Development and validation of a risk prediction model for venous thromboembolism in postpartum women: A multinational cohort study

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Abstract

Objective: Despite venous thromboembolism (VTE) being the leading direct cause of maternal mortality in developed countries, clinical risk prediction of VTE in postpartum women is rudimentary. We aimed to develop and validate a risk prediction model for VTE in the first six weeks of delivery (early postpartum)

Design: Cohort study using records from England-based Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES) and Sweden-based registry data.

Setting: Primary and/or secondary care data covering England and Sweden.

Participants: All pregnant women registered with CPRD-HES linked data between 1997 and 2014, and Swedish medical birth registry between 2005 and 2010 with postpartum follow-up.

Main outcome measure: Multivariable logistic regression analysis was performed on the English data to develop a postpartum VTE risk prediction model which was externally validated in the Swedish data.

Results: We identified 433,353 deliveries in the English and 662,387 in the Swedish cohort. The absolute rate of VTE in English and Swedish cohorts was 7.2 and 7.9 per 10,000 deliveries respectively. Emergency caesarean delivery, stillbirth, varicose veins, pre-eclampsia/eclampsia and comorbidities were the strongest predictors of VTE in the final multivariable model. Discrimination of the model was similar in both cohorts, with a c-statistic >0.70, with excellent calibration of observed and predicted risks. Our model identified more VTE events than the existing national English guidelines (sensitivity: 68% versus 63%) and Swedish (30% versus 21%) at similar thresholds.

Conclusion: We have developed and externally validated a new prediction model that quantifies absolute risk of postpartum VTE. It is based on clinical variables that are available in many developed countries at the point of delivery and could serve as the basis for real time decisions on obstetric thromboprophylaxis.

Keywords: Epidemiology, Postpartum, Risk factors, Prediction model, Cohort study, Venous thromboembolism

What is already known?

The risk of venous thromboembolism (VTE) peaks during the first six weeks of delivery (postpartum) and is one of the leading causes of maternal mortality in developed countries. Whilst targeted thromboprophylaxis can prevent VTE, clinical risk prediction of VTE in postpartum women is rudimentary.

What this paper adds?

We have developed and externally validated a risk prediction model that can be used as a tool to identify high-risk women, as it provides a woman's individual absolute predicted VTE risk within the first six weeks postpartum.

Our prediction model is based on clinical variables that are likely to be available at the point of childbirth and performed better than the current UK and Swedish thromboprophylaxis guidelines.

Introduction

The risk of venous thromboembolism (VTE) increases significantly during pregnancy, peaks during the postpartum period and is one of the leading causes of maternal mortality in developed countries.[1,2] In the UK, 50% of VTE-related maternal deaths occur during the postpartum period.[2] Targeted thromboprophylaxis can prevent postpartum VTE with minimum harm; however there are variations in the threshold (set on the basis of certain risk factors) at which intervention is recommended.[3-6] While risk factors such as prior VTE and certain thrombophilias are recognised to warrant intervention on their own, women with these risk factors represent a small proportion of all women giving birth. Indeed, the vast majority of postpartum VTEs occur in women without these specific risk factors. Recommendations for thromboprophylaxis among a large proportion of postpartum women with only one or more "low to moderate" risk factors (e.g., obesity, caesarean section and postpartum haemorrhage) are inconsistent across countries.[3-5] In the UK, in the postpartum period, women are categorised into low, intermediate and high-risk groups with respect to advice on the duration of pharmacological thromboprophylaxis based on an additive ordinal point-based scoring system assigned to each risk factor[5], which is not externally validated. A similar system is used in Sweden[7], which is more conservative than those in the UK and Canada. Such categorisation, while visually pleasing and easily implemented in practice, may disguise the large variation of the actual VTE risk within those risk groups. Thus using a model to make predictions for individual women is more accurate, and is preferred to the risk grouping approach[8,9], currently lacking in practise. Thus, the aim of our study was to develop and externally validate a new prediction model that can generate absolute predicted risk of first VTE within the first six weeks postpartum based on each woman's individualised clinical risk profile, and compare this to the existing Royal College of Obstetricians and Gynaecologists (RCOG)[5] and Swedish[7] thromboprophylaxis guideline.

Methods

Data sources and study population

For this study, we used data from England to develop our postpartum VTE risk score and data from Sweden to externally validate it. We have previously published VTE incidence in both obstetric populations (England and Sweden) and found comparable estimates.[10,11]

Derivation cohort (England)

The Clinical Practice Research Datalink (CPRD)[12] is a large, longitudinal UK primary care database that covers 6% of the UK population. Approximately 98% of the UK population is registered with GPs, who are responsible for almost the entirety of a patient's medical care.[13] All GPs participating in Clinical Practice Research Datalink (CPRD) are trained to record information using the general practice Vision software. More than 50% of CPRD practices are linked to Hospital Episode Statistics (HES) that contains information on all hospitalisations in England. The anonymised patient identifiers from CPRD and HES have been linked by a trusted third party using NHS number, date of birth, postcode and gender. First, patients are matched on the basis of their NHS number (over 90% of patients are linked in this way). The remaining patients are then linked probabilistically on postcode, date of birth and gender. As HES only covers English hospitals, practices from Northern Ireland, Wales and Scotland were excluded. To develop our risk prediction model, we used data on women (registered with a CPRD-HES linked practice) with no previous history of VTE whose pregnancy ended in live birth or stillbirth between 1997 and 2014 and who had at least six weeks postpartum follow-up.

