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ORIGINAL ARTICLE

Development and validation of a clinical prediction model for 90-day venous thromboembolism risk following total hip and total knee arthroplasty: a multinational study

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Abstract

Background: The risk of venous thromboembolism (VTE) following total hip arthroplasty (THA) and total knee arthroplasty (TKA) is 1.0% to 1.5%, despite uniform thromboprophylaxis.

Objectives: To develop and validate a prediction model for 90-day VTE risk.

Methods: A multinational cohort study was performed. For model development, records were used from the Oxford Royal College of General Practitioners Research and Surveillance Centre linked to Hospital Episode Statistics and Office of National Statistics UK routine data. For external validation, data were used from the Danish Hip and Knee Arthroplasty Registry, the National Patient Registry, and the National Prescription Registry. Binary multivariable logistic regression techniques were used for development.

Results: In the UK data set, 64 032 THA/TKA procedures were performed and 1.4% developed VTE. The prediction model consisted of age, body mass index, sex, cystitis within 1 year before surgery, history of phlebitis, history of VTE, presence of varicose veins, presence of asthma, history of transient ischemic attack, history of myocardial infarction, presence of hypertension and THA or TKA. The area under the curve of the model was 0.65 (95% CI, 0.63-0.67). Furthermore, 36 169 procedures were performed in the Danish cohort, of whom 1.0% developed VTE. Here, the area under the curve was 0.64 (95% CI, 0.61-0.67). The calibration slope was 0.92 in the validation study and 1.00 in the development study.

Conclusion: This clinical prediction model for 90-day VTE risk following THA and TKA performed well in both development and validation data. This model can be used to estimate an individual's risk for VTE following THA/TKA.

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KEYWORDS
clinical decision rules, risk scores, thrombosis, total hip arthroplasty, total knee arthroplasty

1 | INTRODUCTION

Patients who undergo total hip or total knee arthroplasty (THA/TKA) have a high risk of developing postoperative venous thromboembolism (VTE) [1]. Therefore, all guidelines recommend the use of prophylactic anticoagulant therapy, although the type and length of treatment differ among guidelines [1,2].

Despite current preventive strategies, about 1.5% of all patients develop symptomatic VTE [3,4]. At the same time, the thromboprophylaxis therapy that all patients are subjected to is associated with a major bleeding risk [3,5]. Considering that a large proportion of all patients actually have a low VTE risk, this group is unnecessarily exposed to the burden and risks of prophylactic anticoagulants.

The main problem with the current "one-size-fits-all" approach is that patients are considered to have a uniform thrombosis risk. Both patient- and surgery-related risk factors contribute to a person's VTE risk following surgery. Fast-track surgery [6], for example, has greatly reduced VTE risk during the last decade. Multiple studies have shown that the incidence of VTE following fast-track THA/TKA is low (<1.0% within 3 months), while these patients only receive thromboprophylaxis during hospital admission [7,8]. However, considering that the average risk in all patients is still about 1.5% despite standard prophylaxis, there are other patients with a higher risk, such as those with a previous history of VTE [3,9].

Major bleeding induced by thromboprophylaxis occurs in at least 0.5% while minor bleeding, including clinically relevant nonmajor bleeding, occurs in 6% [3,5]. In addition to the general morbidity related to bleeding, a large hematoma or prolonged wound drainage is associated with implant-related infection (and therefore an increased likelihood of revision surgery) which often necessitates extended hospitalization [10,11].

Considering the above, a personalized thromboprophylaxis strategy in which the duration, as well as dosage or type of thromboprophylaxis, can be tailored to an individual's risk would benefit patients and society. To implement such an approach in practice, an individual's postoperative VTE risk must be accurately predicted. Previous attempts have been made to develop new or apply existing VTE risk prediction models [12–19]. However, they all lacked sufficient validation in external populations; often no discrimination or calibration analyses were performed; inadequate reporting of model characteristics makes it impossible to validate or enhance these existing models; lastly, some are too complex, which hampers usability in practice [13,15,18].

To be able to accurately estimate an individual's VTE risk following THA/TKA, this study aimed to develop and externally validate a prediction model for the absolute risk of symptomatic VTE within 90 days following THA/TKA.

Essentials

- Approximately 1.5% of patients undergoing hip/knee arthroplasty still develop venous thromboembolism despite thromboprophylaxis.
- A large multinational cohort study was performed using routine health care data.
- A clinical prediction model was developed and externally validated to estimate the risk of venous thromboembolism.
- Model performance was good and can be used to differentiate between low- or high-risk patients.

