Title: Patient-centered approach to reducing harm from VTE

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Abstract

Purpose: This study had five aims. We created a risk assessment model to identify patients at high risk of VTE. We built a decision analytic model to understand the threshold of risk at which patients should receive VTE prophylaxis. We incorporated the model into the EHR, and we tested the effect of the model in a randomized, controlled trial.

Scope: VTE is a common problem in hospitalized medical patients. Chemical prophylaxis can reduce the rate of VTE, but it should be reserved for patients at high risk of VTE in order to minimize complications, pain, and cost.

Methods: A risk assessment model (RAM) was derived from 5 years of Cleveland Clinic data and was validated using 2 additional years of data. We constructed a two-stage decision analytic model to identify the threshold at which VTE prophylaxis was cost effective. We then embedded the RAM in a smart order set within the EHR and tested it in a randomized, controlled trial. Outcomes included appropriate use of VTE prophylaxis, VTE events, and major bleeding.

Results: The training set included 98,661 patients, of whom 226 (0.2%) developed VTE in the hospital. The final model included 16 variables. The C-statistic was 0.79. The decision analytic model identified 0.8% as the threshold risk at which prophylaxis cost less than $100K/QALY. We successfully embedded the RAM in the EHR. The RCT enrolled approximately 100,000 patients. Data analysis is in progress.

Key Words: Hospital-acquired condition, venous thromboembolism, bleeding, decision analysis.

Purpose

This study had five aims:

1) **Develop and test a dynamic risk calculator for VTE based on US patients**
   Using 10 years of electronic health records from the Cleveland Clinic, we proposed to develop and validate a risk calculator that incorporates changing levels of risk throughout the hospitalization.
2) **Develop and test a risk calculator for bleeding**
   In a similar process, we proposed to create and validate a bleeding risk calculator.
3) **Derive specific thresholds for combinations of VTE and bleeding risk**
   We proposed to create a decision analytic model to balance each patient's risk of VTE and bleeding to compute whether the benefits of prophylaxis outweigh the harms for that patient.
4) **Incorporate the risk calculators into a commercially available electronic health record (EHR)** We proposed to use smart order sets that incorporate patient factors already entered into the EHR to identify patients for whom prophylaxis would be important and to prompt physicians to order prophylaxis when benefits outweigh harms.
5) **Assess the effects of the smart order set on physician behavior and patient outcomes in a randomized trial**

SCOPE

Background

Venous thromboembolic (VTE) complications arising from immobility and hypercoagulability are a serious source of hospital morbidity and mortality. In randomized trials of high-risk patients, chemoprophylaxis with heparin has been shown to reduce the occurrence of VTE. Since 2010, assessment of VTE risk and provision of prophylaxis to all but low-risk patients has been a quality measure endorsed by the National Quality Forum and required by The Joint Commission. However, the overall prevalence of VTE in most medical patients is low. Because of the difficulty in identifying low-risk patients, many hospitals have opted for near-universal prophylaxis, with an attendant increase in complications of prophylaxis, primarily bleeding. Recently, the American College of Physicians recommended that prophylaxis be withheld from low-risk patients for whom the risks of bleeding may outweigh the benefits. However, neither the ACP guidelines nor The Joint Commission requirements recommend a specific risk assessment tool, nor do they offer a definition of low risk. In contrast, the American College of Chest Physicians recommends VTE risk assessment with the Padua Prediction Score. This prediction score, which was validated on 1180 patients in Italy, successfully divided patients into high-risk (11%) and low-risk (0.3%) categories (overall risk, 2.8%). However, typical baseline risks in the US are closer to 1%. Both guidelines recommend not prescribing chemoprophylaxis to patients at increased risk of bleeding.

Context

In attempting to follow these guidelines and meet quality measures, US physicians face several challenges. First, the only prospectively validated VTE risk calculator was validated on a small number of non-US patients and may not perform as well in US hospitals. Second, there is no validated risk calculator for bleeding. Third, the appropriate treatment thresholds for VTE or bleeding have not been identified. Finally, risk calculators are not available at the point of care. As a result, prophylaxis rates have remained stubbornly low in some institutions, while in others the rate of prophylaxis is high but the rate of inappropriate prophylaxis is also high.

Settings

Nine Cleveland Clinic hospitals from 2011 to 2019

Participants

Hospitalized patients admitted to a Medicine Service and eligible for VTE prophylaxis were included. Patients at high risk of bleeding and those who have another indication for anticoagulation were excluded.

Incidence

Incidence of VTE in the hospital (up to 14 days) is approximately 0.3% per admission.

