HHS Public Access

Author manuscript

Thromb Res. Author manuscript; available in PMC 2015 June 16.

Published in final edited form as:

Thromb Res. 2014 January ; 133(1): 25–29. doi:10.1016/j.thromres.2013.09.011.

Risk factors for inpatient venous thromboembolism despite thromboprophylaxis

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Abstract

Introduction—Venous thromboembolism (VTE) is the most common preventable cause of morbidity and mortality in the hospital. Adequate thromboprophylaxis has reduced the rate of hospital-acquired VTE substantially; however, some inpatients still develop VTE even when they are prescribed thromboprophylaxis. Predictors associated with thromboprophylaxis failure are unclear. In this study, we aimed to identify risk factors for inpatient VTE despite thromboprophylaxis.

Materials and methods—We conducted a case-control study to identify independent predictors for inpatient VTE. Among patients discharged from the BJC HealthCare system between January 2010 and May 2011, we matched 94 cases who developed in-hospital VTE while taking thromboprophylaxis to 272 controls who did not develop VTE. Matching was done by hospital, patient age, month and year of discharge. We used multivariate conditional logistic regression to develop a VTE prediction model.

Results—We identified five independent risk factors for in-hospital VTE despite thromboprophylaxis: hospitalization for cranial surgery, intensive care unit admission, admission leukocyte count >13,000/mm^3, presence of an indwelling central venous catheter, and admission from a long-term care facility.

Conclusions—We identified five risk factors associated with the development of VTE despite thromboprophylaxis in the hospital setting. By recognizing these high-risk patients, clinicians can

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Conflicts of interest

All authors declare no conflicts of interest.

The abstract of this paper was presented in the poster format at the American Society of Hematology 54th Annual Meeting and Exposition on December 9, 2012

prescribe aggressive VTE prophylaxis judiciously and remain vigilant for signs or symptoms of VTE.

Keywords

venous thromboembolism; thromboprophylaxis; anticoagulation; risk factors

Introduction

Venous thromboembolism (VTE) causes significant morbidity and mortality in hospitalized patients. Pulmonary embolism (PE) is the most preventable cause of hospital death [1, 2]. Prophylactic anticoagulation decreases the incidence of VTE by 50% to 75%, both in surgical and medical hospitalized patients [3–6]. Therefore, the 2012 American College of Chest Physicians practice guideline recommends pharmacological VTE prophylaxis in hospitalized patients with high risk of thrombosis [7].

Despite appropriate thromboprophylaxis, some inpatients still develop VTE. Approximately half of in-hospital VTEs occur on thromboprophylaxis [8]. Even with pharmacological and/or mechanical thromboprophylaxis, VTEs are common after trauma or orthopedic surgery [9, 10]. Therefore, for high-risk patients, routine thromboprophylaxis may not be sufficient [8, 9]; combining medical prophylaxis with early ambulation or mechanical prophylaxis may be more effective [11, 12]. Thus, identifying this subset of patients with particularly high risk of VTE is important and allows closer observation and potential intensification of thromboprophylaxis.

Limited literature is available regarding the risk factors associated with the failure of prophylactic anticoagulation. In the MEDENOX trial of ill medical inpatients, the rate of VTE was 5% to 6% in patients randomized to standard enoxaparin 40 mg daily and higher in patients who did not receive standard therapy [5]. MEDENOX also identified five risk factors for VTE: presence of an acute infectious disease, age older than 75 years, cancer, a history of VTE, and chronic respiratory disease [13]. However, most of these VTE were asymptomatic and detected only on venographic screening. To investigate risk factors for symptomatic VTE, we performed a case-control study of patients discharged from the BJC Health Care system between January 1, 2010, and May 31, 2011.

Materials and Methods

Patient inclusion and data collection

We conducted a case-control study using data from seven hospitals in the BJC HealthCare system, a large nonprofit health care organization serving Missouri and southern Illinois. The seven hospitals included a university-based tertiary referral center (Barnes-Jewish Hospital, the largest teaching hospital of Washington University in St. Louis) and six affiliated community hospitals. The primary objective of the study was to identify risk factors associated with the occurrence of new inpatient VTE despite appropriate thromboprophylaxis. Cases and controls were prescribed thromboprophylaxis while

hospitalized at one of the seven participating hospitals between January 1, 2010, and May 31, 2011. Cases had symptomatic VTE; controls did not have a VTE.

