Prediction of significant bleeding during vitamin K antagonist treatment for venous thromboembolism in outpatients

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Summary

Bleeding is the most concerning complication associated with anticoagulant therapy but poorly characterized and important for risk/benefit assessment. We developed a risk stratification score to predict vitamin K antagonist (VKA)-associated bleeding in venous thromboembolism (VTE) using the UK Clinical Practice Research Datalink. Significant bleeding events in outpatients consisted of major bleeding and clinically relevant non-major bleeding requiring hospitalisation (CRNMB-H) within 90 days of VKA initiation. A scoring scheme for predicting bleeding was developed from sub-hazard ratios, validated using cross-validation and expressed by the C-statistic. The study cohort consisted of 10,010 patients with first VTE receiving initial VKA treatment, mean age 62±2 years. Between 2008 and 2016, 167 significant bleeding events were recorded (1.7%), i.e. incidence rate was 7.4/100 person-years. Independent predictors for community-acquired significant bleeding included active cancer, trauma/surgical procedure, male gender, dementia, liver disease, anaemia, history of bleeding, cerebrovascular, renal and chronic pulmonary disease, VTE presenting as pulmonary embolism and age over 75. The overall C-statistic was 0.68 (95% CI, 0.60–0.76), 0.75 (0.60–0.88) for major bleeding and 0.65 (0.55–0.75) for CRNMB-H, and higher than in other risk schemes applied to our study population. The developed risk score may identify patients having a significant bleeding risk, in particular major bleeding events, in outpatients.

Keywords: venous thromboembolism, anticoagulants, vitamin K antagonists, bleeding, prediction score.

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Patients with acute venous thromboembolism (VTE) require urgent anticoagulant therapy unless they have a contraindication such as active bleeding (Kearon et al., 2016). Bleeding is the most concerning complication associated with anticoagulant therapy. Bleeding may be either spontaneous or provoked and may either occur in outpatients or in hospital. The most worrying type of bleeding is that occurring in outpatients which may require medical attention, lead to hospitalisation or be fatal.

The rate of bleeding is highest in the first three months after treatment initiation, and the aetiology and pattern of bleeding is considered to be different from bleeding that occurs later (Klok et al., 2015; Kearon et al., 2016). In a meta-analysis of VTE patients, the first three months of vitamin K antagonist (VKA) therapy was associated with a 2.1% risk of major bleeding, and a case-fatality rate of 9.3% (Linkins et al., 2003). However, most of the individual studies examining this subject have had few patients and very few major bleeds, averaging around 350 patients and less than 10 major bleeds per study. Bleeding rates, sites and outcomes vary with VKA and non-VKA oral anticoagulants (NOACs) (Es et al., 2014; Klok et al., 2015; Inohara et al., 2018). During hospitalisation, many procedures and therapies increase the risk of non-anticoagulation-related bleeding events and confound the risk of bleeding associated with VKA. Hence we examined the community-acquired bleeding outcomes in an outpatient cohort of VTE patients during the first three months of therapy with VKA.

Anticoagulation-associated bleeding scores have been derived from different cohorts, mainly atrial fibrillation (Gage et al., 2006; Pisters et al., 2010; Fang et al., 2011; O’Brien et al., 2015), and to a lesser extent venous
thromboembolism (Kuijer et al., 1999; Ruiz-Gimenez et al., 2008; Klok et al., 2016; Seiler et al., 2017), invasive vascular procedures or mixed indications (Landefeld & Goldman, 1989; Beyth et al., 1998). The VTE scores assessed different time periods of anticoagulation treatment, for example restricted to the first month, after the first month, up to three months or up to three years of treatment (Pisters et al., 2010; Klok et al., 2016), and have used various bleeding definitions. Most often, the data source was from healthier, lower-risk clinical trial populations with relatively few bleeds contributing to the scores (Kuijer et al., 1999; Ruiz-Gimenez et al., 2008; Klok et al., 2016).

There is room for improvement in the current recognition of bleeding risk in patients with VTE. An understanding of the predisposing factors allows appropriate advice to be given and facilitates risk/benefit calculations resulting in the optimal length and intensity of anticoagulation therapy. This observational study investigates the predictors for the most clinically significant bleeds: the major bleeds and clinically relevant non-major bleeds requiring hospitalisation (CRNMB-H) in patients with VTE who commence treatment with VKA. We aimed to develop a scoring scheme for better prediction of community-acquired VKA-associated bleeding events.