METHODS

Study Design

We used several different study designs to achieve our stated aims. For aims 1 and 2, we used a cross-sectional design, in which we identified predictors of VTE and bleeding in the hospital. We identified all medical patients admitted to Cleveland Clinic hospitals between 2011 and 2017. The first 5 years comprised the training set, and 2016 and 2017 were reserved as validation sets. Potential VTE events were identified by combination of ICD-9/10 codes and diagnostic testing. All events were verified through chart review. Potential predictors included 30 clinical risk factors identified from previous studies. Multiple logistic regression analysis with step-down variable selection method was used to select the best model. The model was validated both internally and externally using bootstrapping. The final model was tested against the Padua model using the validation set. The bleeding model will be tested against the IMPROVE model.

For aim 3, we used cost-effectiveness modeling. We constructed a decision model consisting of two consecutive modules: a simple decision-tree that followed patients up to 3 months after hospitalization and a lifetime Markov model with 3-month cycles. The model tracked symptomatic deep vein thromboses and pulmonary emboli, bleeding events, and heparin-induced thrombocytopenia. Long-term complications included recurrent VTE, post-thrombotic syndrome, and pulmonary hypertension. For a base case, we considered medical inpatients aged 66 years, having a life expectancy of 13.5 years, having a VTE risk of 1.4%, and having a bleeding risk of 2.7% on average. Patients received enoxaparin 40 mg/day for prophylaxis. Transition probabilities, costs, and utilities were derived primarily from US-based studies to estimate total costs and quality-adjusted life years (QALYs). The efficacy of enoxaparin was based on a meta-analysis of randomized clinical trials. Costs included direct medical costs and were expressed in 2015 US dollars. The study was conducted from the health system perspective. Costs and QALYs were discounted at 3%/year. We also conducted one- and two-way sensitivity analyses, assuming a willingness-to-pay of $100,000/QALY.

For aim 5, we are conducting a step-wedge randomized controlled trial. Cleveland Clinic hospitals were randomized regarding their start date for the intervention, described below. The study was completed on 4/14/19, and data abstraction and analysis is currently underway. Once the data abstraction phase is completed, data analysis will follow intention-to-treat (ITT) principles, with hospitals analyzed in the groups to which they were allocated. All the primary and secondary outcomes are binary variables, which will be summarized as percentages with confidence intervals. Logistic regression models with random effects will be used to compare each outcome between the two groups, in which the random effects account for possible correlations of outcomes within the same hospital. The models will contain strata as a fixed covariate. Exploratory analyses will further adjust the results for both patient-level and hospital-level confounders. Subgroup analyses will be undertaken for high- and low-predicted risk patients. The risks and the thresholds for high- and low-risk categories will be calculated and determined using the risk calculator developed in the early aims. In addition, due to unexpected results of preliminary analyses, we will also conduct an as-treated analysis,

comparing outcomes of patients who received prophylaxis, those who were prescribed prophylaxis but missed one or more doses, and those who did not receive any prophylaxis, adjusted for baseline risk of VTE. A p value <0.05 will be considered statistically significant.

Data Sources/Collection

For all study aims, data were derived from the Cleveland Clinic EHR. All data were extracted electronically. For each predictor variable, we performed spot validation through chart review to ensure that our algorithm had at least 90% accuracy. All outcome variables were validated through chart review.

Interventions

Only aim 5 has an intervention. The intervention is displaying the VTE risk calculator as part of the smart order set. The risk calculator draws its values from the EHR and presents them to the physician in the course of doing the VTE risk assessment, which is part of the admitting orders work flow. The physician then has the option of using the risk assessment or not.

Measures

The primary outcome will be the proportion of patients who receive appropriate VTE prophylaxis. Patients at low risk of bleeding will be considered to have received appropriate prophylaxis if they have a high predicted risk of VTE and receive adequate chemoprophylaxis (low-molecular-weight heparin, unfractionated heparin, or fondaparinux) or a low predicted risk and do not receive prophylaxis. Patients at high risk of bleeding will be considered to have received appropriate prophylaxis if they have a high predicted risk of VTE and receive mechanical prophylaxis (intermittent compression stockings and/or elastic stockings) or a low predicted risk of VTE and do not receive prophylaxis. Threshold for high VTE risk is 0.25%. High risk for bleeding is based on risk factors recommended by the ACCP guidelines.

Thromboprophylaxis will be considered adequate if:

- implemented within 48 hours of hospital admission,
- it includes the daily administration of mechanical prophylaxis or at least 10,000 U of unfractionated heparin, 40 mg of enoxaparin (or 30 mg for patients with CKD), or 2.5 mg of fondaparinux, AND
- covers at least 80% of the time in hospital that the patient is “high risk.”