Validation cohort (Sweden)

The Swedish National inpatient register (IPR) was established in 1965 and has complete national coverage since 1987.[14] More than 99% of all somatic and psychiatric hospital

discharges from across Sweden are registered within the inpatient register. From 2001, IPR also includes hospital-based outpatient consultations. Diagnoses in IPR are coded according to the Swedish International classification of disease system (ICD). It is mandatory for all physicians (private and publically funded) to deliver data to the IPR. Each hospital discharge and outpatient consultation is keyed to an individual's unique personal identity number (PIN)[15] which is issued to every individual in Sweden. The PIN is based on the combination of date of birth and a four digit number and is used by various private and public sectors to identify each individual. It is also used by the National Board of Health and Welfare to link data across various registers at the individual level. The Swedish Medical Birth Registry (SBR) contains information since 1973 on more than 98% of all delivery records in Sweden. The SBR has been subjected to numerous quality checks and the recorded data are of high quality and reliable.[16,17]. For the purpose of validating a postpartum thrombosis risk score, we included information on pregnancies in women with no history of VTE resulting in a live birth or stillbirth between 1 July 2005 and 31 December 2011. Using data from 2005 onwards allowed the acquisition of the national prescription data (National Prescribed Drug Register) for all of the Swedish study population.

Defining VTE

Our outcome was defined as the occurrence of a first VTE (deep vein thrombosis or pulmonary embolism) within the first six weeks after delivery. In both our derivation and validation cohorts, VTE was defined using an algorithm externally validated in the UK's primary care data with high accuracy (positive predictive value =84%).[18] Briefly, the algorithm considered a VTE diagnosis to be valid if it is accompanied by an anticoagulant prescription within 90 days of the event or if the patient died within 30 days of the event. This definition has also shown to produce estimates of VTE during the antepartum and

postpartum in both English[10] and Swedish[11] data that are comparable to existing literature on the subject.

Candidate predictors, missing data and power calculations

For each pregnant woman, information on sociodemographic and lifestyle characteristics, pre-existing comorbidities, pregnancy and delivery characteristics and complications was extracted from each woman's medical record.[19] Definitions and the International Classification of Disease (ICD) codes used for each predictor are summarised in Supplementary Tables 1 and 2. Primarily, our candidate predictors were selected from the most recent version of the Royal College of Obstetrician and Gynaecologist Green thromboprophylaxis guidelines.[5] These guidelines are already based on extensive literature review and expert consensus in opinion. Additionally, we also added predictors not included in the current guideline but were identified as important obstetric VTE risk factors in previous studies which we were able to reliably measure in our data. These included diabetes[20], hypertension[20,21] and infant birth weight.[22] We measured antenatal parity that did not include current birth to avoid confusion over changing parity status during the course of pregnancy and allow for a standardised measure of parity during both antepartum and postpartum periods. For instance a woman considered nulliparous during her first antenatal visit will remain in that category through the course of that pregnancy and the subsequent postpartum period and considered to have parity 1 for her subsequent pregnancy.

Our derivation cohort had missing information on pre-pregnancy body mass index (BMI) (23%) and infant birth weight (20%). We used multiple imputation to replace missing values using a chained equation approach based on all candidate predictors. We created 10 imputed datasets for missing variables that were then combined across all datasets using Rubin's rule to obtain final model estimates. Using the same method, we also imputed values for women

with missing information on pre-pregnancy BMI or their infant's birth weight (8.6%) in our Swedish validation cohort. Based on an estimated 300 VTE events during the first six weeks postpartum and 22 candidate predictors in our derivation cohort, we had an effective sample size of 14 VTE events per predictor, above the minimum requirement suggested by Peduzzi et al.[23]

Statistical analysis for model development and validation

Occurrence of VTE during the first six weeks postpartum was treated as a binary outcome measure. For each of the 22 candidate predictors, we calculated the unadjusted odds ratio (OR) using a univariable logistic regression model. For derivation of the risk prediction model, all candidate predictors were initially included in a multivariable logistic regression model. We fitted a clustering term to take account of consecutive pregnancies within women during the study period, and used fractional polynomials to model potential non-linear relationships between outcome and continuous predictors.

