Extended-Duration Venous Thromboembolism Prophylaxis in Hospitalized Acutely Ill Medical Patients: A Review of the Evidence

Journal of Pharmacy Technology
2015, Vol. 31(5) 228–233
© The Author(s) 2015
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122515581849
pharmatech.sagepub.com

Katie B. Tellor, PharmD, BCPS¹, Anastasia L. Armbruster, PharmD, BCPS¹,
and James M. Hollands, PharmD, BCPS-AQ Cardiology²

Abstract

Objective: To evaluate the risks and benefits of extended-duration thromboprophylaxis (EDT) beyond hospitalization in acutely ill medical patients. **Data Sources:** PubMed was searched from inception (1946) through February 2015 for the search terms venous thrombosis/prevention and control, venous thromboembolism/prevention and control, anticoagulants, and aspirin. **Study Selection and Data Extraction:** Relevant clinical trials evaluating pharmacologic strategies for EDT were screened for inclusion. Bibliographies of articles were extensively reviewed for additional sources. **Data Synthesis:** Three studies, and one additional subgroup analysis, were identified for inclusion. Enoxaparin and rivaroxaban demonstrated a significant reduction in venous thromboembolism (VTE) with EDT, but the benefit with enoxaparin was limited to the highest risk groups and women. The improved efficacy in both studies was accompanied by a ~2.5-fold increase in risk of major hemorrhage. Apixaban was unable to demonstrate a reduction of VTE and was also associated with a significant increase in bleeding. **Conclusions:** EDT should not be routinely provided to all medically ill patients. It may be considered in patients at the highest risk for VTE, but careful consideration must be used due to the increased risk of bleeding.

Keywords

venous thromboembolism, prophylaxis, anticoagulation, thromboprophylaxis, extended duration, apixaban, rivaroxaban, enoxaparin

Background

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), affects approximately 300 000 to 600 000 people each year in the United States. It is estimated that about 10% to 30% of patients diagnosed with a VTE die within 30 days after diagnosis and about one third to one half of patients diagnosed with a DVT experience a complication such as chronic venous insufficiency or postthrombotic syndrome.¹ Because of the significant morbidity and mortality associated with VTE, the American College of Chest Physicians (ACCP) recommend that hospitalized, medically ill patients undergo a baseline assessment to estimate the risk of VTE occurrence based on risk factors for VTE, such as acute myocardial infarction, stroke, heart failure, infection, reduced mobility, or respiratory failure.² A meta-analysis comparing pharmacological thromboprophylaxis for 6 to 21 days or until discharge versus no prophylaxis in hospitalized, acutely ill medical patients demonstrated a significant

decrease in fatal PE (relative risk [RR] = 0.41; 95% confidence interval [CI] = 0.22 to 0.76) with pharmacological prophylaxis without a significant increase in major bleeding (odds ratio [OR] = 1.32; 95% CI = 0.73 to 2.37). When stratified according to baseline risk, high-risk patients experienced decreased symptomatic DVT with prophylaxis (risk difference 34 fewer per 1000; 95% CI = 51 fewer to 0 more). Based on these results, the ACCP guidelines give a strong recommendation to providing VTE prophylaxis to high-risk patients with a low-molecular-weight heparin, low-dose unfractionated heparin, or fondaparinux for 6 to

¹St Louis College of Pharmacy, St Louis, MO, USA

²Philadelphia College of Pharmacy, University of the Sciences, Philadelphia, PA, USA

Corresponding Author:

Katie B. Tellor, PharmD, BCPS, Department of Pharmacy Practice, St Louis College of Pharmacy, 4588 Parkview Place, St Louis, MO 63110, USA.
Email: katie.tellor@stlcop.edu