As detailed (Appendix A), we identified VTE using a modified version of AHRQ PSI 12 (Agency for Healthcare Research and Quality Patient Safety Indicators 12, version 4.2) [14] and confirmed each VTE with chart review. We improved sensitivity by extending the PSI 12 to the non-surgical population. We excluded upper extremity thromboses by excluding all sub-categorized codes of 453.8, except for 453.89. We also excluded patients with any of the following: length of stay <48 hours, age <18 years, or patients assigned to major diagnostic category 14 (pregnancy, childbirth, and puerperium). To reduce the number of false positive VTE, we excluded patients with a VTE diagnosis present on admission and patients with an order for therapeutic anticoagulation for VTE within the first 48 hours of admission. According to our chart reviews, this modified measure had a sensitivity and negative predictive value of 100%, specificity of 84%, and positive predictive value of 74%.

We matched each chart-verified VTE case to three control patients. Controls were matched by hospital, age (within five years), and month and year of hospitalization. We stratified our study population based on type of prophylaxis: pharmacologic vs. mechanical. Among patients prescribed pharmacologic prophylaxis, we randomly sampled 50 VTE case patients and 150 non-VTE matched control patients. All 200 of these patients started receiving pharmacologic prophylaxis (including unfractionated heparin, low-molecular-weight heparin, or warfarin, refer to Table 1 for dosing definition) within the first 48 hours of admission. Among patients prescribed mechanical prophylaxis, we identified 44 VTE cases and matched them to 130 controls (one case had only one matched control available). The final sample size was 366 patients (94 VTE cases and 272 non-VTE controls) because eight controls were excluded due to missing data.

Administrative data were used for patient identifiers and basic demographics (i.e., gender, race, age). All other data were collected by systematic abstraction of the inpatient medical records. For VTE cases, patients were considered positive for a risk factor only if it was documented prior to the VTE diagnosis. VTE risk factors that were not consistently available from the inpatient medical record (i.e., varicose veins and a prior history of smoking) could not be assessed. The definitions and sources of putative risk factors were detailed in Appendix B.

Data analysis

The groups of pharmacologic and mechanical prophylaxis were analyzed separately initially, but similar results were found, and hence we combined them in the final analysis. We used univariate conditional logistic regression to identify multivariate model inputs. All continuous variables, with the exception of age, had skewed distributions, and therefore were log-transformed. Variables with a p-value <0.10 were offered into the multivariable model, but were retained only if the direction of the odds ratio (OR) was consistent with the literature and the p-value was ≤0.05. Leukocyte count was offered as quartiles, with the second quartile ([6.8–9.6]x10^3/mm^3) as reference. We evaluated model fit by examining plots of residuals and influence measures. The c-statistic was estimated using unconditional logistic regression. All analyses were performed using SAS version 9.3.

This study was approved and conducted according to guidelines established by the Institutional Review Board of each institution. The requirement for informed consent was waived because measurements and care performed in the study were part of routine clinical care and confidentiality was maintained.

Results

Patient characteristics

A total of 366 patients were included: 94 VTE cases and 272 matched controls. Overall, patient characteristics in VTE cases were comparable to controls (Table 2). Age, gender, race, and BMI were similar. Among patients with VTE, 62.8% (59/94) had deep vein thrombosis (DVT), while 36.1% (34/94) had pulmonary embolism (PE), and 1 patient (1.1%) had both DVT and PE.

Univariate analysis

We used a univariate conditional logistic regression model to identify VTE risk factors (Table 2). Many clinical factors increased the risk of VTE: acute respiratory diseases, extremity paresis or plegia, infection, prior history of VTE, trauma, indwelling central venous catheter (CVC), bed rest, and surgery. Significant laboratory risk factors included: packed red blood cell or fresh frozen plasma transfusion, blood culture ordered, or admission leukocyte count > 13,000/mm^3. History of cancer (reference to no cancer or active cancer) and hypertension were found to have lower odds of VTE in our study.

Multivariate analysis

The multivariate analysis identified five independent predictors of inpatient VTE (Table 3): cranial surgery, hospitalization in an ICU, admission leukocyte count of >13,000/mm^3, presence of an indwelling CVC, and admission from a long-term care facility. Cranial surgery had a particularly high OR (16.1), while all other factors had OR of 2 to 3. The highest variance inflation factor (VIF) is 1.37, indicating low multicollinearity. Hosmer-Lemeshow χ^2 was not significant for combined or pooled model, suggesting adequate calibration.