Methods

Data source

This study used data from the subset of over 4.5 million individuals in the UK Clinical Practice Research Datalink (CPRD) who were eligible for additional data from the English Hospital Episodes Statistics (HES) including Admitted Patient Care data, Diagnostic Imaging data and Accident and Emergency data, and Death Registration data from the Office for National Statistics. CPRD is based on primary care and includes demographics, medical history, symptoms, diagnoses, referrals, laboratory data (tests and results) and prescriptions issued by general practitioners (GPs). HES Admitted Patient Care data include ethnic origin, admission and discharge dates, coded primary and other main discharge diagnoses, and surgical operations and procedures performed during hospital stay. HES Diagnostic Imaging Dataset is a collection of detailed information about diagnostic imaging tests, such as X-rays and MRI scans, and HES Accident and Emergency data consist of individual records of patient care administered in the accident and emergency setting. Mortality data contain the date and cause of death in death certificates.

Study cohort and design

The study cohort was formed from patients with a record for VTE in general practice or inpatient hospital setting. The cohort consisted of patients with a first VTE between January 2008 and March 2016 who were given VKA within 30 days of the initial VTE. VKA use was identified from: prescriptions for warfarin, acenocoumarol, or phenindione, medical codes indicating VKA use or records of international normalized ratio (INR) monitoring and INR test results.

Potential cases were required to have been registered with the CPRD for at least one year before the first VTE event. This one-year pre-enrolment period was used to describe the baseline characteristics. Patients with a history of VTE before the start of the study period (January 1, 2008) or during the one-year pre-enrolment period, with a history of post-thrombotic syndrome, with a history of ≥ 2 VKA prescriptions before the initial VTE diagnosis, and patients with atrial fibrillation or cardiac valve replacement recorded any time were excluded from the study cohort.

Patients with an abdominal vein thrombosis or intracranial/intraspinal thrombosis recorded within 30 days before or after a GP-diagnosed VTE, or with VKA initiation after the occurrence of the respective study outcome were also excluded from the study cohort.

Definition of venous thromboembolism

All cases with a first diagnosis of VTE during the study period were identified using an algorithm that was previously developed and validated by the authors. Briefly, the algorithm was based on GP-based medical records and clinical notes, use of oral and parenteral anticoagulants, hospital discharge diagnoses and data for causes of death. The sensitivity for detecting VTE was 92.6% and its specificity was 98.8% (Martinez et al., 2014).

Observational period

The observational period started on the date of initiation of VKA treatment, one day following hospital discharge for those with a VTE diagnosed in hospital or seven days after the VTE event for those with a primary-care diagnosis, whichever occurred last. The observational period ended when the patient left the practice, died, discontinued VKA treatment, at the end of the study period (March 2016), a first respective bleeding event, or 90 days after initiation of VKA treatment, whichever occurred first.

The duration of a single prescription of a VKA was derived from the median number of days between consecutive respective prescriptions. Repeat prescriptions of a VKA were concatenated when subsequent prescriptions for VKA were issued within the calculated day supply of the previous prescription. Delays in repeat prescriptions and lack of patient compliance or residual drug effect were accounted for by adding a grace period of 30 days at the end of each VKA prescription. To consider bridging, episodes of VKA treatment with an interruption of up to 21 days were assumed to be continuous when: (i) low molecular weight heparins were prescribed before the end of the calculated oral
anticoagulant exposure including the 30-day grace period, and (ii) new VKAs were prescribed within 21 days after the low molecular weight heparin prescription.

VKA use was considered discontinued when there was no subsequent VKA record before the calculated end of the treatment episode, or there was a recording indicative of anticoagulant discontinuation.

Clinical outcomes

The clinical outcomes consisted of manually reviewed community-acquired significant bleeding events comprising major bleeding and CRNMB-H.

Major bleeding. Major bleeding events were required to be: (i) a fatal bleeding (recorded as one of the first three underlying causes of death), (ii) symptomatic bleeding at a critical site (i.e. intraocular bleeding in non-diabetics, intracranial, intraspinal, pericardial, intra-articular, retroperitoneal or intramuscular bleeding), or a hematoma and a compartment syndrome recorded within seven days, (iii) record of post-haemorrhagic anaemia or a bleeding event followed by a blood transfusion or a record for anaemia within seven days, or (iv) bleeding with a drop in haemoglobin level of > 20 g/l within 14 days (Schulman et al., 2005).