21 days until full mobility is restored or until hospital discharge (Grade 1B).²

Hospitalized, acutely ill medical patients may have risk factors that persist after hospital discharge. One case-control study found an association between outpatient VTE diagnosis and previous hospitalization within the previous 90 days (adjusted OR = 18.2; 95% CI = 14.1 to 23.6) despite a nonsignificant difference in pharmacological prophylaxis administered during hospitalization between cases and controls (53.5% and 47%, respectively, $P = .186$).³ Because of the persistent risk of VTE in some patients, extending the duration of thromboprophylaxis could theoretically improve outcomes. Extended-duration thromboprophylaxis (EDT), defined as prophylaxis continued beyond the initial hospital course and up to 35 days, has been well established and is recommended in orthopedic surgery patients but has not been routinely prescribed to medically ill patients on hospital discharge.^{2,4-6} At the time of publication of the 2012 ACCP guidelines, limited efficacy data were available to support or refute the continuation of pharmacological thromboprophylaxis after discharge from the hospital in the medically ill patient population. Based on limited data, current ACCP guidelines “suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay (Grade 2B).”² Since the publication of the 2012 ACCP guidelines, several oral anticoagulants such as apixaban and rivaroxaban have been approved by the Food and Drug Administration for VTE prophylaxis, and recent studies have been performed evaluating the use of EDT in medically ill patients. In the absence of updated recommendations from the most current guidelines, clinicians are faced with the challenge of EDT on discharge. There has been renewed interest in this strategy with the development of the newer oral anticoagulants, especially given their ease of administration. This article will review the current available data.

Literature Review

PubMed was searched from inception (1946) through February 2015 for the search terms *venous thrombosis/prevention and control*, *venous thromboembolism/prevention and control*, *anticoagulants*, and *aspirin*. Relevant clinical studies in the English language were identified and independently reviewed for inclusion by 2 reviewers with any conflicts resolved by a third reviewer. Bibliographies of all included articles were reviewed and cross-referenced for additional sources. Clinical studies that evaluated EDT in the setting of oncology, general surgery, orthopedic surgery, or patients residing in an intensive care unit were excluded. A total of 3 randomized controlled trials evaluating drug therapy for EDT conducted in medically ill patients were found to be relevant, with a focus on efficacy and safety outcomes of pharmacologic thromboprophylaxis with enoxaparin,

rivaroxaban, and apixaban. Other anticoagulants such as fondaparinux, dalteparin, and dabigatran have not been studied in the setting of EDT in medically ill patients. Table 1 compares the 3 trials evaluating pharmacologic thromboprophylaxis.

Hull et al and Turpie et al

The Extended Prophylaxis for Venous Thromboembolism in Acutely Ill Medical Patients with Prolonged Immobilization (EXCLAIM) study was the first clinical trial to evaluate the safety and efficacy of EDT with a low-molecular-weight heparin, enoxaparin, in acutely ill medical patients.⁷ After a 10-day open-label period of prophylaxis with enoxaparin 40 mg subcutaneously (SC) daily, patients were randomized to continued prophylaxis with enoxaparin or placebo for an additional 28 ± 4 days. The primary efficacy endpoint was the occurrence of VTE during double-blind treatment; the primary safety outcome was the incidence of major hemorrhagic complications during or in the 48 hours following the double-blind period. For this study, major hemorrhage was defined as follows: overt and associated with death; a decrease in hemoglobin ≥ 3 g/dL (changed to ≥ 2 g/dL in post hoc analysis to capture more bleeding events); transfusion of ≥ 2 units of packed red blood cells (PRBC); bleeding requiring surgical intervention; retroperitoneal, intracranial, or intraocular bleeding. Initially, patients were eligible for enrollment if they were ≥ 40 years old, had a life expectancy of at least 6 months, had reduced mobility for 3 days, and were likely to have reduced mobility for an additional 3 days after enrollment. Reduced mobility was defined as follows: level 1 immobility, total bed rest or being sedentary without bathroom privileges; level 2 immobility, with bathroom privileges. Eligibility criteria were modified after an interim analysis found lower than expected rates of VTE. After this interim analysis, to be included with level 2 immobility, patients had to have at least one of the following risk factors: >75 years of age, previous VTE, or active/previous cancer.

Extending the duration of prophylaxis with enoxaparin led to a significant absolute risk difference in VTE at 28 days of -1.53% (2.5% in enoxaparin vs 4.0% in placebo; 95.8% CI = -2.54% to -0.52%) over placebo. This result was driven mostly from a reduction in VTE risk in the level 1 immobility group (absolute risk difference = -2.18% ; 95% CI = -3.80% to -0.57%) and was not statistically different in the level 2 immobility group (absolute risk difference = -1.00% ; 95% CI = -2.31% to 0.31%). In the total study population, major hemorrhage at 30 days was increased in the enoxaparin group using either the 2 g/dL decrease in hemoglobin definition (0.8% vs 0.3%; absolute risk difference = 0.51% ; 95% CI = 0.12% to 0.89%) or the original 3 g/dL decrease in hemoglobin definition (0.44%; 95% CI = 0.1% to 0.78%). Cumulative all-cause mortality

Table 1. Summary of Randomized Controlled Trials With Extended Prophylaxis in Medically Ill Patients.