Discussion

We identified five independent risk factors for VTE despite thromboprophylaxis and their multivariate ORs (95% CI [confidence interval]) were: 16.1 (3.2–80.4) for cranial surgery, 3.0 (1.5–5.9) for hospitalization in an ICU, 2.7 (1.4–5.1) for leukocytosis, 2.5 (1.3–4.7) for a CVC, and 2.1 (1.0–4.2) for admission from a long term care facility.

Thus, this study validates the relationship between VTE and cranial surgery, hospitalization in an ICU, and CVCs [15–17]. In a prior study, half of neurosurgical patients had VTE detectable on screening, while 5% developed symptomatic VTE [17]. Another study found that one-third of patients hospitalized in the ICU developed VTE, although most of those patients had received thromboprophylaxis [15]. A retrospective study found that CVCs doubled the risk of inpatient VTE [16]. Thus, the current study confirms that neurosurgical

patients, intensive care patients, and patients with CVCs have a high risk of VTE, even in the presence of thromboprophylaxis.

In our study, patients with leukocytosis also had a high risk of VTE, as found in some prior studies. Leukocytosis was associated with VTE in a cancer population [19, 20] and in a primary-care population [21]. We found that leukocytosis was a risk factor for VTE among inpatients despite thromboprophylaxis. Leukocytosis is often associated with acute infection, a VTE risk factor [13, 22–25]. The pathogenesis may be related to infection induced systemic inflammation and endothelial disruption leading to a hypercoagulable state. The clinical relevance is that leukocyte count is an objective and rapid assay to identify patients at high VTE risk on admission, without waiting for cultures.

Like leukocytosis, admission from a long-term care facility was a readily identifiable risk factor for inpatient VTE. A previous population based case-control study showed a 5.6 fold increased risk of VTE in nursing home residents [26, 27]. The pathogenesis may be the decreased mobility of long-term care facility residents. This information is readily available and should encourage ambulation and aggressive thromboprophylaxis in this debilitated population.

Prior studies have identified several risk factors of hospital-acquired VTE. The MEDENOX trial found 5 VTE risk factors: age >75 years, cancer, previous VTE, acute infectious disease, and chronic respiratory disease [13]. In an analysis of administrative data, Rothberg *et al.* found that in-hospital VTE was associated with male gender, age (>65 years), prolonged hospitalization (≥6 days), inflammatory bowel disease, malignancy, CVC, mechanical ventilation, chemotherapy, and steroids [16]. A retrospective case-control study in inpatients identified other risk factors for VTE: recent trauma, leg edema, pneumonia, and high platelet count (>250 x 10^3/mm^3) [28]. Each of these studies found a different set of risk factors. No more than one-third of patients received effective thromboprophylaxis in each of these studies, and unlike our study, none of the prior studies focused on inpatients who developed VTE despite thromboprophylaxis with one exception: A study of medical inpatients receiving prophylactic unfractionated heparin, which found that history of VTE was a risk factor for a new VTE [29].

Our study has several limitations. First, it is a retrospective study of 94 cases, and thus may not have sufficient power to detect risk factors that are rare. The small sample size may limit proper stratification to account for potential interactions among additional risk factors. Second, because we matched on age, we were unable to quantify the increased VTE risk in the elderly [30, 31]. Third, the use of thromboprophylaxis was inferred from physician orders rather than thromboprophylaxis administration. However, based on internal data (not shown), more than 90% of prescribed thromboprophylactic doses were administered [32], but compliance with mechanical prophylaxis is variable.. Fourth, because we defined therapeutic enoxaparin as > 60 mg daily dose (Table 1), we may have inadvertently excluded patients who received higher doses of enoxaparin as prophylaxis (such as in morbidly obese patients), thereby limiting our ability to identify obesity as a VTE risk factor.

These limitations are offset by several strengths. The first is generalizability; our study was conducted in several hospitals across the BJC HealthCare system, including a university-based tertiary referral center and several community hospitals. A second strength was that we standardized a practical approach to capture the effect of infection on VTE risk [13]: leukocytosis on admission was associated with 2.7-fold odds of subsequent VTE. Furthermore, all of the five risk factors in our multivariate analysis are easily identifiable on admission, allowing clinicians to pay close attention to high-risk patients and to minimize their risk of VTE.

In conclusion, we identified five risk factors associated with failure of thromboprophylaxis: cranial surgery, hospitalization in an ICU, leukocytosis, presence of a CVC, and admission from a long term care facility. Interventions such as aggressive early ambulation, using enoxaparin instead of unfractionated heparin [33–35], and combining mechanical and pharmacologic thromboprophylaxis [11, 12] have been shown to reduce VTE rate and can be applied early-on during an admission in patients with the risk factors identified in our study. Moreover, the use of new oral anticoagulants [36] in these high risk patients to minimize VTE risk should also be explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding sources

This study was funded in part by the BJC Center for Clinical Excellence, the NIH (R01 HL 097036 and U54HL11230301).

