be as severe as clinically relevant bleeding, the benefit of extended anticoagulation with the full dose of a direct oral anticoagulant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

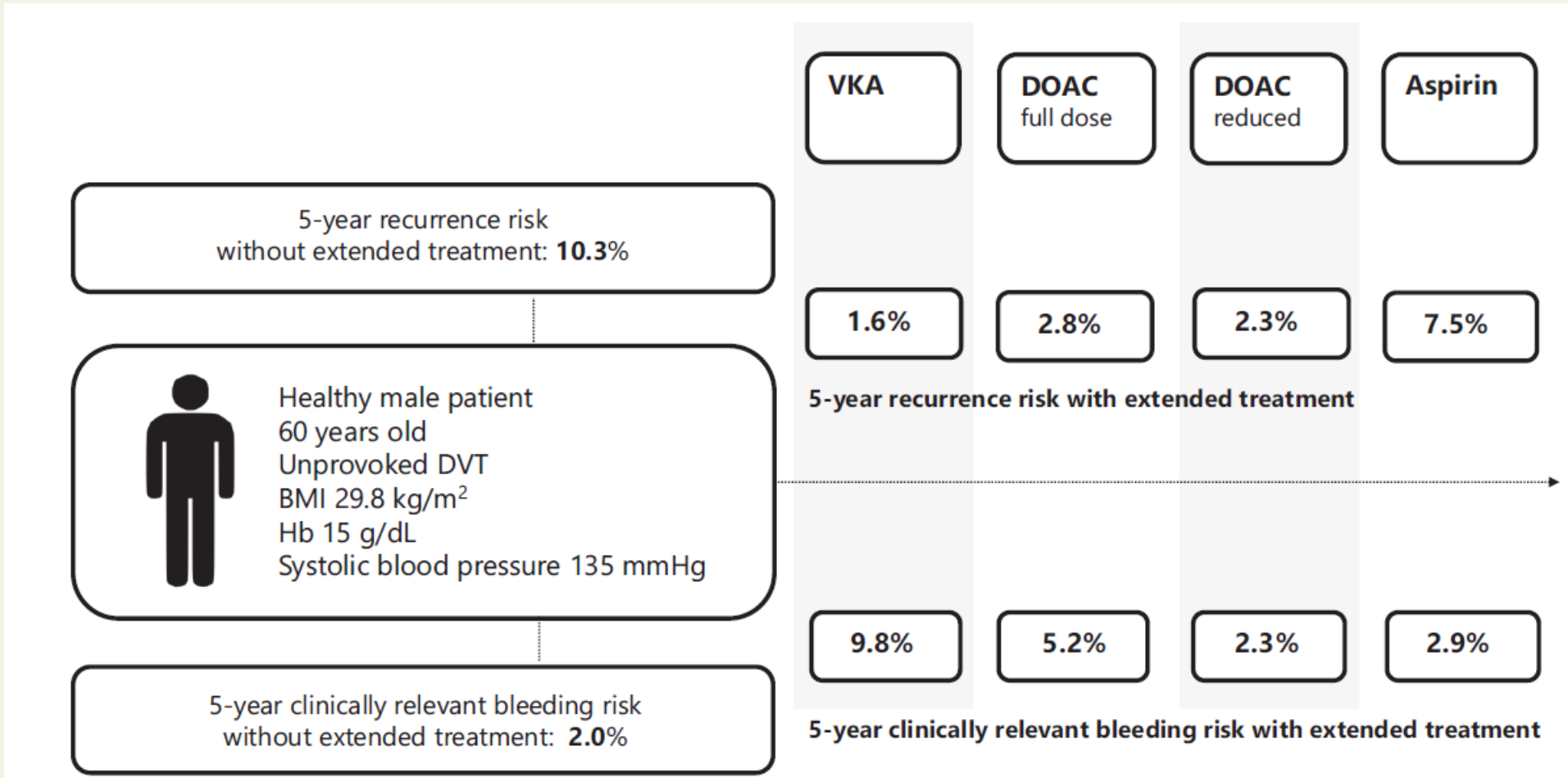

Figure 4 An individual patient example of the VTE-PREDICT risk score to predict the treatment effects of various extended antithrombotic treatment strategies. Estimates for reduced dose direct oral anticoagulants should be interpreted with caution as the pooled treatment effect is partly based on a comparison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

Conclusions

- 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.
- 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.
- 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.