2 | METHODS

2.1 | Data sources and study population

2.1.1 | Development cohort

Data from 3 sources from the United Kingdom (UK) were linked, ie, the Oxford Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) [20], Hospital Episodes Statistics (HES), and Office for National Statistics (ONS). The RCGP RSC is a network of general practices, which extracts data from computerized medical records in the UK (Supplement Text S1). HES data contain information on all hospital admissions and performed surgeries [20]. ONS data include (cause of) death information.

The development cohort consisted of all patients who underwent THA/TKA between January 1, 2010 and December 31, 2018. Patients were extracted from HES data and subsequently linked to the RSC network. In addition, all data on time and cause of death were linked from ONS to verify a complete 90-day follow-up period.

2.1.2 | External validation cohort

Patients were identified through the Danish Hip Arthroplasty and the Danish Knee Arthroplasty Registry and subsequently linked, based on each patient's unique identification number, to the Danish National Patient and the Danish National Prescription Registry (DNPR) [21]. Patients undergoing a THA/TKA between January 2016 and December 2018 were available for this study (Supplement Text S1).

This study was approved by the ethics committees of the separate study cohorts (see ethics statement below).

2.1.3 | Participants

Participants in both cohorts were eligible if they were aged ≥18 years and had undergone a primary THA/TKA within the inclusion time frame. Revision surgeries and procedures indicated for a fracture or hemiarthroplasty were not included. Each surgical procedure was included separately, so a single patient could be present in the data set multiple times (eg, right and left THA/TKA). Patients using therapeutic anticoagulation at the time of surgery, such as for atrial fibrillation (AF), were excluded, and patients using antiplatelet medication were retained. Supplement Table S2 shows codes and systems used to identify primary THA/TKA procedures in the development data.

2.2 | Outcome

The predicted model outcome was postoperative VTE, consisting of symptomatic deep vein thrombosis (DVT) or pulmonary embolism diagnosed within the first 90 postoperative days. More information on the classification of VTE and coding systems used to register VTE is provided in Supplement Text S3–S5.

2.3 | Predictors

Candidate predictors (Table 1) were selected on their potential to predict a VTE, expert opinion, literature (eg, predictors from previously published prediction models for VTE), and availability in both data sets [12–17].

In the development cohort, all predictors were identified by Read/Clinical Terms Version 3 codes from the National Health Service (NHS). Supplement Table S5 shows ICD-10 codes used to identify predictor variables in the validation cohort. Body mass index (BMI) was measured at a mean of 346 days before surgery in the development cohort and for the validation cohort, BMI was registered shortly before arthroplasty.

2.4 | Sample size

A 4-step procedure was performed to increase the potential for developing a robust prediction model, which yielded an overall minimum sample size of 26 914 patients (Supplement Text S6) [22].

2.5 | Missing data

In the development cohort, for most predictors, no missing data were present because of the nature of data collection. Hence, missing values were not present, with the exception of BMI data. BMI data were not imputed but handled as a separate indicator variable during model development.

For the validation data, BMI was systematically collected preoperatively for THA patients. In contrast, for TKA patients only weight data were collected. BMI values for TKA patients were calculated after a single imputation of the patient's height, using sex and age, assuming the same relation between these variables as in THA patients.

2.6 | Statistical analysis

For model development, a multivariable logistic regression model was fitted including all candidate predictors. A backward selection procedure was performed, including interaction terms and restricted cubic splines. Bootstrapping (n = 200) was performed to examine the degree of overfitting. A uniform shrinkage factor was applied to the predictor coefficients. Finally, the model intercept was re-estimated resulting in the final prediction model. Model performance was assessed by determining model discrimination and calibration. Discrimination was assessed by calculating the area under the curve (AUC) while calibration was assessed by plotting a calibration curve showing the agreement between observed vs predicted VTE risks.

As a sensitivity analyses, to verify predictor selection and the degree of potential overfitting, a least absolute shrinkage and selection operator logistic regression was performed, which led to an almost identical set of predictors and predicted probabilities. Supplement Text S7 provides an extensive description of the complete modeling process.

As the VTE incidence was slightly lower in the validation cohort, the model's intercept was recalibrated based on VTE incidence in this cohort.