The authors thank Nicole Hepner for her insightful comments on an earlier version of the manuscript.

Abbreviations (shown in the order of appearance in the manuscript)

VTE	venous thromboembolism
PE	pulmonary embolism
MEDENOX trial	“prophylaxis in medical patients with enoxaparin” trial
AHRQ PSI 12	Agency for Healthcare Research and Quality Patient Safety Indicators 12, version 4.2
OR	odds ratio
DVT	deep vein thrombosis
INR	international normalized ratio
ICU	intensive care unit
CI	confidence interval
CVC	central venous catheter

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Table 1

Dosing definition of VTE prophylaxis and therapy in the current study (VTE = venous thromboembolism; N/A = not applicable).

Medication	VTE prophylaxis	VTE therapy
Argatroban	N/A	Any daily dose
Bivalirudin	N/A	Any daily dose
Dalteparin	≤ 5000 units daily dose	> 5000 units daily dose
Desirudin	N/A	Any daily dose
Enoxaparin	30 to 60 mg daily dose	> 60 mg daily dose
Fondaparinux	2.5 mg daily dose	> 2.5 mg daily dose
Heparin (subcutaneous)	≤ 22,500 units daily dose	> 22,500 units daily dose
Heparin (intravenous)	N/A	Any daily dose
Lepirudin	N/A	Any daily dose
Warfarin	Any daily dose	N/A

Thromb Res. Author manuscript; available in PMC 2015 June 16.

Table 2

Univariate Conditional Logistic Regression Predictors of VTE in Prophylaxed Patients

Variable*	VTE (n = 94) N (%)	No VTE (n = 272) N (%)	OR / Mean Difference	95% CI	p Value
Demographics					
Age (mean years ± SD)	62.5 (16.6)	62.6 (16.6)	0.2	−3.7 to 4.0	0.94
Female Gender	43 (45.7)	149 (53.2)	0.7	0.5–1.2	0.21
Non-White Race*	18 (19.2)	68 (24.3)	0.7	0.4–1.3	0.30
BMI (anti-log mean)**	28.2	27.8	1.0	1.0–1.1	0.57
Current Smoker	12 (12.8)	53 (18.9)	0.6	0.3–1.2	0.15
Length of Stay (LOS) until VTE (anti-log mean days)	**6.3**	**4.6**	**1.4**	**1.2–1.6**	**< 0.001**
Cancer					
Active Cancer (reference never or history of cancer)	16 (17.0)	46 (16.4)	1.1	0.6–2.0	0.87
History of Cancer (reference never or active cancer)	**3 (3.2)**	**44 (15.7)**	**0.2**	**0.1–0.6**	**0.01**
Chemotherapy	4 (4.3)	17 (6.1)	0.7	0.2–2.1	0.50
Other Comorbid Conditions					
Acute Respiratory Failure	**8 (8.5)**	**9 (3.2)**	**2.7**	**1.0–6.9**	**0.04**
Chronic Obstructive Pulmonary Disease (COPD)	8 (8.5)	40 (14.3)	0.6	0.3–1.3	0.17
Congestive Heart Failure (CHF)	15 (16.0)	36 (12.9)	1.3	0.7–2.5	0.43
Diabetes	24 (25.5)	84 (30.0)	0.8	0.5–1.4	0.42
Hypertension	**51 (54.3)**	**181 (64.6)**	**0.6**	**0.3–1.0**	**0.04**
Myocardial Infarction (MI)	5 (5.3)	6 (2.1)	2.7	0.8–9.5	0.12
Peripheral Artery Disease	6 (6.4)	14 (5.0)	1.3	0.5–3.6	0.59
Stroke	3 (3.2)	3 (1.1)	3.0	0.6–14.9	0.18
Neurological Disease	13 (13.8)	27 (9.6)	1.5	0.7–3.2	0.24
Renal Disease	18 (19.2)	52 (18.6)	1.1	0.6–2.0	0.88
Spinal Cord Injury	**3 (3.2)**	**1 (0.4)**	**9.0**	**0.9–86.5**	**0.06**
Extremity Paresis or Plegia	**9 (9.6)**	**10 (3.6)**	**2.8**	**1.1–7.4**	**0.04**
VTE in Prior Year	6 (6.4)	8 (2.9)	2.3	0.8–6.5	0.13
Infection					
Any Infection	**29 (30.9)**	**36 (12.9)**	**2.8**	**1.6–4.9**	**< 0.001**