CRNMB-H. CRNMB-H consisted of bleeding events that resulted in hospitalisation but did not satisfy the criteria of major bleeding. CRNMB-H was identified from hospital diagnosis codes (recorded as first or second discharge diagnosis) or hospital procedure codes.

Manual review. By utilizing HES Admitted Patient Care, Diagnostic Imaging and Accident and Emergency data, and GP-records including symptoms, signs, laboratory results and diagnostic imaging tests, therapies including transfusions, discharge diagnoses and causes of death, all potential significant bleeding events were reviewed by three specialist physicians experienced in management of VTE who were blinded to any anticoagulation treatment. The following information was assigned to each case: (i) whether the bleeding was community or hospital-acquired, (ii) whether the bleeding was acute or chronic, (iii) the site of bleeding (critical site, gastrointestinal, urogenital, other), (iv) whether the bleeding led to hospitalisation, (v) whether the bleeding required a blood transfusion, was associated with a record of post-haemorrhagic anaemia or a drop in haemoglobin level of > 20 g/l, and (vi) whether the bleeding was fatal. Bleeding events that occurred in the hospital setting were excluded. Community-acquired significant bleeding events were then adjudicated into major bleeding and CRNMB-H.

Covariates

Baseline characteristics of interest were age, gender, body mass index (BMI), smoking and drinking status, type of incident VTE comprising pulmonary embolism (PE) and deep vein thrombosis (DVT), and history of bleeding events.

Study variables were clinical conditions known as provoking factors, i.e. cancer, all surgical procedures (major and minor), trauma, pregnancy or childbirth, and oestrogen and hormone replacement therapy. Cancer comprised any admission to hospital with a diagnosis of cancer (excluding non-melanoma skin cancer), radiation or chemotherapy treatment, or bone marrow transplantation. Cancer was considered active for 90 days following a cancer-related recording. Repeat cancer-related recordings were concatenated to form active cancer episodes when subsequent diagnoses or therapies were recorded within 90 days of the previous cancer-related recording. Other potential outcome predictors included liver disease, anaemia, renal disease, hypertension, dementia, cerebrovascular disease, chronic pulmonary disease and peripheral vascular disease and were defined from hospital discharge diagnoses and medical codes entered by GPs, use of non-steroidal anti-inflammatory drug, antiplatelets and corticosteroids. Renal disease was also defined by a creatinine clearance < 50 ml/min derived from serum creatinine levels. Haemoglobin levels < 130 g/l in males and < 120 g/l in females also defined anaemia. Use of non-steroidal anti-inflammatory drug, antiplatelets and corticosteroids was defined from GP-issued prescriptions.

Statistical analyses

Selection of score components and score development. Clinical and laboratory variables consistently identified as components in published risk scales were classified as established risk factors. Other potential predictors for either major bleeding or CRNMB were chosen based on expert opinion among the study investigators. All established risk factors were included in the final Fine and Gray model (Fine & Gray, 1999). Other potential predictors were included in the final model as follows: (i) for each potential predictor, a univariate competing risk regression (accounting for the competing risk of death unrelated to bleeding) was performed. Those with a P-value of > 0.2 based on the likelihood ratio test for the association between the respective factor and the bleeding event were not considered in the further analysis. (ii) The final set of other potential predictors included in the final model were determined by a stepwise multivariate competing risk regression including all established risk factors and potential predictors derived as described in (i). Risk factors were removed in a stepwise manner if P > 0.2. (iii) The set of risk factors remaining in the final model were used for all subsequent analyses. The scoring scheme for the prediction of community-acquired significant bleeding events was developed from the sub-hazard ratios from the final model.

Model validation. The derived score for prediction of community-acquired significant bleeding events during VKA treatment was validated by assessing its discrimination and calibration.