All analyses were performed using R Statisticsl Software (version 4.2.1; R Core Team) To allow for easy application of the prediction model in practice, an online web-based calculator and a mobile phone application were developed.

3 | RESULTS

3.1 | Participants

In the development cohort, 52 111 patients underwent 64 032 THA/TKA procedures. In the validation cohort, 33 263 patients underwent a total of 36 169 THA/TKA procedures (Table 2). The mean age was 71 years vs 68 years in the development and validation cohorts, respectively. The incidence of VTE was slightly higher in the development cohort (1.4%) than in the validation cohort (1.0%). Overall, patients in the development cohort had more comorbidities than in the validation cohort.

TABLE 1 An overview of the candidate predictor variables.

Predictor[a]	Type of variable	Category
Age at surgery	Continuous	-
Sex	Binary	Male/Female
Body mass index	Continuous	-
Family history of VTE (first degree relative)	Binary	Yes/No
Heart failure	Binary	Yes/No
Hypertension	Binary	Yes/No
Coronary artery disease	Binary	Yes/No
Peripheral artery disease	Binary	Yes/No
Chronic obstructive pulmonary disease	Binary	Yes/No
Asthma	Binary	Yes/No
Chronic kidney disease	Binary	Yes/No
Chronic liver disease	Binary	Yes/No
Cancer	Binary	Yes/No
Cancer within 5 years of surgery	Binary	Yes/No
Cystitis within 1 year of surgery	Binary	Yes/No
Rheumatoid arthritis	Binary	Yes/No
Immobility	Binary	Yes/No
Hepatitis	Binary	Yes/No
Inflammatory bowel disease	Binary	Yes/No
Myocardial infarction	Binary	Yes/No
Dementia	Binary	Yes/No
Factor V Leiden	Binary	Yes/No
Prothrombin gene mutation	Binary	Yes/No
Protein S deficiency	Binary	Yes/No
Protein C deficiency	Binary	Yes/No
Lupus anticoagulant	Binary	Yes/No
Thrombophilia	Binary	Yes/No
Phlebitis	Binary	Yes/No
Use of hormonal replacement therapy within 1 year of surgery	Binary	Yes/No
Pneumonia within 1 year of surgery	Binary	Yes/No
Pyelonephritis within 1 year of surgery	Binary	Yes/No
Sepsis within 1 year of surgery	Binary	Yes/No
Stroke within 1 year of surgery	Binary	Yes/No
Stroke	Binary	Yes/No
Transient ischemic attack within 1 year of surgery	Binary	Yes/No
Transient ischemic attack	Binary	Yes/No
Varicose veins ("medically attended")	Binary	Yes/No
VTE in patient history	Binary	Yes/No
Antibiotic use within 1 year of surgery	Binary	Yes/No

VTE, venous thromboembolism.

[a] If no time frame is indicated, for instance for heart failure, the predictor was considered as "having a history of (heart failure) prior to date of surgery". Note that predictors are not causality related with VTE

TABLE 2 Patient demographics for the development and validation cohort.

	Development cohort	Validation cohort
Total, *n*	64.032	36.169
VTE, *n* (%)	876 (1.4)	362 (1.0)
Deep vein thrombosis	532 (0.8)	232 (0.6)
Pulmonary embolism	344 (0.5)	130 (0.4)
Median duration in days until VTE (IQR)	20 (9-41)	16 (9-37)
Mean age at surgery (SD)	71 (11)	68 (10)
Female, *n* (%)	38.451 (60.0)	21.131 (58.4)
Mean BMI kg/m^2 (SD)[a]	26.1 (10.5)	28.7 (5.6)
Total knee arthroplasty, *n* (%)	33.449 (52.2)	17.793 (49.2)
History of transient ischemic attack, *n* (%)	1.701 (2.7)	886 (2.4)
History of myocardial infarction, *n* (%)	2.129 (3.3)	1 436 (4.0)
History of hypertension, *n* (%)	31.295 (48.9)	11.397 (31.5)
History of asthma, *n* (%)	10.112 (15.8)	1.955 (5.4)
Cystitis within 1 year before surgery, *n* (%)	615 (1.0)	247 (0.7)
History of phlebitis, *n* (%)	3.118 (4.9)	226 (0.6)
Presence of varicose veins, *n* (%)	9.326 (14.6)	2.718 (7.5)
History of venous thromboembolism, *n* (%)	2.549 (4.0)	1.632 (4.5)

BMI, body mass index; VTE, venous thromboembolism.
[a] Body mass index was missing for 7.072 records in the development cohort and for all total knee arthroplasty patients in the validation cohort.