Variable*	VTE (n = 94) N (%)	No VTE (n = 272) N (%)	OR / Mean Difference	95% CI	p Value
Blood Infection	**13 (13.8)**	**9 (3.2)**	**5.7**	**2.1–15.0**	**< 0.001**
Blood Culture Ordered	**21 (22.3)**	**16 (5.7)**	**5.0**	**2.4–10.4**	**< 0.001**
First leukocyte count > 13,000/mm^3	**39 (41.5)**	**52 (19.1)**	**3.1**	**1.8–5.2**	**< 0.001**
Surgery					
Surgery	**47 (50.0)**	**101 (36.1)**	**1.9**	**1.2–3.2**	**0.01**
> 1 Surgery	**14 (14.9)**	**5 (1.8)**	**10.0**	**3.3–30.6**	**< 0.001**
Cranial Surgery	**14 (14.9)**	**3 (1.1)**	**14.0**	**4.0–48.7**	**< 0.001**
Non-Cranial Surgery	33 (35.1)	98 (35.0)	1.0	0.6–1.7	0.94
Craniospinal Surgery	8 (8.5)	15 (5.4)	1.7	0.7–4.0	0.27
Orthopedic Surgery	7 (7.5)	23 (8.2)	0.9	0.4–2.2	0.83
Other Surgery	19 (20.2)	60 (21.4)	0.9	0.5–1.7	0.82
Trauma	**17 (18.1)**	**15 (5.4)**	**3.6**	**1.7–7.4**	**< 0.001**
Transfusion					
Fresh Frozen Plasma (FFP) Transfusion	**10 (10.6)**	**9 (3.2)**	**3.8**	**1.4–10.2**	**0.01**
Packed Red Blood Cells (PRBCs) Transfusion	**37 (39.4)**	**47 (16.8)**	**3.2**	**1.9–5.3**	**< 0.001**
PRBCs Transfusion in first 48 hours of admit	16 (17.0)	38 (13.6)	1.3	0.7–2.5	0.39
Platelet Transfusion	**6 (6.4)**	**7 (2.5)**	**3.0**	**0.9–10.1**	**0.08**
FFP, PRBCs, or Platelet Transfusion	**40 (42.6)**	**56 (20.0)**	**2.9**	**1.8–4.8**	**<0.001**
Laboratory					
First Platelets count < 140,000/mm^3	14 (14.9)	46 (16.4)	0.9	0.5–1.8	0.73
First Prothrombin Time (PT) > 15.7 seconds	**31 (33.0)**	**64 (22.9)**	**1.7**	**1.0–3.0**	**0.05**
First Partial Thromboplastin Time (PTT) > 36.0 sec	19 (20.2)	48 (17.1)	1.2	0.7–2.3	0.47
Medications					
Antiplatelet	27 (28.7)	103 (36.8)	0.7	0.4–1.2	0.15
Thrombogenic prescription	9 (9.6)	18 (6.4)	1.7	0.7–4.2	0.27
Miscellaneous					
Admitted from Chronic or Long Term Care (LTC)	**36 (38.3)**	**49 (17.5)**	**3.2**	**1.8–5.7**	**< 0.001**
Any Bedrest (including with bathroom privileges)	**45 (47.9)**	**80 (28.6)**	**2.4**	**1.5–4.0**	**< 0.001**
Critical Care Patient	**54 (57.5)**	**47 (16.8)**	**7.0**	**4.0–12.5**	**< 0.001**
Indwelling Central Venous Catheter (CVC)	**60 (63.8)**	**75 (26.8)**	**4.8**	**2.9–8.0**	**< 0.001**

* Non-White Race: No VTE group includes 2 Asian and 3 Other Race patients

** BMI: excludes 30 control patients with missing height and/or weight data

† WBC: excludes 8 control patients with no WBC lab

Table 3

Multivariate conditional logistic regression model (VTE = 94, no VTE = 272)

Risk factors	OR	95% CI	p value
Cranial surgery	16.1	3.2–80.4	<0.001
Intensive care patient	3.0	1.5–5.9	0.002
Admission leukocyte count > 13,000/mm^3	2.7	1.4–5.1	0.003
Indwelling central venous catheter	2.5	1.3–4.7	0.007
Long term/chronic care facility	2.1	1.0–4.2	0.04

Note: 8 controls were excluded from the pooled model due to missing leukocyte values