The discrimination of the new score, i.e. the ability to separate individuals who develop a bleeding event from those who do not, was assessed by estimation of the C-statistics.
using five-fold cross-validation with 40 replications. C-statistics were derived and validated within the complete study cohort. Furthermore, the new scoring scheme was validated within the subcohort of patients with DVT/PE, of patients with cancer at baseline, for the first month (unstable anticoagulation) and the two subsequent months after VKA initiation (stable anticoagulation), and for the two components of the study outcome (major bleeding and CRNMB-H). In addition, we examined whether our score had better discrimination (C-statistic) when compared directly to existing clinical scores to predict major bleeding within 90 days of anticoagulation therapy in patients with VTE (Kuijer et al., 1999; Ruiz-Gimenez et al., 2008; Klok et al., 2016).

To assess the calibration of the score, the aggregated score points were collapsed into ‘low’, and ‘high’ risk groups using a cut-off score which empirically indicated to optimally discern low- from high-risk groups and incidence rates were calculated. Furthermore, the study cohort was split into five subgroups based on quintiles of risk. Within each of these five subgroups, the observed and expected number of bleeding cases was compared and a goodness-of-fit test was performed based on these comparisons (Hosmer & Leme-show, 1999).

All statistical procedures were performed using Stata MP Version 14.2 (StataCorp LLC, College Station, TX). The study protocol was approved by the Independent Scientific Advisory Committee for CPRD research, protocol 16_018RMnA.

Results

A total of 10,208 patients with incident VTE and initiation of VKA use, mainly warfarin 99.9%, within 30 days were identified. Of those, 198 were excluded, most of them because of a concurrent history of potential major bleeding or CRNMB-H events (Fig 1). The study cohort at risk of community-acquired significant bleeding events consisted of 10,010 patients, mean age 62.2 ± 17.1, mean BMI 28.9 ± 6.4, and DVT in 57.0%, PE in 43.0% and 16.8% current smokers. A provoking factor before the VTE was found in 33.5% and included medical illness (10.9%), active cancer (7.5%), trauma (6.3%) and surgical procedure (6.6%). The mean Charlson index was 4.5 ± 3.2, and 14.0% had a history of anaemia in the six months before the VTE. A past history of major bleeding was recorded in 3.4% and CRNMB in 31.1% (Table I).

During the 2258 person-years of observation, 167 community-acquired significant bleeding events were observed during the 90 initial days of VKA use, 44 major bleeding events and 123 CRNMB-H events. A significant fatality rate was observed for major bleeds, 27.3% (Table II). The 90-day cumulative incidence of community-acquired significant bleeding events following initiation of VKA treatment was 1.8%, 0.5% for major bleeding and 1.3% for CRNMB-H (Figure 2). The risk of community-acquired significant bleeding decreased notably during anticoagulation to about one-third of the initial risk at three months after VKA treatment initiation (Figure 3).

Predictors for the community-acquired significant bleeding events were male gender (two points), age over 75 (one point), VTE presenting as PE (one point), BMI below 25 (one point) or over 30 (one point), history of major bleeding or CRNMB (one point), new diagnosis of active cancer after VTE (six points), known active cancer at VTE (two points), trauma/surgical procedure (three points), liver disease (two points), dementia (two points), anaemia within 182 days before the VTE (one point), renal disease (one point), cerebrovascular disease (one point) and chronic pulmonary disease (one point) (Table III).

The overall incidence rate of community-acquired significant bleeding events was 7.4 (167 of 2258 person-years) per 100 person-years of VKA treatment and increased by score, 5.5 per 100 person-years in the low-risk group with ≤6 score points and 28.1 per 100 person-years in the high-risk group (Table IV).

The score yielded a C-statistic of 0.68 (95% CI 0.60 to 0.76) for community-acquired significant bleeding events. In patients with DVT and PE, the C-statistic was 0.70 (0.57 to 0.81) and 0.65 (0.51 to 0.77) respectively. The application of our score to patients with and without cancer yielded a C-statistic of 0.65 (0.44 to 0.87) and 0.65 (0.54-0.74) respectively, in the unstable and stable anticoagulation phase 0.68.

Fig 1. Ascertainment of VKA-naïve cohort with first VTE at risk of community-acquired significant bleeding. CRNMB-H: clinically relevant non-major bleeding requiring hospitalisation; NOAC: non-VKA oral anticoagulant; VKA: vitamin K antagonist; VTE: venous thromboembolism.

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NSAID: nonsteroidal anti-inflammatory drug; VTE: venous thrombosis.