3.2 | Model development

Among 39 candidate predictors, 12 predictors were selected and included in the prediction model entitled the Thrombosis Risk Prediction following total hip and knee arthroplasty score (TRiP[plasty] [Box 1]). The univariate odds ratios for included predictors are shown in Supplement Table S8. Modeling age and BMI with cubic splines improved performance. The AUC was 0.65 (95% CI, 0.63-0.67) in the total population with a similar performance across the THA/TKA population separately (Table 3). Calibration analyses showed a slope of 1.00 with an excellent agreement between observed and predicted risks up to 4% (Figure). Beyond this threshold, the model was overestimating an individual's VTE risk.

3.3 | Model validation

The AUC was 0.64 (95% CI, 0.61-0.67). The calibration slope (Figure) was 0.92 and showed a similar agreement between observed and predicted risks up to 4% as in the development study.

3.4 | Clinical performance

Table 4 shows observed and predicted risks across 3 groups of patients categorized by their postoperative predicted VTE risk (<1%, 1%-1.5%, and >1.5%). Danish (validation) patients undergoing THA/TKA were more often predicted to be in the lowest VTE risk category than English (development) patients. In the validation cohort, the sensitivity and specificity of a dichotomized score with a predicted risk at <1% vs ≥1% were 70.3% and 47.0%, respectively.

3.5 | TRiP(plasty) score application

Supplement Figure S9 shows a mobile phone application that has been developed for IOS (iPhone Operating System) and Android. Alternatively, the TRiP(plasty) score can be calculated online http://www.thrombosisriskprediction.com. The application calculates an individual's predicted postoperative VTE risk following THA/TKA within 90 days by using the validated logistic regression equation from Box 1.

4 | DISCUSSION

We developed and externally validated a prediction model for postoperative VTE risk in a large multinational cohort study. The TRiP(plasty) score consists of 12 clinical predictors that can be easily obtained before initiating surgery. Model discrimination was 0.65 and 0.64 during development and validation, respectively. More importantly, calibration was excellent up to a risk of 4%. The TRiP(plasty) score can be used to accurately select individuals at low or high risk of

BOX 1. The TRiP(plasty) score following total hip and knee arthroplasty. The predicted risk for VTE can be calculated by calculating the Prognostic Index (PI) by multiplying the estimated coefficients with the values of the predictor variables for an individual patient. The sum of these terms added to the intercept results in the PI. The PI can then be used to calculate the estimated risk of postoperative VTE by exp(PI)/(1+exp(PI)). The regression formula to calculate an individual's VTE risk is based on the recalibrated analyses derived from the validation study as this analysis was performed in contemporary data (eg, median stay 1-day).

Thrombosis Risk Prediction following total hip or knee arthroplasty score to estimate VTE risk at 90-days following either THA or TKA.

TRiP(plasty) score

Age at surgery (years)

Body mass index (kg/m^2)

Sex (male = 1, female = 0)

Cystitis within 1 year before surgery (urinary tract infection requiring treatment) (yes = 1, no = 0)

History of phlebitis (superficial vein thrombosis) (yes = 1, no = 0)

History of venous thromboembolism (yes = 1, no = 0)

History of varicose veins (only if medically attended) (yes = 1, no = 0)

History of asthma (yes = 1, no = 0)

History of transient ischemic attack (yes = 1, no = 0)

History of myocardial infarction (yes = 1, no = 0)

Hypertension (also if using antihypertensives) (yes = 1, no = 0)

Procedure type (total knee arthroplasty = 1, total hip arthroplasty = 0)

Regression formula:

Prognostic index = -11.21512366 - 0.0025112037* Age + 3.1802692e-05* pmax(Age – 52, 0)^3 + 3.0289566e-05* pmax(Age – 66, 0)^3 - 0.00045484162 * pmax(Age – 72, 0)^3 + 0.00056371658* pmax(Age – 78, 0)^3 - 0.00017096722* pmax(Age – 87, 0)^3 + 0.28151553* BMI - 0.00088295423* pmax(BMI - 15.1, 0)^3 + 0.0015184276* pmax(BMI - 21.7, 0)^3 + 0.00010410438* pmax(BMI - 26.8, 0)^3 - 0.00078436427* pmax(BMI -30.8, 0)^3 + 4.4786473e-05* pmax(BMI - 39.1, 0) ^{3} + 0.10483374* Sex + 0.82177659* Cystitis + 0.39953645* Phlebitis + 1.2908304* VTEhistory + 0.1565422* Varicose + 0.17636548* Asthma + 0.2653638* TIA + 0.52510786* MIhistory - 0.052137583* Hypertension - 0.0066283685* Procedure type + 0.23627308* Hypertension * Procedure type - 0.76886068* MIhistory * Procedure type

