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Venous Thromboembolism Prophylaxis: Need for Continuous Assessment Due to Changes in Risk During the Same Hospitalization

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Abstract

Objective: To explore the role of venous thromboembolism (VTE) risk reassessment in hospitalized medically ill patients without a change in level of care.

Patients and Methods: In this exploratory retrospective study, the medical records of 171 consecutive adult patients (≥18 years) hospitalized under the medicine service for more than 3 days without a change in the level of care from January 1, 2015, to March 1, 2015, were reviewed. The primary outcome was a change in the risk score between day 1 and day 3 of hospital stay (using the Padua Prediction Score). The secondary outcomes were changes in risk stratification class (low vs high) and cost-benefit analysis.

Results: The risk score was significantly different between day 1 and day 3 (4.7±1.7 vs 4.2±1.8; P=.008). All the patients with low risk on day 1 remained at low risk on day 3. However, 25 of 136 patients (18.4%) with high risk on day 1 were reclassified as low risk on day 3 (P<.001). No patients changed from low risk to high risk at day 3. The reclassification could have saved $35 per patient-day of inappropriate pharmacological prophylaxis in addition to patient discomfort, bleeding risk, and heparin-induced thrombocytopenia.

Conclusion: This is the first study to suggest the need for regular assessment for VTE risk on medicine wards because of changing patient risk. Regular reassessment could reduce health care waste and patient discomfort.

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Venous thromboembolism (VTE) is an important cause of morbidity and mortality in hospitalized patients.[1] In patients admitted to medical wards, the incidence of VTE approximates 1 in 1000.[2,3] However, because of its nonspecific symptoms, this figure remains underestimated.[4,5] The American College of Chest Physicians recommends VTE prophylaxis for most medical patients in whom the benefits outweigh the risks. According to the ninth edition of their guidelines, hospitalized patients under medical service should undergo appropriate risk stratification using the Padua Prediction Score at the time of admission, at change in the level of care, and at the time of discharge.[6] This assessment is to be followed by pharmacological or mechanical VTE prophylaxis in patients with high risk and without any contraindications.[7] However, some patients have a prolonged hospital stay without a change in the level of care because of slowly improving medical conditions, especially older individuals with complex needs. The goal of this study was to evaluate the role of reassessing VTE risk in medical patients who had a hospital stay of more than 3 days without change in their level of care.

PATIENTS AND METHODS

We performed a retrospective medical record review of 200 consecutive adult patients

(≥18 years) admitted to general medical wards at Sinai Hospital in Baltimore, Maryland, between January 1, 2015, and March 1, 2015. The exclusion criteria included (1) admission to a nonmedical service, (2) admission to the intensive care unit, (3) hospital stay of less than 3 days, (4) admission for pulmonary embolism or deep venous thrombosis (DVT), (5) active bleeding or recent blood loss, (6) anticoagulation therapy, and (7) pregnancy. After exclusions, a total of 171 patients were eligible for analysis. The individual patient's risk for VTE was calculated using the Padua Risk Prediction model.[6] The score was then reassessed at day 3 of hospital stay. This study was approved by the Sinai Hospital Institutional Review Board.

Definitions

Venous thromboembolism prophylaxis was defined to include both pharmacological and nonpharmacological therapies. The former category consisted of low-molecular-weight heparin, unfractionated heparin, and fondaparinux at prophylactic doses (dalteparin, ≤5000 IU/d; enoxaparin, ≤40 mg/d, and fondaparinux, 2.5 mg/d). The nonpharmacological therapies included ambulation, graduated compression stockings, and intermittent pneumatic compression devices.

Primary and Secondary Outcomes

The primary study end point was a change in the Padua risk score at day 3 of hospital stay.[5] Reassessment at day 3 was chosen because of 3 risk factors in the Padua risk score that can potentially change over a 3-day period, including heart failure (improvement defined as >92% oxygen saturation while the patient breaths room air and is receiving oral diuretic agents), acute myocardial infarction (improvement defined as >24 hours after cardiac catheterization or troponin levels trending down with patients receiving dual antiplatelet therapy), and acute infection (resolution defined as improvements in hemodynamic status—eg, heart rate, blood pressure, white blood cell count, temperature, oxygenation, and/or radiologic findings after receiving appropriate antibiotic therapy for 3 days or since last blood culture findings were negative).[8,9] The secondary outcome was a change in risk stratification class (low vs high) and cost-benefit analysis. A Padua risk score of 4 or greater was considered high risk. For a calculated Padua risk score of 4 or greater, pharmacological prophylaxis (unless contraindicated) was deemed appropriate, and for a score of less than 4, mechanical or no prophylaxis was deemed appropriate.