Table I. Baseline characteristics of the study cohort at risk of community-acquired significant bleeding events (N = 10 010).

| Study cohort* |     |
|---------------|-----|
| Male sex, n (%) | 4978 (49-7) |
| Age, yr        | 62.2 ± 17.1 |
| Body mass index, kg/m² | 28.9 ± 6.4 |
| Current smoker, n (%) | 1667 (16-8) |
| Type of first VTE, n (%) |     |
| Deep vein thrombosis | 5706 (57-0) |
| Pulmonary embolism    | 4304 (43-0) |
| History of bleeding prior to first VTE, n (%) |     |
| Major bleeding        | 344 (3-4) |
| Clinically relevant non-major bleeding | 3112 (31-1) |
| Presence of provoking factors for VTE, n (%) |     |
| Active cancer        | 746 (7-5) |
| Cancer history (>90 days) | 601 (6-0) |
| Surgical procedure (30 days) | 660 (6-6) |
| Trauma (30 days)     | 630 (6-3) |
| Medical illness (90 days) | 1090 (10-9) |
| Pregnancy            | 72 (0-7) |
| Delivery or termination of pregnancy (90 days) | 133 (1-3) |
| Oestrogens and hormone replacement therapy (30 days) | 196 (2-0) |
| Charlson index       | 4.5 ± 3.2 |
| Other comorbidities, n (%) |     |
| Hypertension         | 5469 (54-6) |
| Polycythaemia        | 52 (0-5) |
| Superficial thrombophlebitis | 283 (2-8) |
| Varicose veins       | 1 334 (13-3) |
| Anaemia (182 days)   | 1 399 (14-0) |
| Renal disease        | 2 282 (22-8) |
| Liver disease        | 216 (2-2) |
| Peptic ulcer disease | 476 (4-8) |
| Any history of stroke | 163 (1-6) |
| Comedications at VTE, n (%) |     |
| Current antplatelet use | 1 196 (11-9) |
| Current NSAID use    | 1 247 (12-5) |
| Use of corticosteroids (182 days) | 1 348 (13-5) |

NSAID: nonsteroidal anti-inflammatory drug; VTE: venous thrombosis.

*Plus/minus values are means ± SD.

(0.60 to 0.76) and 0.66 (0.54 to 0.79) respectively, for major bleeding 0.75 (0.60 to 0.88) and for CRNMB-H 0.65 (0.55 to 0.75) (Table V). The goodness-of-fit test for the scoring yielded a satisfactory calibration, \( P = 0.38 \).

The application of the existing bleeding risk schemes to our study population yielded consistently lower C-statistics for community-acquired significant bleeding and for its components major bleeding and CRNMB-H from 0.55 to 0.69 (Table VI).

**Discussion**

Accurate prediction of the risk of significant bleeding events in patients with VTE is essential for the management of anticoagulation therapy. Our score of 13 demographic and clinical variables has an added value and compares favourably with the three existing bleeding risk schemes for VTE yielding consistently higher C-statistics for the risk of community-acquired significant bleeding and in particular for its component major bleeding. Our score accurately differentiates patients with VTE anticoagulated with VKA into high-risk and low-risk bleeding categories. For community-acquired significant bleeding events the rates for the high-risk and low-risk categories were 28·1 per 100 person-years and 5·5 per 100 person-years respectively. The rates for major bleeding were 10·3 versus 1·2 per 100 person-years and for clinically relevant non-major bleeding requiring hospitalisation were 17·9 versus 4·3 per 100 person-years respectively.

We were able to recognize and confirm many of the risk factors for bleeding described variably in previous studies including age ≥75 years, liver disease, renal disease, a history of major and clinically relevant non-major bleeding and anaemia (Nieto et al., 2010; Fang et al., 2011; Kearon et al., 2016; Klok et al., 2016). Our scoring scheme included baseline characteristics prior to the first VTE and new events provoking bleeding after VKA initiation. Post-VTE diagnosed cancer was the strongest predictor for community-acquired significant bleeding events with six score points followed by trauma or surgical procedures with three score points. All other predictors were allocated either two or one score points each. We found that 14-4% of all bleeding events (22.7% of major bleeding and 11.4% of CRNMB-H) were associated with new provoking factors (i.e. new cancer diagnosis, trauma or surgical procedure) after VKA initiation. The inclusion of new provoking events after VKA initiation resulted in a dynamic scoring scheme. Such information on new provoking events should be taken into account and the patient’s bleeding risk and benefit be reconsidered. Many established bleeding schemes are based on the information available at the time of initiation of anticoagulation treatment and do not include any events that either increase or decrease the bleeding risk afterwards. The C-statistic of our score improved by 0.03 overall and for both bleeding subtypes when new provoking events after VKA initiation were considered. Established bleeding schemes might become better predictors for bleeding events if they consider new provoking events.