	Hull et al ⁷ and Turpie et al ⁸	Cohen et al ⁹	Goldhaber et al ¹⁰
Trial name	EXCLAIM	MAGELLAN	ADOPT
N	5963	6024	4495
Treatment regimens	Enoxaparin 40 mg SC daily for 10 ± 4 days followed by enoxaparin 40 mg SC daily or placebo for an additional 28 ± 4 days	Rivaroxaban 10 mg PO daily for 35 ± 4 days	Apixaban 2.5 mg PO twice daily for 30 days
Mobility definition	<p>Level 1: Total bed rest or sedentary without bathroom privileges</p> <p>Level 2: With bathroom privileges</p> <p>Level 2 definition was modified during an interim analysis to require an additional risk factor for VTE (age >75 years, previous VTE, cancer)</p>	<p>Enoxaparin 40 mg SC daily for 10 ± 4 days, followed by placebo</p> <p>Reduced mobility: Complete immobilization (confined to bed or chair with bathroom privileges) for ≥1 day and anticipated decreased mobility (confined to bed or chair 50% of day) for ≥4 days after randomization and anticipated decreased mobility thereafter</p>	<p>Enoxaparin 40 mg SC daily during hospitalization (minimum of 6 days)</p> <p>Moderate: Allowed for walking within the hospital room or to the bathroom</p> <p>Severe: Confinement to bed or chair at bedside</p>
Inclusion criteria	<p>Acute medical illness</p> <p>Life expectancy ≥6 months</p>	<p>Admitted <72 hours before randomization</p> <p>Acute medical illness (including active cancer)</p>	<p>Expected hospital stay ≥3 days</p> <p>CHF, acute respiratory failure, infection (without septic shock), acute rheumatic disorder, or IBD</p>
Composite endpoint	Symptomatic or asymptomatic proximal DVT, symptomatic or fatal PE	Asymptomatic proximal DVT, symptomatic DVT, symptomatic nonfatal PE, and VTE-related death for the first 10 days	Sudden death where PE could not be excluded, fatal or nonfatal PE, symptomatic DVT, or asymptomatic proximal-leg DVT
Safety outcome	Major bleeding at 30 days	Clinically relevant bleeding: composite of major or clinically relevant nonmajor bleeding	Bleeding
Major bleeding definition	Overt and associated with death	Any of the following criteria	Criteria in combination with fatal or overt bleeding
Hemoglobin decrease	≥3 g/dL decrease (≥2 g/dL used in post hoc analysis for consistency with other trials)	≥2 g/dL decrease	≥2 g/dL decrease (in a 24-hour period)
Transfusion ≥2 units PRBC or whole blood	Included	Included	Included
Critical site	Retroperitoneal, intracranial, intraocular	Intracranial, intraspinal, intraocular, pericardial, retroperitoneal, intra-articular, or intramuscular with compartment syndrome	Intracranial, intraspinal, intraocular, pericardial, or retroperitoneal bleeding
Surgical intervention	Included	Included	Included
Other bleeding definition	Minor bleeding: Those that were overt and did not meet the criteria for a major hemorrhage including: epistaxis lasting more than 5 minutes or requiring intervention, ecchymosis or hematoma larger than 5 cm, hematuria not associated with urinary catheter trauma, subconjunctival or gastrointestinal hemorrhage, or wound hematoma	Clinically relevant nonmajor bleeding: Events not meeting criteria for major bleeding but required medical intervention, unscheduled contact with a physician, temporary cessation of study treatment or discomfort for the patient such as pain, or impairment of activities of daily life	Clinically relevant nonmajor bleeding: Acute, overt bleeding including: epistaxis that required medical attention or persisted for at least 5 minutes, gastrointestinal bleeding containing frank blood or coffee-ground material, endoscopically confirmed bleeding, spontaneous hematuria or hematuria persisting for 24 hours or more after urinary tract catheterization, unusual bruising, radiographically confirmed hematoma, or hemoptysis
Baseline obesity	BMI ≥ 30 kg/m ² EDT enoxaparin: 34.2% EDT placebo: 33.7%	BMI ≥ 35 kg/m ² EDT rivaroxaban: 15.1% EDT placebo: 15.3%	BMI ≥ 30 kg/m ² EDT apixaban: 44.5% EDT placebo: 44.3%

(continued)

Table 1. (continued)