Statistical Analyses

Categorical variables are expressed as number (percentage) and continuous variables as mean ± SD, with $P \leq .05$ considered statistically significant. The Fisher exact test was used for comparison of categorical variables. The Student t test was utilized for normally distributed continuous data sets, and the Welch t test was used for continuous data sets that did not follow a normal distribution (commercially available IBM SPSS Statistics 22).

RESULTS

Patient Characteristics

We compared the group of patients who had a major change in overall risk (from high to low risk) with the group with no change in risk. The group with a change in overall risk over a 3-day period had a significantly higher proportion of patients with acute infections at admission ($P<.001$) and a lower proportion of patients who were older than 70 years ($P=.01$) and patients with active cancer ($P=.03$) than the group that did not have a change in risk (Table 1).

Primary and Secondary Outcomes

The calculated VTE risk score was significantly different between day 1 and day 3 (4.7±1.7 vs 4.2±1.8; $P=.008$) (Figure). All the patients with low risk on day 1 remained at low risk on day 3. However, 25 of 136 patients (18.4%) with high risk on day 1 were restratified as low risk on day 3 ($P<.001$). No patients changed from low risk to high risk at day 3. The reclassification could have saved 79 patient-days ($1976) of inappropriate pharmacological prophylaxis and additional cost of monitoring complete blood cell count every other day for heparin-induced thrombocytopenia (total of $35 per patient-day) in addition to patient discomfort and bleeding

TABLE 1. Baseline Demographic Characteristics of the Study Population[a,b]

Variable	Overall population (n=171)	Patients with a change in risk between day 1 and day 3 (n=25)	Patients without a change in risk between day 1 and day 3 (n=146)	*P* value
Age (y)	65.2±18.3	67.2±19.0	64.9±18.2	.57
Age >70 y	94 (55.0)	8 (32.0)	86 (58.9)	.01
Active cancer	22 (13.0)	0 (0)	22 (15.1)	.03
Previous VTE	14 (8.0)	1 (4.0)	13 (8.2)	.46
Reduced mobility	104 (61.0)	14 (56.0)	90 (61.6)	.59
Acute myocardial infarction	7 (4.0)	0 (0)	7 (4.1)	.30
Acute heart failure	29 (17.0)	3 (12.0)	26 (17.8)	.47
Acute stroke	3 (2.0)	1 (4.0)	2 (1.3)	.35
Acute infection	97 (57.0)	23 (92.0)	74 (51.4)	<.001
Body mass index >30 kg/m^2	57 (33.0)	5 (20.0)	52 (35.6)	.12
Calculated risk (Padua score)				
Admission	4.7±1.7	4.2±0.6	4.8±1.8	.06
Day 3	4.2±1.8	3.0±0.2	4.4±1.9	<.001

[a]VTE = venous thromboembolism.
[b]Data are presented as mean ± SD or No. (percentage) of patients.

risk in 25 patients (mean of 3 days per patient IQR 2 to 4 days). In the study population, no major bleeding events, clinically relevant nonmajor bleeding events, VTE events, or deaths were noted.

DISCUSSION

To our knowledge, this is the first study to suggest that the risk of VTE can change in hospitalized patients who stay for more than 3 days on medical wards without change in their level of care. Further, this study found that a reassessment of VTE risk 3 days after hospitalization can reduce the number of patients receiving pharmacological prophylaxis, thus avoiding the additional cost, risk for bleeding events, and heparin-induced thrombocytopenia as well as the discomfort associated with subcutaneous injections.