Pmax()

Because age and BMI are modeled with splines, pmax() is included in the formula. pmax() checks which of the 2 values (before and after the comma) is bigger and returns the biggest value. To better understand this, we use 3.1802692e-05 * pmax(Age – 52, 0)^3 as example. If we fill this part of the formula for a patient of 40 years, we get 3.1802692e-05 * pmax(40-52, 0)^3. Because 40 – 52 is less than 0, pmax() returns 0 as this is the largest number and this results in 3.1802692e-05 * 0. Hence, this part of the formula is not added to the prognostic index of the concerning patient. For a patient of 60 however, the pmax() would be pmax(60-52, 0)^3 → 8^3 → 512, which results in 3.1802692e-05 * 512 = 0.01628298 being added to the prognostic index.

VTE who might benefit from an individualized thromboprophylactic approach.

Two international high-quality data sources were used consisting of a large and unselected population. Methods of collecting and registering predictors differed somewhat between cohorts. Despite these differences, risk estimations were very similar in both analyses. This assures that the TRiP(plasty) score performs well across different settings and countries. All predictors are easily available when recording patient history, allowing for simple implementation in clinical practice. This is in contrast to other VTE risk scores that often need assessment of biomarkers or genetics [23]. It is important to realize that predictors are not necessarily causally related (and cannot be interpreted as such) with VTE. For instance, cystitis within 1 year of surgery was found to be predictive for VTE which is unlikely to be causal but probably functions as a proxy for overall frailty [24]. Model validation was performed in a contemporary cohort with a short duration of stay which allows for transferability of results to current clinical practice.

Our study has some limitations which need to be addressed. First, it focuses on elective THA/TKA; patients undergoing arthroplasty for trauma were therefore excluded. Patients with a hip fracture have a high risk of VTE and the duration of the preoperative and postoperative immobilization period can be extensive [25]. There is no evidence that thromboprophylaxis can be reduced following trauma

TABLE 3 Model performance.

	Development cohort	Validation cohort after recalibration[a]
	Area under the curve (95% CI)	
THA + TKA	0.65 (0.63-0.67)	0.64 (0.61-0.67)
THA	0.68 (0.65-0.71)	0.63 (0.58-0.68)
TKA	0.63 (0.60-0.66)	0.63 (0.59-0.67)
	Calibration slope	
THA + TKA	1.00	0.92
THA	1.07	0.95
TKA	0.94	0.86

THA, total hip arthroplasty; TKA, total knee arthroplasty.
[a] Following recalibration of the model's intercept.

and hence, risk prediction is not indicated for these patients. Patients on long-term anticoagulation (eg, for AF) around surgery were also excluded as we aimed to estimate an individual's VTE risk in order to potentially reduce or increase thromboprophylaxis. Neither is applicable to this patient group. Second, the incidence of VTE was slightly different between the English (1.4%) and the Danish cohort (1.0%), which led to a recalibration of the model's intercept. This is also reflected by the difference in the proportion of patients with a predicted VTE risk <1.0%. In Denmark, 70% of patients had a predicted VTE risk <1.0% whereas in England, "only" 35% were classified as such. This may partially be explained by the type of patients included. In general, patients in the development cohort had more comorbidities. As data from general practitioners were linked to HES data, patients who underwent arthroplasty in private (non-NHS) facilities