Through backward elimination, we excluded (except for age at delivery, which was considered a prior predictor and retained in the model regardless of statistical significance[24]) candidate predictors from the multivariable model that were not statistically significant (p-value >0.1 based on change in log-likelihood). Following elimination, excluded predictors were re-inserted into the final model to further check whether they became statistically significant. Fractional polynomial terms were also re-checked at this stage and re-estimated if necessary. The risk equation for predicting the log-odds of VTE was formed using the estimated beta coefficients multiplied by the corresponding predictors included in our model together with the average intercept across patient clusters. This process ultimately led to an equation for the predicted absolute risk of VTE:

Predicted risk of VTE = $1 / (1 + e^{-riskscore})$

where the 'risk score' is the predicted log-odds of VTE from the developed model. Performance of the model was assessed in terms of the c-statistic and calibration slope (where 1.00 is ideal). The c-statistic represents the probability that for any randomly selected pair of women with and without a VTE, the women who experienced VTE had a higher predicted risk.[25] A value of 0.50 represents no discrimination and 1.00 represents perfect discrimination. Internal validation was then performed to correct measures of predictive performance for optimism (overfitting) by bootstrapping 100 samples of the derivation data. We repeated the model development process in each boostrap sample (as outlined above, including variable selection) to produce a model, applied the model to the same bootstrap sample to quantify apparent performance, applied the model to the original dataset to test model performance (calibration slope and c-statistic) and optimism (difference in test performance and apparent performance). We then estimated the overall optimism across all models (e.g. derive shrinkage coefficient = average calibration slope from each of the bootstrap samples).[26] To account for overfitting during the development process, the original beta coefficients were multiplied by the uniform shrinkage factor in the final model. At this point, the intercept was re-estimated based on the shrunken beta coefficients to ensure that overall calibration was maintained, producing a final model.

Our risk prediction model was applied to each individual within the external validation cohort based on the presence of one or more risk factors (Box 1). We examined the performance of this final model (in the original English data and then in the Swedish data) in terms of discrimination by calculating the c-statistic. Calibration was examined by plotting agreement between predicted and observed risks across deciles of predicted risk. For this external validation in Swedish data, we re-calibrated the intercept based on the incidence of VTE and

mean centring all predictors; however, we also assessed the performance of our model by applying the intercept from the English data because of the similar baseline VTE risk in both populations. The existing UK[5] guidelines were applied to the English data and the Swedish guidelines[7] to the Swedish data to assess the number of women who qualified for pharmacological thromboprophylaxis. This decision was based on the clinical risk factors we were able to measure reliably in our data. We then calculated the sensitivity, specificity and positive predictive value (PPV) for those women and compared them with the same proportion of women with the highest risk based on our prediction model. This analysis was repeated after excluding those already prescribed thromboprophylaxis. We also formally compared the number of VTE events that were identified and missed, based on our prediction model and separately on the existing guidelines and vice versa using McNemar's test for discordant pairs, in both the English and Swedish data. Finally we carried out a decision curve analysis[25,27] to compare our prediction model to the existing thromboprophylaxis guidelines in the English and Swedish data. This analysis assumes that the threshold probability of the disease at which a patient would opt for intervention is informative on how the patient weighs the relative harm of false positive or a false negative prediction. This is then used to calculate the net benefit of the model across a wide range of threshold probabilities.[25] The most basic interpretation of a decision curve is that the model with the highest net benefit at a particular threshold has the highest clinical value.[27]

All statistical analyses were carried out using Stata version 13.This study was conducted and reported in line with the Transparent Reporting of a multivariate prediction model for Individual Prediction or Diagnosis (TRIPOD) guidelines.[26] This project was approved by the independent scientific advisory committee (reference number=10_193R) for the English data and by Ethics Review Board in Stockholm (reference number=2013/2229-31/1) for the Swedish data.

Patient involvement

As this was an analytical study using large real-world data, we did not have any patient or user group involvement.

Results

Study participants

In our derivation cohort from England, we analysed information on 321,415 women experiencing 433,353 delivery episodes that resulted in live births or stillbirths with complete six weeks of post-delivery follow-up. Our validated Swedish cohort had information on 498,918 women experiencing 662,387 deliveries. Basic characteristics of the study population are summarised in Table 1. Broadly, women in both cohorts had similar pre-pregnancy BMI, delivery age and prevalence of comorbidities (with the exception of varicose veins). Compared to England, women in Sweden were less likely to smoke and experienced fewer delivery related complications.

Model development, performance measure and validation

In total, in the English development dataset 312 VTE events occurred during the first six weeks postpartum with an absolute rate of 72 per 100,000 deliveries. Univariable associations between postpartum VTE and potential predictors are listed in Supplementary Table 3. Of the 22 candidate predictors, 15 were statistically significantly associated with VTE in our final multivariable model (Table 2). Apparent and internal validation performance statistics of our risk prediction model are given in Table 3. After adjusting for optimism, our final risk prediction model was able to discriminate postpartum women with and without VTE with a c-statistic of 0.70 (0.67-0.73) The agreement between the observed and predicted proportion of events demonstrated excellent apparent calibration (Figure 1a), but a uniform shrinkage factor of 0.94 was needed to adjust predictor coefficients in the final model for optimism (Table 2). Box 1 presents our final risk prediction model which we integrated in a windows based calculator. Figure 2 shows a screen shot of our windows based risk calculator which can be integrated into a designated website or a general practice/hospital computer system.

External validation

In our independent cohort, 521 women experienced postpartum VTE with an absolute rate of 79 per 100,000 deliveries. Applying our final risk prediction model (Box 1) to the independent population after re-calibration of the intercept to the Swedish population gave a c-statistic of 0.73 (95% CI 0.71-0.75) and excellent calibration (Figure 1b and supplementary Figure 1), with the calibration slope only slightly above 1 (Table 3). The mean predicted risk of VTE based on our model was calculated to be 0.08% (min=7.73×10^{-13} max=12.9%) Two clinical examples of the application of our risk prediction model are presented in Box 1.