The current American College of Chest Physicians guidelines[10] and the Agency for Healthcare Research and Quality recommend regular reassessment of VTE risk at admission, change in level of care, and discharge. These recommendations stem from multiple trials documenting a reduction in VTE events with extended use of prophylaxis in high-risk patients at the time of discharge.[11-13] Spencer et al[13] reviewed the medical records of 1897 patients with VTE and found that 73.7% of episodes occurred in the outpatient setting. Of these episodes, 36.8% occurred in individuals hospitalized for a medical illness in the preceding 3 months; VTE was diagnosed within 1 month after hospitalization in two-thirds and from 2 to 3 months after hospitalization in one-third.[13] In the MEDENOX (Prophylaxis in Medical Patients With Enoxaparin) study comparing enoxaparin prophylaxis with placebo for up to 14 days, 8 VTE events (8% of the total) occurred between days 15 and 110, 4 of which were fatal events.[12] However, these trials did not assess the increased risk of bleeding associated with pharmacological prophylaxis. The Extended Prophylaxis for Venous Thromboembolism in Acutely Ill Medical Patients With Prolonged Immobilization (EXCLAIM) study compared extended use of enoxaparin with placebo for both safety (major bleeding) and efficacy (incident VTE) outcomes.[11] In this trial, 6085 hospitalized patients with acute medical illness and

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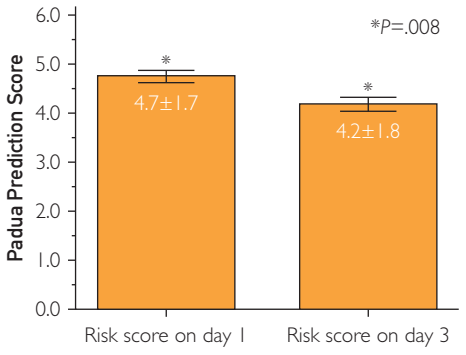

FIGURE. Change in Padua risk prediction score between hospital days 1 and 3.

reduced mobility were randomized to receive enoxaparin, 40 mg/d subcutaneously (2975 patients), or placebo (2988 patients) for 28±4 days after receiving open-label enoxaparin for an initial 10±4 days. Compared with placebo, extended-duration enoxaparin prevented 6 fewer symptomatic proximal DVTs per 1000 (95% CI, 3-7 fewer) at a cost of 5 more major bleeding events per 1000 (95% CI, 1-14 more).

Direct oral anticoagulants have also been evaluated for extended thromboprophylaxis in an outpatient setting among medically ill patients.[14-17] In the ADOPT (Apixaban Dosing to Optimize Protection From Thrombosis) trial, apixaban (2.5 mg twice daily) was evaluated for extended thromboprophylaxis for a period of 30 days and compared with enoxaparin (subcutaneously at 40 mg once daily) for a period of 6 to 14 days among 6528 acutely ill patients with at least one additional risk factor for VTE.[14] Apixaban was found to be nonsuperior to subcutaneous enoxaparin in reducing the 30-day composite of death related to VTE, pulmonary embolism, symptomatic DVT, or asymptomatic proximal leg DVT (2.71% vs 3.06%, respectively; *P*=.44) and was associated with significantly more major bleeding events than enoxaparin at day 30 (0.47% vs 0.19%; relative risk [RR], 2.58; 95% CI, 1.02-7.24; *P*=.04).[14] In the APEX (Acute Medically Ill VTE Prevention With Extended Duration Betrixaban) trial,[15] betrixaban (80 mg once daily) was compared with enoxaparin (subcutaneously at 40 mg once daily) among 7513 acutely medially ill patients for extended prophylaxis (enoxaparin 10±4 days and betrixaban 35-42 days). In this exploratory analysis, betrixaban was suggested to have a benefit in reducing the composite primary outcome of asymptomatic proximal DVT and symptomatic VTE in the overall cohort (5.3% vs 7.0%; RR, 0.76; 95% CI, 0.63-0.92; *P*=.006) compared to enoxaparin with similar major bleeding events (0.7% vs 0.6%; RR, 1.19; 95% CI, 0.67-2.12; *P*=.55).[15] In the MAGELLAN (Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin) trial,[16] rivaroxaban (10 mg once daily for 35±4 days) was compared to subcutaneous enoxaparin (subcutaneously 40 mg daily for 10±4 days) in 8101 patients. Rivaroxaban was found to be noninferior to enoxaparin for standard duration thromboprophylaxis and reduced the composite of asymptomatic proximal or symptomatic VTE in patients with extended prophylaxis at day 35 (4.4% vs 5.7%; RR, 0.77; 95% CI, 0.62-0.96; *P*=.02). However, rivaroxaban was associated with a higher bleeding rate both at standard duration follow-up (2.8% vs 1.2% [*P*<.001] compared to enoxaparin at day 10 and 4.1% vs 1.7% [*P*<.001] compared to placebo).[16] In the MARINER (Medically Ill Patient Assessment of Rivaroxaban Versus Placebo in Reducing Postdischarge Venous Thromboembolism Risk) trial,[17] extended rivaroxaban (10 mg daily) thromboprophylaxis was compared with placebo for the duration of 45 days postdischarge among 12,019 medically ill patients. The results revealed no significant differences in the primary composite outcome of symptomatic VTE or death due to VTE (0.83% vs 1.10%; hazard ratio [HR], 0.76; 95% CI, 0.52-1.09; *P*=.14) and major bleeding events (0.28% vs 0.15%; HR, 1.88; 95% CI, 0.84-4.23). However, rivaroxaban was associated with a reduction in the prespecified secondary end point of symptomatic nonfatal VTE compared to placebo (0.18% vs 0.42%; HR, 0.44; 95% CI, 0.22-0.89).[17] The target population warranting extended prophylaxis remains to be defined—those in whom the added value of thromboprophylaxis with respect to clinical benefits would outweigh the risks of bleeding and development of heparin-induced