	Hull et al ⁷ and Turpie et al ⁸	Cohen et al ⁹	Goldhaber et al ¹⁰
Efficacy outcomes	<p><i>Total population</i></p> <p>EDT enoxaparin: 2.5%</p> <p>EDT placebo: 4.0%</p> <p>ARR = -1.53%; 95.8% CI = -2.54% to -0.52%</p> <p><i>Immobility groups</i></p> <p>Level 1:</p> <p>EDT enoxaparin: 2.3%</p> <p>EDT placebo: 4.5%</p> <p>ARR = -2.18%; 95% CI = -3.80% to -0.57%</p> <p>Level 2:</p> <p>EDT enoxaparin: 2.6%</p> <p>EDT placebo: 3.6%</p> <p>ARR = -1.00%; 95% CI = -2.31% to 0.31%</p> <p><i>Ischemic stroke</i></p> <p>EDT enoxaparin: 2.4%</p> <p>EDT placebo: 8.0%</p> <p>ARR = -5.6; 95% CI = -10.5 to 0.7; P = .0236</p>	<p><i>Total population</i></p> <p>EDT rivaroxaban: 4.4%</p> <p>EDT placebo: 5.7%</p> <p>RR = 0.77; 95% CI = 0.62 to 0.96</p>	<p><i>Total population</i></p> <p>EDT apixaban: 2.71%</p> <p>EDT placebo: 3.06%</p> <p>ARR = -0.39%; 95% CI = -1.37% to 0.59%</p>
Safety outcomes	<p><i>Total population</i></p> <p><i>Total bleeding</i></p> <p>EDT enoxaparin: 6.3%</p> <p>EDT placebo: 3.9%</p> <p>Absolute difference = 2.37%; 95% CI = 1.26 to 3.48</p> <p><i>Major bleeding (2 g/dL definition)</i></p> <p>EDT enoxaparin: 0.8%</p> <p>EDT placebo: 0.3%</p> <p>Absolute difference = 0.51%; 95% CI = 0.12 to 0.89</p> <p><i>Minor bleeding</i></p> <p>EDT enoxaparin: 5.5%</p> <p>EDT placebo: 3.5%</p> <p>Absolute difference = 1.97%; 95% CI = 0.91 to 3.02</p> <p><i>Ischemic stroke</i></p> <p><i>Total bleeding</i></p> <p>EDT enoxaparin: 6.1%</p> <p>EDT placebo: 2.6%</p> <p>Absolute difference = 3.4%; 95% CI = -0.6 to 7.5; P = .0972</p> <p><i>Major bleeding</i></p> <p>EDT enoxaparin: 1.5%</p> <p>EDT placebo: 0%</p> <p>Absolute difference = 1.5%; 95% CI = -0.2 to 3.2; P = .0881</p> <p><i>Minor bleeding</i></p> <p>EDT enoxaparin: 4.5%</p> <p>EDT placebo: 2.6%</p> <p>Absolute difference = 1.9%; 95% CI = -1.7 to 5.6; P = .3082</p>	<p><i>Clinically relevant bleeding (day 35)</i></p> <p>EDT rivaroxaban: 4.1%</p> <p>EDT placebo: 1.7%</p> <p>RR = 2.5; 95% CI = 1.85 to 3.25; P < .001</p> <p><i>Major bleeding (day 35)</i></p> <p>EDT rivaroxaban: 1.1%</p> <p>EDT placebo: 0.4%</p> <p>RR = 2.9; 95% CI = 1.60 to 5.15; P < .001</p>	<p><i>All bleeding</i></p> <p>EDT apixaban: 7.73%</p> <p>EDT placebo: 6.81%</p> <p>RR = 1.13; 95% CI = 0.95 to 1.34; P = .18</p> <p><i>Major plus clinically relevant nonmajor bleeding</i></p> <p>EDT apixaban: 2.67%</p> <p>EDT placebo: 2.08%</p> <p>RR = 1.28; 95% CI = 0.93 to 1.76; P = .12</p> <p><i>Major bleeding</i></p> <p>EDT apixaban: 0.47%</p> <p>EDT placebo: 0.19%</p> <p>RR = 2.58; 95% CI = 1.02 to 7.24; P = .04</p>

Abbreviations: SC, subcutaneous; VTE, venous thromboembolism; CHF, congestive heart failure; IBD, inflammatory bowel disease; DVT, deep vein thrombosis; PE, pulmonary embolism; PRBC, packed red blood cells; BMI, body mass index; EDT, extended-duration thromboprophylaxis; ARR, adjusted risk ratio; CI, confidence interval; RR, relative risk.