Major bleeding, defined in terms of the International Society for Thrombosis and Haemostasis (ISTH) or other criteria, is often reported in studies examining risk and risk prediction and yet there are little data in the literature on CRNMB-H. CRNMB-H is important in terms of morbidity.
and resource use and is likely to be a factor in determining whether patients continue or stop anticoagulation. Additionally, some types of major bleeding, for example some intra-articular bleeds not requiring hospitalisation, may not be as clinically significant as some ‘non-major’ bleeds such as gastrointestinal bleeds requiring hospitalisation and endoscopy. Therefore we investigated predictors of the combination of major bleeding and CRNMB-H as this might be clinically more relevant than major bleeding alone. Major bleeding was associated with a significant case-fatality rate of 27.3%. Gastrointestinal and intracranial bleeding were most commonly associated with mortality. The frequency of bleeding in the different sites was consistent with other recent studies (Green et al., 2018).

We examined the first three months of anticoagulation with VKA because the risk of bleeding is highest over that time period, and particularly high in the first month (Kearon et al., 2016). This may in part be due to known or previously

Table II. Type and site of community-acquired significant bleeding events within 90 days of VKA treatment of first venous thromboembolism.

| Type                                | Significant bleeding events, n (%) | Fatal events, n (%) |
|-------------------------------------|-----------------------------------|--------------------|
| Major bleeding                      | 44 (100-0)                        | 12 (27-3)          |
| Intracranial bleeding               | 20 (45-5)                         | 5 (25-0)           |
| Gastrointestinal bleeding           | 9 (20-5)                          | 5 (55-6)           |
| Other critical site bleeding*       | 15 (34-1)                         | <5                 |
| Clinically relevant non-major bleeding requiring hospitalisation | 123 (100-0) | NA |
| Bleeding complicating a procedure†  | 5 (4-1)                           |                    |
| Epistaxis                           | 14 (11-4)                         |                    |
| Upper gastrointestinal bleeding     | 24 (19-5)                         |                    |
| Lower gastrointestinal bleeding     | 11 (8-9)                          |                    |
| Undetermined site gastrointestinal bleeding | 6 (4-9) | |
| Gynaecological bleeding             | 9 (7-3)                           |                    |
| Haematuria                          | 37 (30-1)                         |                    |
| Haemoptysis                         | 13 (10-6)                         |                    |
| Other site of bleeding‡             | <5                                |                    |

NA: not applicable.
*Haemopericardium, intraocular bleeding or haemarthrosis.
†Refers to patients with in-hospital procedures who were discharged and then readmitted because of a bleeding event.
‡Comprises haemorrhage of prostate, haemorrhage not elsewhere classified (probable haematuria), haemoperitoneum and intramuscular bleeding.

Fig 2. Cumulative incidence of community-acquired significant bleeding, clinically relevant non-major bleeding requiring hospitalisation and major bleeding by time since initiation of vitamin K antagonist therapy.

Cumulative incidence of bleeds accounting for (non-bleeding-related) mortality as a competing risk
unknown risk factors, the temporal relationship to provoking factors, the combining of parenteral anticoagulants with VKA or the early instability of VKA dosing and response.

The clinical value of the three-month bleeding risk prediction score is to identify patients with a high risk to prevent significant bleeding by closer monitoring of anticoagulation and being sensitized for the bleeding risk, and considering treatment with anticoagulants other than VKA.

**Strengths and weaknesses of the study**

The study cohort was real-world-based, consisting of a large unselected and heterogeneous cohort of over 10,000 patients with VTE treated with VKA, and followed up for three months, the period which is associated with a high risk of bleeding events (Figure 3).