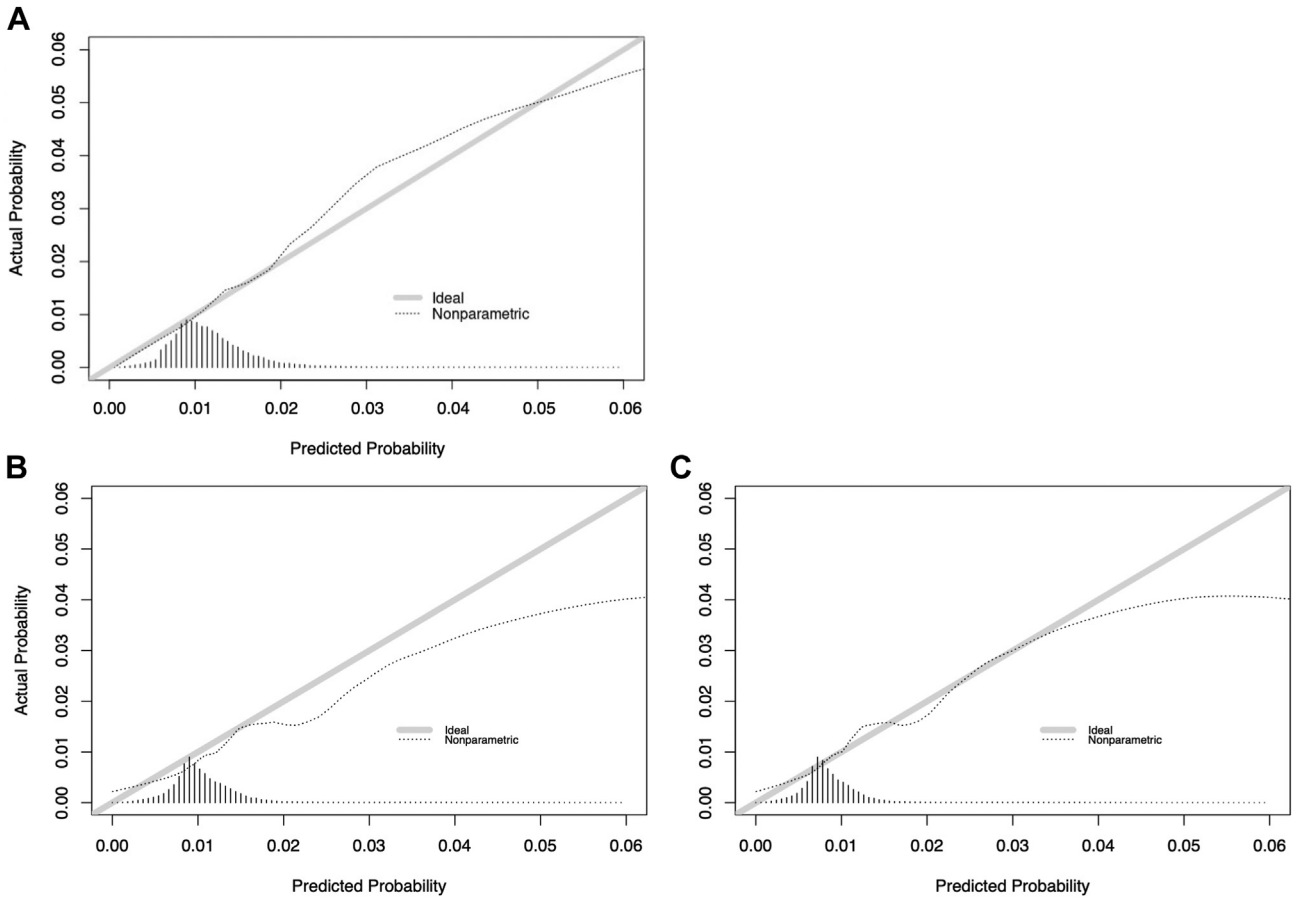

FIGURE A) Calibration plot in development cohort. B) Calibration plot in validation cohort. C) Calibration plot after recalibration of the intercept in the validation cohort. Gray line: ideal calibration line in which the predicted and observed probabilities for venous thromboembolism are similar. Dotted black line: non-parametric calibration line for the TRiP(plasty) score.

TABLE 4 Stratified mean observed and predicted risks by the TRiP(plasty) score.