Comparing prediction models to the existing guidelines

According to the UK's postpartum thromboprophylaxis guideline[5], 35% of women in the English data qualified for pharmacological thromboprophylaxis for at least 10 days post-delivery. The sensitivity and PPV of the current UK guideline based on our data was calculated to be 63% and 0.13% respectively. Applying our prediction model to identify this proportion of women (i.e. 35% of women would qualify, which related to having a predicted absolute risk threshold of 6.3 per10,000 deliveries) resulted in slightly higher sensitivity (68%) and PPV (0.14%.) In the Swedish population, 6% of the postpartum women qualified for pharmacological thromboprophylaxis based on national guidelines. The sensitivity and PPV was calculated to be 21% and 0.26% respectively. Identifying this proportion of postpartum women based on our model (i.e. 6% qualifying, which related to an absolute risk threshold of 18 per 10,000 deliveries) resulted in a sensitivity of 30% and a PPV of 0.38%. McNemar's test for discordant pairs comparing VTEs identified using our prediction model and the existing guidelines was statistically significant in both the English (P=0.02) and Swedish (P<0.001) cohorts (supplementary table 4). These results remained virtually unchanged when we excluded 1% and 3% of women who were prescribed pharmacological thromboprophylaxis in the English and Swedish data (Supplementary Table 4). Our model

performance at various arbitrary thresholds is presented in Supplementary Table 5. Finally for each modelled threshold probability of VTE, our model gave higher net benefit than the existing guidelines (Supplementary Figure 2 and 3).

Discussion

We have developed a new risk prediction model to calculate the absolute risk of VTE during the first six weeks postpartum in a large representative sample of postpartum women in England. This model was then externally validated in a Swedish national cohort. Overall, our prediction model had excellent calibration and useful discrimination, with a c-statistic of >0.70 in both the English and Swedish data. Our risk prediction model performed better than the current UK and Swedish national thromboprophylaxis guidelines in terms of sensitivity and PPV at similar thresholds based on the risk factors that we were able to reliably capture in the women's medical/pregnancy records.

Our risk prediction algorithm has several advantages over those currently in use in many developed countries. The model is based on absolute risks determined and validated in two very large[28] and independent populations. It is built from easily available clinical and demographic variables, implying that it can be straightforwardly applied in clinical practice and readily amenable to further external validation in many countries which have routine data available for such a purpose. Whilst our model equation may seem complicated compared to the existing thromboprophylaxis guidelines, it can be easily integrated to a user-friendly online calculator to be implemented in practice being not dissimilar to those for QThrombosis.[29]

In our study we found that <1% and 3% of women were prescribed pharmacological thromboprophylaxis during the postpartum period in the English and Swedish data, respectively. Whilst our model performance remained unchanged when we excluded women already prescribed thromboprophylaxis it is likely that we have underestimated this proportion of women in the English data due to unavailability of prescriptions emanating from secondary care. We believe, however, that it is unlikely that thromboprophylaxis

practices will have a huge impact on our estimates as the risk of VTE is significantly high well beyond the recommended intervention period of up to 7 days[30] (guideline changed to 10 days in 2015[5]) post-delivery for vast majority of high risk women in the UK.[31] Furthermore, there is evidence suggesting inadequate use of thromboprophylaxis[32,33], a belief supported by the finding of no significant change in the incidence of postpartum VTE in our English data over time along with the recent increase in national VTE-related deaths observed in the UK.[2,34]

Although our model has excellent calibration across the observed spectrum of absolute predicted risks, this spectrum mainly includes predicted risks that are small even for women with multiple risk factors. However, it should be recognised a large portion of these women qualify for pharmacological thromboprophylaxis based on these small risks according to the current guidelines. This is because VTE is the leading cause of direct maternity mortality in the UK and VTE-related death may be prevented through targeted thromboprophylaxis. Our model enables prediction of postpartum VTE at an individual level which is an improvement upon the currently used un-validated ordinal point-based system that categorises women into low, intermediate and high risk groups.

Whilst our model identifies more VTE events than the current UK and Swedish guidelines and has been externally validated, it also missed 32% of postpartum VTEs. This is not surprising given that a previous nationwide study from UK reported that only 70% of those with antenatal pulmonary embolism had classical VTE risk factors. However, as a screening tool, our prediction model will have important implications for identifying those in whom thromboprophylaxis may be recommended.

We excluded women with a history of VTE from our study as they represent a small proportion of women for whom the decision to give anticoagulants is less controversial. We also did not include information on a variety of risk factors (e.g., protein C and S deficiency, Factor V Leiden and prothrombin gene mutation, family history of VTE) in our model. However, by excluding individuals with a history of VTE from our study, we may have limited its impact on our estimates. Furthermore, universal screening for some of those risk factors (e.g., Factor V Leiden) is not routinely recommended in pregnant women and therefore pragmatically it cannot be used to predict the risk of first VTE in the wider general population. Regardless of the exclusion of those factors, our model currently provides the individualised predicted absolute risk estimates for VTE for the majority of postpartum women. The current RCOG thromboprohylaxis guideline[5] recommends VTE risk assessment intrapartum or immediately after childbirth. Thus our risk assessment tool can be used to quantify VTE risk during that period. However, our prediction model should not be used for women with one or more risk factors not measured in our model (e.g. immobilization due to fracture) and should not be relied upon to the exclusion of clinical judgment for prescribing thromboprophylaxis.