did not differ between groups. Subgroup analysis revealed significant tests for interaction with sex and age. Women appeared to have statistically significant reductions in VTE (absolute risk difference = -2.71%; 95.8% CI = -4.15% to -1.28), whereas men did not (-0.36%; 95.8% CI = -1.79% to 1.07%). Women, however, also had an increased risk of bleeding (0.66%; 95% CI = 0.11% to 1.21%), an outcome that was not seen in men (0.34%; 95% CI = -0.2% to 0.89%). A subgroup analysis of the EXCLAIM trial evaluated EDT in ischemic stroke patients, a patient population at high risk for VTE.⁸ Significant reductions in VTE were seen in the EDT group compared to patients receiving placebo (2.4% vs 8.0%; $P = .0236$); however, it was also associated with a nonsignificant 1.5% absolute increase in major hemorrhage (95% CI = -0.2 to 3.2; $P = .0881$).

Cohen et al

Rivaroxaban for thromboprophylaxis in acutely ill medical patients (MAGELLAN) trial was designed to compare EDT with oral rivaroxaban (a factor Xa inhibitor) to standard-duration SC enoxaparin for the prevention of VTE in medically ill patients.⁹ In this randomized controlled trial, 8101 patients were randomized to subcutaneous enoxaparin, 40 mg once daily, for 10 ± 4 days and oral placebo for 35 ± 4 days or subcutaneous placebo for 10 ± 4 days and oral rivaroxaban, 10 mg once daily, for 35 ± 4 days. The primary efficacy outcome was a composite of asymptomatic proximal DVT, symptomatic DVT, symptomatic nonfatal PE, and VTE-related death for the first 10 days, which was prespecified for noninferiority. A secondary superiority analysis was performed at 35 days. The primary safety outcome was a composite of clinically relevant bleeding: major bleeding and clinically relevant nonmajor bleeding occurring up to 48 hours after the last administered dose of medication. Patients were eligible for inclusion if they were at least 40 years of age, hospitalized for acute medical illness (including active cancer) with reduced mobility. Reduced mobility was defined as complete immobilization (confined to bed or chair with bathroom privileges) for ≥ 1 day and anticipated decreased mobility (confined to bed or chair 50% of day) for ≥ 4 days after randomization and anticipated decreased mobility thereafter.

The primary efficacy outcome at day 10 ($N = 5931$) occurred in 2.7% receiving rivaroxaban and 2.7% receiving enoxaparin (relative risk [RR] = 0.97; 95% CI = 0.71 to 1.31; $P = .003$ for noninferiority). The day 35 analysis ($N = 6024$) demonstrated superiority for the primary efficacy outcome in patients receiving rivaroxaban versus placebo; EDT with rivaroxaban led to a RR reduction of 0.77% (95% CI = 0.62 to 0.96; $P = .02$). However, there was also a statistically significant increase in clinically relevant bleeding: 4.1% compared to 1.7% in the placebo group ($P < .001$). The prespecified analysis of net clinical benefit or harm did not show a benefit with rivaroxaban at day 10 or day 35.

While treatment with rivaroxaban was efficacious in preventing VTE, this came with a significant increase in bleeding events and overall failed to demonstrate a net clinical benefit. When examining specific events contributing to the primary efficacy endpoint, a large portion (103 of 131) events were asymptomatic DVT identified on ultrasonography with consistently low rates of VTE-related death observed between both groups. Clinically, ultrasonography is not performed in patients recently discharged from the hospital. Patients included in this trial were representative of typical acutely medically ill patients and the benefits of EDT was not demonstrated.

Goldhaber et al

Apixaban dosing to optimize protection from thrombosis (ADOPT) trial was designed to evaluate oral apixaban (a factor Xa inhibitor) compared to enoxaparin to reduce the risk of VTE in medically ill patients during hospitalization and in the extended period after discharge.¹⁰ In this randomized controlled trial, 6528 patients were randomized to receive enoxaparin 40 mg SC daily for 6 to 14 days (only during hospitalization, minimum of 6 days) or apixaban 2.5 mg PO twice daily for 30 days. The primary efficacy outcome was a composite of VTE-related death, fatal or nonfatal PE, symptomatic DVT, or asymptomatic proximal-leg DVT. The primary safety outcome included major and clinically relevant bleeding. Patients ≥ 40 years of age who were hospitalized for congestive heart failure (CHF), acute respiratory failure, infection (excluding septic shock), acute rheumatic disorder, or inflammatory bowel disease with an expected stay of at least 3 days were eligible for inclusion. Other than those with CHF or respiratory failure, patients required an additional risk factor: age ≥ 75 , previous VTE, cancer, body mass index ≥ 30 kg/m², hormone therapy, or chronic CHF or respiratory failure. Additionally patients had to be moderately or severely limited in their mobility. Moderate mobility restriction allowed bathroom privileges, while severe restriction included confinement to bed or chair.