Secondary outcomes will include total days of prophylaxis per patient, rate of VTE per patient day among high-risk patients, rate of major bleeding per patient day among high-risk patients, average cost of prophylaxis, average cost of hospitalization, and average length of stay. For all patients, in hospital VTE will be initially identified through ICD-9 codes. For the subset of patients who receive primary care in the CCHS, we will identify post-discharge events via ICD-10 codes during hospital, emergency room, or ambulatory visits.

All ICD-10 diagnoses will be verified through review of the EHR. Only episodes that are confirmed by a diagnostic test (lower-extremity duplex, CT or VQ scanning, venography, or angiography) will be counted.

We will use the definition of the International Society of Haemostasis and Thrombosis for major bleeding:

1. fatal bleeding or
2. symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
3. bleeding causing a fall in hemoglobin level of 2 g/dL OR leading to transfusion of ≥2 units of whole blood or packed red blood cells.

Although this definition does not contain a time frame, we will include only falls in hemoglobin or transfusions that occur within any 72-hour window. Bleeding episodes will be identified by a combination of ICD-10 codes for bleeding in a critical organ admission and by transfusion records in the EHR. All episodes of life-threatening or fatal bleeding will be confirmed by chart review.

Limitations

There are a number of limitations to this study. First, there was no forcing function to ensure that physicians use the risk calculator. Although we made every effort to convince physicians to use it, many chose not to, which will bias our results toward the null. We will also conduct a per protocol analysis, comparing those patients for whom the physician used the calculator to the control group. However, this loses some of the benefits of randomization, because use of the calculator may introduce confounding. Second, we are able to capture only inpatient VTE events for all patients. This is important because only a minority of VTE events occur prior to discharge. However, these are the events most likely to be influenced by prophylaxis. Moreover, we will perform a subgroup analysis for patients who receive their primary care at Cleveland Clinic and who would therefore be likely to present to a Cleveland Clinic facility if they developed post-discharge VTE.

RESULTS

Principal Findings (all findings should be considered preliminary unless published following peer review)

1. We were able to create a risk prediction model for VTE in the hospital. The model had good discrimination and performed better than the Padua model in our validation set.
2. Our decision analytic model identified a threshold for prophylaxis based on VTE risk. We also found that the threshold was sensitive to patient age, but we did not think this could be operationalized within our randomized trial.
3. We found that the overall benefit of prophylaxis was relatively insensitive to bleeding risk.

Outcomes

Aim 1. Our training set included 98,661 patients, of whom 226 (0.2%) had a VTE develop in the hospital. The final model included 16 variables: age, sex, smoking status, history of VTE, thrombophilia, respiratory failure, chronic kidney disease, inflammatory arthritis, decubitus ulcer, cancer, acute infection, activity level, peripherally inserted central catheter, central line, mechanical ventilation, and steroids. The C-statistic for the training set was 0.79. Individual predicted risks ranged from 0.03% to >28%. The validation set included 10,753 patients, of whom 55 (0.5%) developed VTE. The C-statistic for our model was higher than that of the Padua model (0.79 vs. 0.63). At our optimal treatment threshold of 0.3%, our model identified 2680 (25%) patients as high risk (average risk, 1.42%) and 8080 (75%) as low risk (average risk, 0.21%); Padua at a threshold of 4 identified 8011 (75%) as high risk (average risk, 0.69%) and 3102 (25%) as low risk (average risk, 0.06%).

Aim 2. In progress. Throughout the study, we have had difficulty identifying outcomes through the electronic health record, which led to numerous delays. As a result, the bleeding outcomes, which were less important for the prophylaxis decision (as discovered in aim 3) have been left for last. This model will be completed once the results of the RCT are finalized.

Aim 3. In the base case, prophylaxis had an incremental cost of $44,091/QALY saved compared with no prophylaxis. In the sensitivity analysis, prophylaxis would cost >$100,000/QALY if VTE risk was <0.85%, bleeding risk was >12%, life expectancy was <5.4 years, patient's age was >76.5 years, or the cost of LWMH exceeded $98/dose. If VTE risk was <0.2% or bleeding risk was >25%, the harms of prophylaxis outweighed the benefits. The prophylaxis threshold was relatively insensitive to the cost of LMWH and bleeding risk but very sensitive to life expectancy.

Aim 5. In progress. Enrollment for the RCT is completed, but we have not yet validated the outcome data from the EHR. After that is complete, we will perform the specified analyses.

Discussion

This final report includes the main findings of our studies to date. The first aim successfully produced a risk assessment model (RAM) that can be used on admission for medical patients and that outperformed the currently recommended RAM (Padua) in our validation cohort. Our RAM is well calibrated and has reasonable discrimination. Additional validation in external cohorts from other organizations would be desirable prior to widespread usage. In addition, our RAM was calibrated based on 14-day events. It performed substantially better in predicting 14-day events than 45-day events. We found that it was possible to calibrate the model on one outcome or the other and that we could produce better discrimination using the 14-day outcome. We also felt that the 14-day outcome was more likely to be affected by prophylaxis in the hospital. Other models, such as Padua, were developed using 90-day outcomes. That may be one reason that our model outperformed theirs.