We acknowledge that our model does not take into account disease severity for specific comorbidities due to data limitations and inadequate number of VTE events leading to a lack of power to stratify on disease severity, if known. However, our prediction model is in line with the existing guidelines that also do not take into account disease severity. It must also be recognised that women who become pregnant are generally healthier and have lower prevalence of pre-existing comorbidities compared to the general population. In our study the prevalence of cardiac, renal and inflammatory bowel disease was around 1% (even after using our broad definitions). Thus the proportion of women experiencing severe cardiac and renal disease during pregnancy will be even lower and it is likely that these women will be

cared for very differently to those with well controlled comorbidities. We also believe that whilst in theory our model could be improved by ascertaining more detail on the severity of risk factors, this would negatively impact on the ability to apply this in practice where risk factor information will need to be obtained accurately in a relatively short clinical assessment.

Although several studies have examined risk factors for VTE during the postpartum period, studies specifically designed to develop and validate the risk prediction model are scarce. Previously, two risk models were constructed using Swedish data, one based on a weighted risk score for exposures associated with at least a 5-fold increase in VTE risk,[7,35] and the other, an individualised risk assessment tool, based on absolute risks of VTE.[36] Both risk models failed to include some of the common clinical risk factors e.g. postpartum, haemorrhage, type of caesarean section, puerperal infection which are risk factors known to be important predictors of VTE.[5] Furthermore, the former model (weighted risk score) was based on a small number of pregnant women (<2500) from a single centre that does not comprehensively inform the performance of the model. Currently, the UK[5], Sweden[7] and Canada[4] use a point-based algorithm to identify high-risk postpartum women for pharmacological thromboprophylaxis. The US guidelines[3] are more conservative and advice against the routine use of pharmacological thromboprophylaxis. These guidelines neither take into account the individualised absolute risk of VTE based on women's complex clinical risk profile nor have they been externally validated, which is crucial to facilitate their translation into practice.

Our study has three important implications for clinical practice. First, our prediction model can be used as a tool to identify high-risk women based on their absolute predicted VTE risk within the first six weeks postpartum. The algorithm is based on standard clinical variables

that are likely to be available at the point of childbirth and that could be readily integrated into secondary care computer systems or developed into an app for handheld devices for ease of use. Second, our prediction model performed better than the current UK and Swedish thromboprophylaxis guidelines (based on the risk factors recorded in data registries) in terms of identifying a higher proportion of VTE events. Finally, our risk prediction model could be used to establish new treatment thresholds in clinical practice through consensus development of national guidelines. For example, the Swedish approach of targeting 6% of women may be a template for the UK as the incidence of VTE does not vary much between the two countries. On the other hand, it may be possible that the current Swedish cut-off is too conservative and may be leading to under-treatment. Naturally, such changes in guidelines will need to take into account the perspectives of the health care providers, practitioners and women in each country and consider the potential benefits and harms of any threshold that is chosen which is beyond the scope of this study.

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Conflict-of-interest disclosure:

CNP was co-developer of the currently available guidelines on VTE prophylaxis in pregnancy issued by the Royal College of Obstetricians and Gynaecologists (green top guideline 37a). CNP has also received honoraria for giving lectures from Leo Pharma and Sanofi Aventis (makers of tinzaparin and enoxaparin LMWHs used in obstetric thromboprophylaxis) and has received payment from Leo Pharma for development of an educational 'slide kit' about obstetric thromboprophylaxis. No other authors have conflicts of interest to declare.

Details of Contributions

AAS, LJT, JW, KMF and MJG conceived the idea for the study, with OS, RR and JFL also making important contributions to the design of the study. AAS carried out the data management and analysis and wrote the first draft of the manuscript. OS and CNP provided clinical input at all stages of the project. All authors were involved in the interpretation of the data, contributed towards critical revision of the manuscript and approved the final draft. AAS had full access to all of the data and had final responsibility for the decision to submit for publication.

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Data sharing

No additional data available.

References

1. Drife J. Thromboembolism. *Br Med Bull* 2003; **67**: 177-90.

2. Knight M TD, Kenyon S, Shakespeare J, Gray R, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Surveillance of maternal deaths in the UK 2011-13 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009-13. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2015.

3. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141**(2 Suppl): e691S-736S.

4. Chan W, Rey E, Kent N, et al. Venous Thromboembolism and Antithrombotic Therapy in Pregnancy. *Journal of obstetrics and gynaecology Canada: JOGC= Journal d'obstetrique et gynecologie du Canada: JOGC* 2014; **36**(6): 527-53.

5. Royal College of Obstetricians and Gynaecologist. Thrombosis and embolism during pregnancy and puerperium, Reducing the risk (Green-top Guideline No.37a). London: RCOG Press; 2015.

6. James A. Practice bulletin no. 123: thromboembolism in pregnancy. *Obstet Gynecol* 2011; **118**(3): 718-29.

7. Lindqvist PG, Hellgren M. Obstetric thromboprophylaxis: the Swedish guidelines. *Advances in hematology* 2011; **2011**: 157483.