Our analysis was based on a total of 167 bleeding events compared with a total of 110 bleeding events (25 major bleeding and 85 CRNMB) any time after randomisation in the most recently conducted study (Klok et al., 2016). Internal validity was achieved by using cross-validation by randomly splitting the study cohort into five subcohorts, and estimating the C-statistic with 40 replications. This approach yielded a C-statistic of 0.68 (95% CI, 0.60 to 0.76) and good calibration by the goodness-of-fit test (P = 0.38). As these were incident cases of VTE including the early phase of anticoagulation, we were unable to investigate the association with labile INR measurements.

Despite the cross-validation used in the current score development, the discriminatory power of our score may be overestimated and hence our score needs to be confirmed and validated externally in other cohorts. The application of established bleeding risk schemes to our study population

| Significant bleeding events | Adjusted SHR (95% CI) | Score points |
|-----------------------------|-----------------------|-------------|
| Male sex                    | 94                    | 1.66 (1.19–2.30) | 2          |
| Age 75+, yr                 | 66                    | 1.21 (0.78–1.87) | 1          |
| Type of VTE                 |                       |              |            |
| Pulmonary embolism          | 81                    | 1.29 (0.94–1.77) | 1          |
| Body mass index, kg/m²     |                       |              |            |
| <25                         | 53                    | 1.41 (0.93–2.14) | 1          |
| 30+                         | 53                    | 1.30 (0.87–1.93) | 1          |
| History of bleeding         |                       |              |            |
| Major bleed or clinically relevant non-major bleeding | 75 | 1.63 (1.19–2.24) | 1          |
| Provoking factors for VTE*  |                       |              |            |
| Early post-VTE active cancer| 16                    | 7.92 (4.33–14.49) | 6          |
| Trauma/surgical procedure  | 15                    | 2.36 (1.32–4.22) | 3          |
| Persisting active cancer    | 19                    | 1.69 (0.99–2.88) | 2          |
| History of other comorbidities |                 |              |            |
| Liver disease               | 7                     | 1.67 (0.77–3.62) | 2          |
| Dementia                    | 11                    | 2.29 (1.09–4.79) | 2          |
| Anaemia (182 days)          | 47                    | 1.65 (1.12–2.43) | 1          |
| Renal disease               | 61                    | 1.41 (0.94–2.12) | 1          |
| Cerebrovascular disease     | 21                    | 1.57 (0.94–2.62) | 1          |
| Chronic pulmonary disease   | 94                    | 1.31 (0.94–1.82) | 1          |

CI: confidence interval; SHR: sub-hazard ratio; VTE: venous thromboembolism.

*Time-dependent mutually exclusive provoking status, applying the hierarchy 'Early post-VTE active cancer' > 'Persisting active cancer' > 'Trauma/surgical procedure'.

Table III. Score for prediction of community-acquired significant bleeding events (major bleeding or clinically relevant non-major bleeding requiring hospitalisation) within 90 days of VKA initiation.
yielded consistently lower C-statistics for community-acquired significant bleeding and for its components (Beyth et al., 1998; Nieto et al., 2010). However, our data source had incomplete information for some of the laboratory tests which may have resulted in underestimating their validity. Our score was not developed to predict the bleeding risk beyond the first three months after VKA initiation. More studies are needed to describe the bleeding risk after three months of anticoagulation, to assess the benefit and risk of long-term anticoagulation (Seiler et al., 2017).

VTE and bleeding events were defined based on coded information rather than clinical data. However, our VTE algorithm has previously been validated and showed a sensitivity of 92.6% and a specificity of 98.8% (Martinez et al., 2014). Bleeding events were defined according to ISTH criteria and were validated by manual review of all available patient records from three physicians that independently assessed all potential bleeding events.

Table IV. Incidence rates per 100 person-years of community-acquired significant bleeding events within 90 days of VKA initiation by risk category.

| Population at risk, n | Significant bleeding events, n (%) | Person-years | Crude incidence rates* (95% CI) |
|-----------------------|------------------------------------|--------------|---------------------------------|
| Community-acquired significant bleeding | | | |
| Low-risk group (Score points ≤ 6) | 9 165 | 115 (1.3) | 2 074 | 5.5 (4.6–6.7) |
| High-risk group (Score points ≥ 7) | 845 | 52 (6.2) | 185 | 28.1 (21.0–36.9) |
| Major bleeding | 10 010 | 44 (0.4) | 2 258 | 1.9 (1.4–2.6) |
| Low-risk group (Score points ≤ 6) | 9 165 | 25 (0.3) | 2 074 | 1.2 (0.8–1.8) |
| High-risk group (Score points ≥ 7) | 845 | 19 (2.2) | 185 | 10.3 (6.2–16.0) |

CI: confidence interval.
*Incidence rates calculated per 100 person-years.