EDT with apixaban was not superior to standard course enoxaparin with regard to the primary efficacy outcome; at 30 days ($N = 4495$), the primary efficacy outcome occurred in 2.71% of patients in the apixaban group versus 3.06% in the enoxaparin group (RR = 0.87; 95% CI = 0.62 to 1.23; $P = .44$). However, the study was underpowered, due to only 64% of patients undergoing follow-up ultrasound. It was estimated that a sample size of 6524 patients was needed for 90% power to demonstrate superiority assuming an event rate of 2.5% in the apixaban group and 4% in the enoxaparin group. After the parenteral-treatment period was complete, 31 patients in the enoxaparin group and 18 in the apixaban group experienced an event (RR = 0.59%; 95% CI = 0.33 to 1.05). By day 30, major bleeding occurred in 0.47% of apixaban patients and 0.19% of enoxaparin patients (RR = 2.58; 95% CI = 1.02 to 7.24; $P = .04$).

The design of this trial was not consistent with typical medical care. Patients received enoxaparin for 6 to 14 days, presumably beyond discharge from the hospital. Consistent with other trials, ultrasonography was performed on patients with inclusion of asymptomatic DVT in the primary efficacy outcome. These factors limit the ability to apply this study in clinical practice.

Summary

There have been inconsistent outcomes with providing EDT in medically ill patients. Both EXCLAIM (enoxaparin) and MAGELLAN (rivaroxaban) showed a significant reduction in VTE during the extended-duration period. However, for enoxaparin, the benefit seemed to be limited to the highest risk groups and in women.⁷⁻⁹ The improved efficacy in both studies was tempered by a ~2.5-fold increase in the risk of major hemorrhage and was not associated with a decrease in all-cause mortality or VTE-related death. Apixaban was unable to show benefit in the primary efficacy outcome in ADOPT; however, the trial may have been underpowered for the event rate seen in the study.¹⁰ Apixaban was also associated with a significant increase in bleeding events. In each of these 3 trials, though an increase in bleeding was seen with EDT, the absolute rates were relatively low, <1%.

Given the inconsistent data, EDT should not be provided routinely to all medically ill patients. EDT may be considered on a case-by-case basis in patients at high risk for VTE. In patients at high risk for VTE in whom EDT is prescribed, careful consideration to bleeding risk should also be given, as EDT is associated with ~2.5-fold increased risk of bleeding.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Tellor participated in Pfizer's Midwest Atrial Fibrillation Advisory Board meeting; Dr Armbruster has no conflicts of interest; Dr Hollands has no conflicts of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. *Am J Prev Med*. 2010;38:S495-S501. doi:10.1016/j.amepre.2009.12.017.
2. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in non-surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e195S-e226S. doi:10.1378/chest.11-2296.
3. Herner SJ, Paulson DC, Delate T, Witt DM, Vondracek TG. Evaluation of venous thromboembolism risk following hospitalization. *J Thromb Thrombolysis*. 2011;32:32-39. doi:10.1007/s11239-010-0542-9.
4. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet*. 2001;358:9-15.
5. Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: a systematic review. *Ann Intern Med*. 2001;135:858-869. doi:10.7326/0003-4819-135-10-200111200-00006.
6. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e278S-e325S. doi:10.1378/chest.11-2404.
7. Hull RD, Schellong SM, Tapson VF, et al. Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility. *Ann Intern Med*. 2010;153:8-18. doi:10.7326/0003-4819-153-1-201007060-00004.
8. Turpie AGG, Hull RD, Schellong SM, et al. Venous thromboembolism risk in ischemic stroke patients receiving extended-duration enoxaparin prophylaxis: results from the EXCLAIM study. *Stroke*. 2013;44:249-251. doi:10.1161/STROKEAHA.112.659797.
9. Cohen AT, Spiro TE, Buller HR, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368:513-523. doi:10.1056/NEJMoa1111096.
10. Goldhaber SZ, Leizorovicz A, Kakkar AK, et al. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med*. 2011;365:2167-2177. doi:10.1056/NEJMoa1110899.