8. Steyerberg EW, Moons KG, van der Windt DA, et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 2013; **10**(2): e1001381.

9. Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: A framework for researching clinical outcomes. *BMJ* 2013; **346**: e5595.

10. Abdul Sultan A, Tata LJ, Grainge MJ, West J. The Incidence of First Venous Thromboembolism in and around Pregnancy Using Linked Primary and Secondary Care Data: A Population Based Cohort Study from England and Comparative Meta-Analysis. *Plos One* 2013; **8**(7): e70310.

11. Abdul Sultan A, West J, Stephansson O, et al. Defining venous thromboembolism and measuring its incidence using Swedish health registries: a nationwide pregnancy cohort study. *BMJ Open* 2015; **5**(11): e008864.

12. Clinical Practice Research Database. http://www.cprd.com/intro.asp (accessed December, 29, 2015.

13. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; **44**(3): 827-36.

14. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC public health* 2011; **11**(1): 450.

15. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009; **24**(11): 659-67.

16. Centre for Epidemiology The National Board of Health and Welfare. The Swedish Medical Birth Registry - A Summary of Content and Quality. 2003; **(Article no: 2003-112-3)**.

17. Cnattingius S, Ericson A, Gunnarskog J, Källén B. A quality study of a medical birth registry. *Scandinavian Journal of Public Health* 1990; **18**(2): 143-8.

18. Lawrenson R, Todd JC, Leydon GM, Williams TJ, Farmer RD. Validation of the diagnosis of venous thromboembolism in general practice database studies. *Br J Clin Pharmacol* 2000; **49**(6): 591-6.

19. Abdul Sultan A, Grainge MJ, West J, Fleming KM, Nelson-Piercy C, Tata LJ. Impact of risk factors on the timing of first postpartum venous thromboembolism: a population-based cohort study from England. *Blood* 2014; **124**(18): 2872-80.

20. Liu S, Rouleau J, Joseph KS, et al. Epidemiology of pregnancy-associated venous thromboembolism: a population-based study in Canada. *J Obstet Gynaecol Can* 2009; **31**(7): 611-20.

21. James AH, Jamison MG, Brancazio LR, et al. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. *Am J Obstet Gynecol* 2006; **194**(5): 1311-5.

22. Blondon M, Quon BS, Harrington LB, Bounameaux H, Smith NL. Association between newborn birth weight and the risk of postpartum maternal venous thromboembolism: a population-based case-control study. *Circulation* 2015; **131**(17): 1471-6; discussion 6.

23. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; **49**(12): 1373-9.

24. Abdul Sultan A, Tata LJ, West J, et al. Risk factors for first venous thromboembolism around pregnancy: a population based cohort study from the United Kingdom. *Blood* 2013; **121**(19): 3953-61.

25. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006; **26**(6): 565-74.

26. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med* 2015; **162**(1): W1-W73.

27. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ* 2016; **352**: i6.

28. Riley RD, Ensor J, Snell KI, et al. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. *BMJ* 2016; **353**: i3140.

29. Hippisley-Cox J, Coupland C. Development and validation of risk prediction algorithm (QThrombosis) to estimate future risk of venous thromboembolism: prospective cohort study. *BMJ* 2011; **343**: d4656.

30. Royal College of Obstetricians and Gynaecologists. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. Green-top Guideline No. 37a. London: RCOG Press; 2009.

31. Kamel H, Navi BB, Sriram N, Hovsepian DA, Devereux RB, Elkind MS. Risk of a Thrombotic Event after the 6-Week Postpartum Period. *N Engl J Med* 2014.

32. Friedman AM, Ananth CV, Lu Y-S, D'Alton ME, Wright JD. Underuse of Postcesarean Thromboembolism Prophylaxis. *Obstet Gynecol* 2013; **122**(6): 1197-204.

33. Knight M. Antenatal pulmonary embolism: risk factors, management and outcomes. *BJOG* 2008; **115**(4): 453-61.

34. Knight M KS, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ (Eds.) on behalf of MBRRACEUK. Saving Lives, Improving Mothers' Care - Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–12. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2014.

35. Lindqvist PG, Torsson J, Almqvist A, Bjorgell O. Postpartum thromboembolism: severe events might be preventable using a new risk score model. *Vasc Health Risk Manag* 2008; **4**(5): 1081-7.

36. Lindqvist PG, Kublikas M, Dahlbäck B. Individual risk assessment of thrombosis in pregnancy. *Acta Obstet Gynecol Scand* 2002; **81**(5): 412-6.