	Observed 90-day VTE risk		Proportion of population	
Predicted risk	Development	Validation	Development	Validation
0%-1%	0.70%	0.76%	35.4%	69.4%
≥1%-1.5%	1.29%	1.28%	41.1%	23.1%
≥1.5%	2.52%	2.40%	23.4%	7.5%
			100.0%	100.0%

were not included in the development cohort (estimated at 24% of total performed arthroplasties in the UK). In contrast, in the validation cohort, patients undergoing arthroplasty at private clinics were included. This may explain the differences as patients treated in private facilities are usually healthier and thus have a lower VTE risk [26]. Alternatively, differences in not only socioeconomic status but also postoperative rehabilitation could have led to a higher VTE risk in England than in Denmark (time frame, 2016-2019). Patients in England had, during the study time frame (2010-2019), a median length of stay of 4-days (IQR, 3-4) compared with 1 day (IQR, 1-2) in Denmark. Nonetheless, it is important to realize that an average risk in a population is determined by the prevalence of the risk factors in that population. The effect of a separate risk factor on the risk is not determined by its prevalence (eg, smoking increases the risk of lung cancer X-fold irrespective of the prevalence of smoking). This implies that the coefficients in a model should perform equally in different populations, despite differences in prevalence and therefore also in average risk. This is clearly the case in our study, where model performance, in particular calibration, was very good and similar between the 2 populations, even if the average risk differed. Third, the calibration analyses showed an overestimated risk above a risk threshold of 4% in both cohorts. As only 3.0% and 1.3% of patients in the development and validation cohort, respectively, had a predicted risk above 4%, these risks were underrepresented during modeling or validation. Clinically, this overfitting, however, has nearly no clinical implications as individuals with a VTE risk of, for example, 4% or 8% will most likely be treated similarly; they might both need an intensified thromboprophylaxis strategy as compared with the current prophylactic advice. It can be argued that it is most relevant to properly distinguish low-risk patients because a decision to lower or omit anticoagulation completely in this group may have serious consequences if the estimation has been flawed. Fourth, both countries had 2 very different thromboprophylaxis protocols following surgery. Unfortunately, individual patient data on the actual administered thromboprophylaxis were not available. In England, NICE (National Institude for Health and Care Excellence's guidelines (2009) advised to provide thromboprophylaxis for 28 to 35 days following THA and for 10 to 14 days following TKA, in combination with mechanical prophylaxis at admission. This advice was in place for the study period, supported by a national VTE prevention program [27]. In Denmark, thromboprophylaxis is advised for max 10 days following THA/TKA, unless arthroplasty is performed in hospitals that run specific fast-track THA/TKA programs. In that case, when the hospital stay does not exceed 5 days, thromboprophylaxis is only recommended during in-hospital stay. By comparing these national guidelines, the NICE guidelines direct toward more extensive prophylaxis than the Danish guidelines. This may mean that with similar thrombosis prophylaxis strategies, the difference in baseline risks between the 2 populations might have been stronger. However, the similar performance of the model in both cohorts suggests that the model performance itself would not have been affected by a stronger baseline difference. Therefore, we assume that the predicted risks by the model were not influenced by the intensity or duration of thromboprophylaxis as administered. Similarly, in a previous study on the risk of VTE following arthroplasty using data from the Nordic Arthroplasty Register Association group, the authors reported no difference in VTE risk following a short (1-5 days), standard (6-14 days), or extended (>15 days) thromboprophylaxis interval [28]. Lastly, misclassification, in particular for the outcome, could have influenced model performance. All patients with VTE were "medically attended" and therefore considered to be symptomatic. In the development data, VTE was identified using NHS Read codes from the RCGP RSC records. The RCGP RSC sentinel network has been used extensively to study VTE. This includes diabetes, and more recently explores possible adverse events of interest extensively following COVID-19 vaccination [29–32]. To verify the validity of the VTE diagnoses, the incidence of VTE was calculated within the RCGP RSC population and found to be 1.5/1000 person-years which is comparable with previous population-based incidence reports [33–36]. Furthermore, the validity of cardiovascular disease prevalence in RCGP RSC has been studied before and found to be in line with that of the population in the UK [37]. In the validation cohort, a diagnosis of VTE was obtained from the DNPR. VTE diagnostic codes have been studied extensively in earlier studies. For a first VTE, the accuracy of VTE diagnoses within the DNPR is high at 88% (95% CI, 80-93) [38]. In addition, the validity of VTE is most likely not related to exposure of interest (THA/TKA) in our study. Altogether, misclassification will therefore have a negligible impact on model performance.