thrombocytopenia (with enoxaparin) and costs of the thromboprophylaxis.

Among hospitalized medically ill patients, no role of regular VTE risk assessment has been described without a change in level of care. In this pilot study of 171 patients, we found that a regular reassessment of VTE risk without a change in level of care could have saved 3 additional days of inappropriate pharmacological prophylaxis per patient who had a change in risk at day 3. In our study, all the patients with a major change in VTE risk score were reclassified from high risk to low risk at day 3. This change can be attributed to the resolution of the incident infection, heart failure, or myocardial infarction as risk factors for VTE in these patients. Infection has been reported to be a significant risk factor for VTE in multiple studies.[18,19] On the corollary, the resolution of infection would reduce the risk of VTE. An acute infection can lead to activation of the coagulation system, thus linking it with a higher risk of VTE.[19] We observed an increased incidence of infection at admission in patients with a significant change in risk at day 3 ($P<.001$), the resolution of which likely contributed to lowering of overall risk at reassessment (Table 1). Although in our study all patients with a major change in VTE risk changed from high risk to low risk, in the real world, many patients experience in-hospital complications including respiratory failure, heart failure exacerbation, acute myocardial infarction, stroke, and acute infections. The incidence of these in-hospital complications has been reported to be as follows: worsening heart failure exacerbation, up to 11%[20]; acute myocardial infarction, 42 per 100,000[21]; stroke, 2.2% to 17%[22]; and acute hospital-acquired infections, 4% to 12%.[23,24] The incidence of these reported complications reveals that patients can potentially increase from low risk to high risk and thus would warrant a change in the type of prophylaxis to prevent VTE. Hence, we propose a need for regular assessment of VTE risk in patients hospitalized for more than 3 days without change in their level of care. The results of our initial observation will be validated in a larger prospective study by introduction of a clinical decision support tool reevaluating the VTE risk at regular intervals in patients with a hospital stay of more than 3 days with a pop-up window if a change in prophylaxis is indicated and results compared between units. There will be an additional focus on clinical outcomes, which this pilot study was underpowered to detect.

CONCLUSION

This is the first study to suggest the need for regular assessment for VTE risk on medicine wards because of changing patient risk. Regular reassessment could result in reduced health care waste and patient discomfort.

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Drs Chaudhary and Kirchoff contributed equally to this work.

Abbreviations and Acronyms: **DVT** = deep venous thrombosis; **HR** = hazard ratio; **RR** = relative risk; **VTE** = venous thromboembolism

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