Tables

Table 1: Basic characteristics of the two study populations

Variable	Derivation cohort (England) N=433,353		Validation cohort (Sweden) N=662,387	
	N[†]	%[†]	N[†]	%[†]
VTE events	**315**	**0.07**	**521**	**0.08**
Social and demographic factors				
Mean age at delivery, years (SD)	29.38	(5.90)	30.32	(5.23)
Mean body mass index (SD)[1]	24.05	(4.90)	24.62	(4.57)
Smoker[2] (latest record before delivery)	93,264	21.52	32,502	4.91
Deliveries in 2004 or thereafter	280,498	64.73	662,387	100
Comorbidities[3]				
Varicose veins	10,935	2.52	5,156	0.78
Cardiac disease	4,431	1.02	5,072	0.77
Renal disease	4,168	0.96	6,666	1.01
Inflammatory bowel disease	2,126	0.49	5,285	0.80
Pregnancy complications				
Pre-eclampsia/eclampsia	9,966	2.30	24,013	3.63
Diabetes[4]	14,604	3.37	14,948	2.26
Hypertension[4]	41,300	9.53	7,980	1.20
Nulliparous[5]	244,233	56.36	293,176	44.26
Parity 1	130,121	30.03	242,341	36.59
Parity 2	38,599	8.91	88,803	13.41
Parity 3 or more	20,400	4.71	38,067	5.75
Delivery characteristics/complication				
Pre-term birth (<37 weeks)	31,526	7.27	31,728	4.79
Postpartum haemorrhage	42,978	9.92	48,383	7.30
Spontaneous/Assisted vaginal delivery	328,416	75.78	547,654	82.68
Elective caesarean section	44,143	10.19	58,012	8.76
Emergency caesarean section	60,794	14.03	56,721	8.56
Multiple delivery (Twins or more)	6,550	1.51	9,308	1.41
Stillbirth	1,972	0.46	2,286	0.35
Puerperal acute infection	13,681	3.16	48,383	7.30
Infant's mean birth weight in grams (SD)[6]	3368.35	(596.80)	3519.80	(581.9)
Missing information				
Infant birth weight	87,305	20.14	930	0.14
Body mass index	98,868	22.81	57,173	8.63

[1]Pregnancies with missing pre-pregnancy BMI; 23% (England), 8.6% (Sweden).
[2]Latest smoking record before delivery.
[3] Comorbidities recorded ever before delivery. Specific disease group for comorbidities presented in Supplementary Table 1.
[4]Including gestational and pre-existing.
[5]Antenatal parity.
[6]Pregnancies with missing infant birth weight information; 20% (England), 0.1% (Sweden).
SD=Standard deviation.
[†]Except where specified.

Table 2: Final multivariable analysis for VTE risk within six weeks of delivery in the derivation cohort

Variable	Model 1 (Based on backward elimination)			Beta coefficients
	OR*	95%CI		
Smoker (latest record before delivery)	1.25	0.97	1.62	0.22684105
Varicose veins	3.39	2.25	5.10	1.2210805
Comorbidities (cardiac, renal disease or IBD)	2.33	1.47	3.71	0.8476927
Pre-eclampsia/eclampsia	2.06	1.32	3.20	0.72127433
Diabetes	1.52	0.97	2.39	0.42119233
Nulliparous (antenatal)	Reference			
Parity 1	1.18	0.91	1.53	0.16456948
Parity 2	1.62	1.13	2.33	0.48143018
Parity 3 or more	1.76	1.56	2.68	0.5664196
Postpartum haemorrhage	1.65	1.21	2.24	0.50183134
Spontaneous/Assisted vaginal delivery	Reference			
Elective caesarean section	1.76	1.26	2.44	0.56321456
Emergency caesarean section	2.11	1.60	2.80	0.75035197
Stillbirth	3.16	1.29	7.73	1.1514008
Postpartum infection	2.99	2.07	4.33	1.0969922
Fractional polynomial transformed				
Age^3				-0.00007986
Age^3×ln (Age)				0.00002147
BMI^3				0.00026641
BMI^3×ln (BMI)				-0.00006501
Infant birth weight^-2				-22156315
Infant birth weight^-2×ln (birth weight)				3455223.4
Constant$^{\delta}$				-9.103121

* For binary variables, OR is based on women without a particular risk factor under study.

$^{\delta}$ Average across population.

Note: The constant was re-estimated after adjusting the model for optimism to ensure that overall calibration was maintained.

OR=Odds ratio; CI=Confidence interval; IBD=Inflammatory bowel disease; BMI=Body mass index.

Note: Multiple imputation was carried out for missing BMI and birth weight data (10 imputations). Age included in the model as an a priori predictor. Predictors were retained in the model at the10% level of significance.

Table 3: Model diagnostics

Measure	Apparent performance	Test performance	Average optimism	Optimism corrected	External validation (Swedish data)
C-statistic	0.72 (0.69-0.75)	0.70 (0.70-0.71)	+0.020	0.70 (0.67-0.73)	0.73 (0.71-0.75)
Calibration slope	1.00 (0.88-1.11)	0.94 (0.93-0.95)	+0.061	0.94 (0.81-1.04)	1.11 (1.01-1.20)

Notes:

C-statistic: Probability that for any randomly selected pair of women with and without a VTE, the women who experienced VTE had a higher predicted risk.[25] A value of 0.50 represents no discrimination and 1.00 represents perfect discrimination.

Apparent performance: Refers to performance estimated directly from the data set that was used to develop the prediction model.

Test Performance: Determined by developing a model in each bootstrap sample (100 samples with replacement), calculating performance (bootstrap performance) and applying the bootstrap model in the original sample.

Average optimism: Average difference between model performance in bootstrap data and test performance in original dataset.

Optimism corrected: Subtracting average optimism from apparent performance.