At the same time, we created a decision analytic model to identify the appropriate threshold of VTE risk at which to initiate prophylaxis. We found that the model was relatively insensitive to bleeding risk, because prophylaxis has little impact on the risk of major bleeding. We therefore deferred work on the bleeding risk model while we performed the RCT. The decision model found that prophylaxis is cost effective for patients with a predicted risk of VTE of at least 0.8%. This threshold is sensitive to life expectancy, because most benefits of VTE prophylaxis are long term. Patients with longer life expectancy derive more benefits from prophylaxis, and vice versa. This finding is novel and has not been considered previously. Because VTE prophylaxis has not been demonstrated to reduce mortality, all benefits come from reducing other complications of VTE, including pulmonary hypertension and post-phlebitic syndrome, and these benefits accrue over a lifetime. The harms of prophylaxis, including bleeding and heparin-induced thrombocytopenia, occur immediately and do not have long-term implications. Thus, patients with longer life expectancy have a more favorable ratio of benefits to harms. Future recommendations regarding prophylaxis should consider patient age not only as a risk factor but also as a moderator of potential gains from prophylaxis.

Our randomized trial has completed enrollment, but the final events have not been adjudicated; therefore, we were unable to present our main findings. We did find that physicians were generally hesitant to use the calculator, despite abundant messaging from our department of hospital medicine, local champions, and the use of audit and feedback. One obstacle was trying to educate thousands of physicians across diverse hospitals with different local cultures. Use of the calculator varied substantially from one hospital to another, ranging from a low of 5% to a high of 75%. In the future, we intend to incorporate the calculator as a hard stop in our order set across the health system. We are also conducting a qualitative study to better understand why physicians chose not to use it.

These investigations have yielded a rich dataset that is poised to produce a number of important manuscripts. Over the coming year, we plan to publish the following analyses:

1. Our VTE RAM (including 14- and 45-day outcomes) compared with the Padua model.
2. A qualitative study exploring why physicians are hesitant to use a RAM for deciding about VTE prophylaxis.

3. An observational study of the use of VTE prophylaxis prior to implementation of the RAM, demonstrating how well physicians were able to intuit risk (or calculate it using other RAMs).
4. Our bleeding RAM compared with the IMPROVE model.
5. An observational study of the effectiveness of VTE prophylaxis, comparing patients who received prophylaxis every day, those who missed one or more doses, and those who did not receive it, adjusted for baseline risk of VTE. We will also stratify the analysis based on length of stay to see whether prophylaxis is effective for patients with a length of stay shorter than 6 days, which was a general inclusion criteria in previous RCTs of prophylaxis efficacy.
6. An observational study of the incidence, of HIT, the cost of investigating HIT, and risk factors for HIT.
7. An observational study of the risk of VTE in stroke patients as well as the efficacy of VTE prophylaxis in this population.

Conclusions

It is possible to predict VTE with data available in the EHR at admission. Patients with an overall 90-day risk of at least 0.8% (or a 14-day risk of 0.25%) should receive prophylaxis, although this threshold can be adjusted for age or life expectancy. A risk calculator using this information can be incorporated into an EHR, but, unless it is a hard stop, physicians may be reluctant to use it. Our study assessing the impact on patient outcomes is closed to enrollment. Results should be available shortly.

Significance

VTE is a common hospital-acquired complication. VTE prophylaxis can reduce VTE in surgical patients and, to a lesser extent, in medical patients. Risk stratification is key to maximizing the ratio of benefit to harm from VTE prophylaxis. Our risk assessment model can be used for this purpose and appears to outperform other models. Patients with a 14-day risk of 0.25% or greater may benefit from VTE prophylaxis. Because more than half of patients are below this threshold, use of the model could avoid prophylaxis for large numbers of patients. If our RCT demonstrates improved patient outcomes, it could be widely adopted.

Implications

Implications are unclear at this point. Results of the RCT should be available in the coming months.

LIST OF PUBLICATIONS AND PRODUCTS

Le P, Martinez KA, Pappas MA, **Rothberg MB**. *A decision model to estimate a risk threshold for venous thromboembolism prophylaxis in hospitalized medical patients*. J Thromb Haemost, 2017 Jun;15(6):1132-1141. PMID: 28371250

Rothberg MB, Hamilton A, Kou L, Hu B, Pappas MA. *Development and Validation of a Risk Assessment Model for VTE in Hospitalized Medical Patients*. J Gen Intern Med, 2018, S156.