A systematic review in 2018 reported 5 existing risk prediction models for postoperative VTE following joint replacement [39]. None of these models has been generally implemented in practice because of methodological issues, including inadequate reporting of model statistics, lack of data availability, and lack of sufficient (external) validation. For example, in a retrospective study among 24 567 patients, 1.1% of patients developed pulmonary embolism (no available DVT data). A nomogram was developed but no external validation was performed [14]. In a cohort study from the United States, 1 721 806 THA/TKA procedures were performed, of whom 0.9% developed in-hospital VTE. Out-of-hospital VTEs were not considered [13]. A risk score was developed, including 26 predictors, which showed good calibration; however, discriminatory statistics were not reported. No clear external validation analyses were shown and no model parameters were provided to enable external validation. Nevertheless, the authors did present the association between VTE and predictors

included in the model, some of which, overlapped with candidate predictors in our study. Bateman performed an (underpowered) external validation of the Caprini score to predict postoperative VTE risk, the Caprini score did not prove to be an accurate risk stratification tool due to poor discrimination. Furthermore, the complexity of the score led to misclassification and calculation errors [15,40]. A similar finding was reported by another validation study [12]. In a recent study, a risk model for DVT, pulmonary embolism, and major bleeding was developed separately using machine learning techniques. Unfortunately, no external validation was performed and the algorithm consisted of >40 items which makes it, in our opinion, impractical to work with [18].

The TRiP(plasty) score may potentially lead to new preventive strategies by accurately estimating an individual's postoperative VTE risk. With this knowledge, the dosage and duration of thromboprophylaxis can be tailored toward an individual's risk [41]. There is no agreement on risk thresholds to classify patients as low- or high-risk individuals and determining a tolerable postoperative VTE risk is not straightforward. Current clinical practice, however, leads to a VTE risk in the entire THA/TKA population of about 1.0% to 1.5%, which is deemed acceptable. The TRiP(plasty) score was able to identify a large (70% of the validation population) low-risk group with a mean VTE risk of only 0.76%. One could argue to lower the amount of thromboprophylaxis in this group (predicted VTE risk <1.0%), for example, to an in-hospital-only regime. Several Danish cohort studies have shown the safety (no increased VTE risk) of such an approach in a selected fast-track surgery setting [7,8,42]. In contrast, the TriP(-plasty) score was able to identify 22% of patients with a VTE risk of 1.3% and another 7.7% of patients with a VTE risk of 2.4%, who develop VTE despite thromboprophylaxis (in the validation cohort). The current dose and duration of thromboprophylaxis are not sufficient to prevent VTE in these patients, given the occurrence of VTE despite thromboprophylaxis. Hence, an intensified thromboprophylaxis regimen (for instance therapeutic dose and extended duration) might be warranted to further lower VTE risk in patients with a high risk. Overall, such an individualized approach could save health care costs and potentially lead to less thrombosis and bleeds. Especially as the number of THAs/TKAs worldwide is expected to grow significantly, which will lead to tens of thousands of patients who will be affected by VTE and its long-term consequences, such as post-thrombotic syndrome, pulmonary hypertension, bleeding complications due to anticoagulant treatment, recurrent VTE, and even death [43].

An individualized thromboprophylaxis strategy warrants further investigation to test its efficacy and safety, preferably by a so called "impact" study. Meanwhile, the TRiP(plasty) score can be used to assess and manage VTE risk in clinical practice on an individual basis.

ETHICS STATEMENT

The development study was approved by the London – Surrey Borders Research Ethics Committee (Feb 2019; ref 19/LO/0114) And Joint Research and Surveillance Centre Committed of the RCGP and the University of Surrey. The validation study was reported to the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number 880).

AUTHOR CONTRIBUTIONS

B.N., M.W., L.R., S.I.C., S.C., and R.A. conceived and designed the study. B.N., M.S., A.B.P., E.B.K., S.d.L., and R.A. acquired, linked, and cleaned the data. B.N., M.S., E.B.K., and S.I.C. were responsible for statistical analysis. B.N. wrote the first draft. All authors interpreted the results and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DECLARATION OF COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form. B.N. and S.C. declare support from The Netherlands Thrombosis Foundation and B.N., L.R., and M.W. declare support from Sanofi for this investigator-initiated study. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

DATA AVAILABILITY

UK data were obtained from the Oxford Royal College of General Practitioners Research and Surveillance Centre, Hospital Episodes Statistics and Office for National Statistics. Danish data were obtained from the Danish Hip Arthroplasty Registry, the Danish Knee Arthroplasty Registry, the Danish National Patient Registry, and the Danish National Prescription Registry. Data are not publicly available.

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SUPPLEMENTARY MATERIAL

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