Table 4: Comparing current guidelines to the risk prediction model

	English data **Total number of postpartum women = 433,353** **Total number of VTE events = 312** **(Imputed results)**		**Swedish data** **Total number of pregnancies = 662,387** **Total number of VTE events = 521** **(Imputed results)**		
Statistics	**Women prescribed thromboprophylaxis based on the current RCOG postnatal thromboprophylaxis guidelines¥**	**Risk prediction model (England) Top 35% cut-off (Threshold=6.3 per 10,000 deliveries)**	**Women prescribed thromboprophylaxis based on the Swedish national guidelines§**	**Risk prediction model (Sweden) Top 6% cut-off (Threshold=18 per 10,000 deliveries)**	**Risk prediction model (Sweden) Top 35% cut-off (Threshold=7.2 per 10,000 deliveries)**
Total number of postpartum women warranting thromboprophylaxis (%)	149,402 (34.5%)	149,402 (34.5%)	41,254 (6.2%)	41,254 (6.2%)	231,835 (35%)
Observed VTE events*	197	212	109	158	355
Mean Predicted risk per 10,000 pregnancies	12.3	13.0	25.8	31.6	14.2
Sensitivity %	63.1 (57.5-68.5)	67.9 (62.5-73.1)	20.9 (17.5-24.7)	30.3 (26.4-34.5)	68.1 (63.9-72.1)
Positive predictive value %	0.13 (0.11-0.15)	0.14 (0.12-0.16)	0.26 (0.21-0.31)	0.38 (0.32-0.45)	0.15 (0.13-0.17)
Specificity	65.6 (65.4-65.7)	65.6 (65.4-65.7)	93.8 (93.7-93.8)	93.8 (93.7-93.9)	65.1 (64.9-65.2)

¥Women with either two low risk factors (Varicose veins, age>35 years, overweight, 30≥BMI<40 kg/m^2, parity 3 or more, smoker, puerperal infection, elective caesarean section, multiple delivery, pre-term birth, stillbirth, preeclampsia/eclampsia or postpartum haemorrhage) or one high-risk factor (comorbidities (IBD, cardiac disease, renal disease), BMI≥40 kg/m^2, or emergency caesarean section)).

§Women with two clinical risk factors (elective caesarean section, age≥40 years, BMI≥30 Kg/m^2, or any comorbidities (cardiac disease, IBD or renal disease)).

BMI=Body mass index; IBD=Inflammatory bowel disease.

Sensitivity: The percentage of true positive VTE cases correctly identified based on current thromboprophylaxis guidelines/risk prediction model

Specificity: the percentage women without VTE diagnosis correctly identified based on thromboprophylaxis guidelines/risk prediction model

Positive Predictive Value: the likelihood that women above the treatment threshold will develop VTE

*In women warranting thromboprophylaxis

Box 1 Risk prediction model

Risk score from a logistic regression model to predict VTE in the first six weeks postpartum

Risk score= -9.103 + 0.94 × {0.227*smoker* + 1.221*varicose veins* + 0.848*comorbidities(cardiac, renal or inflammatory bowel disease)* + 0.721*pre-eclampsia/eclampsia* 0.421*diabetes* + 0.502*postpartum haemorrhage* + 1.151*stillbirth* + 1.097*postpartum infection* + (0.750*emergency section*/ 0.563*elective section)* + (0.165*parity of 1*/ 0.481*parity of* 2/0.566*parity of 3 or more)* – 0.0000798*age at delivery*^{3} + 0.0000214(*age at delivery*^{3} log (*age at delivery*)) + 0.00026641*BMI*^{3} - 0.0000650(BMI^{3}log (*BMI*)) - 22156315*infant birth weight*$^{-2}$ + 3455223.4(infant birth weight^{-2} log (baby's birth weight))}

All variables are coded as binary (0 or 1 for absence or presence of a risk factor), except for age, BMI and birthweight. These three variables were transformed based on fractional polynomial regression (first degree) analysis. The value -9.103 is the intercept and other numbers are the estimated regression coefficients for the predictors, which indicate their mutually adjusted relative contribution to the outcome risk. The regression coefficients represent the log odds ratio for a change of 1 unit in the corresponding predictor.

The predicted risk of VTE=1/1+e$^{-riskscore}$

Example 1: A 20-year-old nulliparous woman who underwent an emergency caesarean section and has a BMI of 32 Kg/m^2. She had no history of prior comorbidities, developed no pregnancy-related complications and delivered baby with the birthweight of 3368 grams. She has a predicted risk of 0.11% of developing a VTE within the first six weeks of delivery.

Interpretation: if 1000 women are followed with the same risk factors 1 will develop VTE within six weeks of childbirth.

Example 2: A 36-year-old woman with a BMI of 45 Kg/m^2 who underwent an emergency caesarean section complicated with postpartum haemorrhage and infection. She had a history of cardiac disease and varicose veins. Her predicted VTE risk is 4.9% within the first six weeks of delivery.

Interpretation: if 1000 women are followed with the same risk factors 49 will develop VTE within six weeks of childbirth.

Note: log = Natural Logarithm

Figure legends

Figure 1: Assessing calibration in the derivation and validation cohort

Figure 2: Screenshot of windows based risk prediction program