Table V. Application of developed scores to subgroups of study cohort and of community-acquired significant bleeding events.

| Population at risk, n | Significant bleeding events, n (%) | Person-years | Crude incidence rates* (95% CI) |
|-----------------------|------------------------------------|--------------|---------------------------------|
| Community-acquired significant bleeding | | | |
| Low-risk group (Score points ≤ 6) | 9 165 | 90 (1.0) | 2 074 | 4.3 (3.5–5.3) |
| High-risk group (Score points ≥ 7) | 845 | 33 (3.9) | 185 | 17.9 (12.3–25.1) |

CRNMB-H: clinically relevant non-major bleeding requiring hospitalisation.
*First month of VKA treatment.
†Second and third month of VKA treatment.

Table VI. C-statistics of established bleeding scores in VTE within 90 days following initiation of treatment with vitamin K antagonists.

| Score | Community-acquired significant bleeding | Major bleeding | CRNMB-H |
|-------|----------------------------------------|---------------|---------|
| Our score | 0.68 | 0.75 | 0.65 |
| Ignoring risk factor changes after VKA initiation* | 0.65 | 0.72 | 0.62 |
| Klok et al., 2016 | 0.66 | 0.69 | 0.64 |
| Ruiz-Gimenez et al., 2008 | 0.62 | 0.64 | 0.61 |
| Kuijer et al., 1999 | 0.56 | 0.59 | 0.55 |

CRNMB-H: clinically relevant non-major bleeding requiring hospitalisation; VKA: vitamin K antagonist; VTE: venous thromboembolism.
*Censoring patients at time of a time-dependent provoking event, e.g. trauma/surgical procedure or new use of oestrogens and hormone replacement therapy after VKA initiation.

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In-hospital pharmacy data including anticoagulation use are not available in CPRD. Moreover, medical diagnoses including venous thromboembolism or bleeding events are recorded as hospital discharge diagnoses but the day of occurrence during the hospitalisation is either unknown or uncertain. Consequently, in-hospital data were insufficient to establish the temporal relationship between the status of VKA treatment and the onset of a bleeding event or whether a provoking event preceded the bleeding. To diminish the misclassification of exposure and of outcome which could have resulted in confounded study findings, we excluded bleeding events that occurred during the same hospitalization. For the same reason, patients with a first bleeding event and with a significant bleeding during the same hospital stay were excluded from the study cohort and the developed risk score restricted to predict significant bleeding events during VKA treatment in outpatients only. Currently, a significant percentage of patients with VTE are anticoagulated with VKA. However, this percentage is diminishing as the use of NOACs has increased over the past years. The site and frequency of bleeding differ by anticoagulant type. However, there was an insufficient number of patients with VTE treated with NOACs in our study cohort to investigate predictors of bleeding in association with NOACs separately. Therefore, more studies are needed to identify patients at high risk of bleeding among NOAC users.

Conclusions

A simple risk score was effective in quantifying the risk of VKA-associated community-acquired significant bleeding events in a large cohort of patients with first venous thromboembolism. The risk score was particularly effective for the identification of patients at a high risk of major bleeding. It may prove useful to prevent major bleeding by facilitating the awareness for the bleeding risk and for considering treatment with anticoagulants other than VKA.

Author contributions

CM and ATC were responsible for conception/design of the study. AK, CW and CM were responsible for data acquisition and analysis. All authors were involved in interpretation of the data. CM and ATC were involved in drafting the manuscript, and all authors critically revised it for important intellectual content. CM is the guarantor.

Non-Author Contributions and Disclosures

Prof. Saskia Middeldorp and Dr Marjolein Brekelmans from the Amsterdam UMC, University of Amsterdam, Department of Vascular Medicine, the Netherlands, reviewed and validated all potential bleeding events. Both clinicians were blinded to the exposure of interest.

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Conflicts of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: this work received funding in part from Bristol-Myers Squibb and Pfizer.

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