

Dose-adjusted enoxaparin thromboprophylaxis in hospitalized cancer patients: a randomized, double-blinded multicenter phase 2 trial

Jeffrey I. Zwicker,¹ Joanna Roopkumar,² Maneka Puligandla,³ Benjamin L. Schlechter,⁴ Anish V. Sharda,¹ David Peereboom,² Robin Joyce,¹ Bruno Bockorny,⁵ Donna Neuberg,³ Kenneth A. Bauer,¹ and Alok A. Khorana²

¹Division of Hematology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; ²Division of Hematology and Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH; ³Department of Data Sciences, Dana-Farber Cancer Institute, Boston, MA; ⁴Gastrointestinal Cancer Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; and ⁵Division of Oncology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Key Points

- Asymptomatic VTE is common among high-risk hospitalized patients with cancer receiving fixed-dose enoxaparin.
- The findings of this phase 2 study suggest that weight-adjusted thromboprophylaxis is well-tolerated in hospitalized patients with cancer.

Hospitalized patients with cancer are at an increased risk of developing venous thromboembolism (VTE). The recommendation for routine pharmacologic thromboprophylaxis in hospitalized patients with cancer to prevent VTE is based on extrapolation of results from noncancer cohorts. There are limited data to support the efficacy and safety of fixed-dose low-molecular-weight heparin (LMWH) regimens in high-risk hospitalized patients with cancer. We conducted a randomized, double-blinded, phase 2 trial in hospitalized patients with active cancer at high risk of developing VTE based on Padua risk score. Patients were randomly assigned to fixed-dose enoxaparin (40 mg daily) vs weight-adjusted enoxaparin (1 mg/kg daily) during hospitalization. The primary objectives were to evaluate the safety of dose-adjusted enoxaparin and evaluate the incidence of VTE with fixed-dose enoxaparin. Blinded clinical assessments were performed at day 14, and patients randomly assigned to fixed-dose enoxaparin subsequently underwent a bilateral lower extremity ultrasound. A total of 50 patients were enrolled and randomized. The median weight of patients enrolled in weight-adjusted enoxaparin arm was 76 kg (range, 60.9-124.5 kg). There were no major hemorrhages or symptomatic VTE in either arm. At time of completion of the blinded clinical assessment, there was only 1 incidentally identified pulmonary embolus that occurred in the weight-adjusted arm. In the group randomly assigned to fixed-dose enoxaparin who subsequently underwent surveillance ultrasound, the cumulative incidence of DVT was 22% (90% binomial confidence interval, 0%-51.3%). This phase 2 trial confirms a high incidence of asymptomatic VTE among high-risk hospitalized patients with cancer and that weight-adjusted LMWH thromboprophylaxis is feasible and well-tolerated. This trial was registered at www.clinicaltrials.gov as #NCT02706249.

Introduction

Venous thromboembolism (VTE) is estimated to account for up to 5% of all deaths during hospitalization and is a leading cause of preventable in-hospital mortality.^{1,2} Approximately 75% of all VTE-related deaths are thought to be hospital-acquired.³ VTE associated with hospitalization further exacerbates the financial liability associated with acute medical illness.⁴ Recognizing the burden on health care and the preventable nature of venous thromboembolic events during hospitalization, a number of governmental

Submitted 3 March 2020; accepted 15 April 2020; published online 22 May 2020.
DOI 10.1182/bloodadvances.2020001804.

Individual participant data that underlie the results reported in this article, after de-identification, will be available beginning 9 months and ending 36 months after article

publication for individual participant data meta-analyses. For original data, please contact Jeffrey I. Zwicker (jzwicker@bidmc.harvard.edu).

© 2020 by The American Society of Hematology

regulatory agencies have drawn attention toward the importance of thromboprophylaxis during hospitalization.⁵⁻⁸

Because of the strong association between cancer and thrombosis, the issue of thromboprophylaxis is particularly resonant among those caring for hospitalized patients with cancer. Major professional organizations including the American Society of Clinical Oncology, National Comprehensive Cancer Network, American College of Chest Physicians, and European Society of Medical Oncology have all issued recommendations for the prescription of pharmacologic thromboprophylaxis of hospitalized patients with cancer.⁹⁻¹² However, these guidelines are largely extrapolated from data generated from general medical patients. In the 3 phase 3 registration trials comparing low-molecular-weight heparins (LMWHs) with placebo in hospitalized medical patients, only 6% of patients carried a diagnosis of cancer and there was no statistical benefit for thromboprophylaxis (ie, prevention of both symptomatic and asymptomatic VTE) in the subgroup analysis of patients with cancer included in these trials.¹³ For instance, in the MEDENOX trial, the incidence of VTE was 9.7% for patients with cancer receiving enoxaparin thromboprophylaxis, whereas in the ARTEMIS study, the rate of VTE was 17% in patients with cancer randomly assigned to fondaparinux.¹³⁻¹⁵ In all studies, the incidence of thrombosis was higher in the cancer subgroup receiving thromboprophylaxis compared with patients without cancer, suggesting that fixed doses may be inadequate in this population. In a recent prospective cohort study, 80% of patients with cancer diagnosed with symptomatic VTE after hospitalization received fixed dosing of LMWH thromboprophylaxis.¹⁶

Despite the long-known association between malignancy and thrombosis, there are no randomized trials of inpatient thromboprophylaxis specifically in patients with cancer, such that the absolute benefit, toxicity, and even appropriate dosing of routine thromboprophylaxis in patients with cancer are unknown. Fixed-dose LMWH is the standard approach for primary prevention of VTE during hospitalization. However, anti-factor Xa levels after a fixed dose of enoxaparin 40 mg once daily are often below what is considered necessary for effective thromboprophylaxis.¹⁷ We conducted a randomized, double-blinded, phase 2 trial to determine point estimates of VTE, feasibility, and tolerability of weight-adjusted enoxaparin compared with fixed-dose enoxaparin in hospitalized patients with cancer considered high risk for VTE.

Methods

Study design and patients

We conducted an investigator-initiated, randomized, double-blinded phase 2 trial at Beth Israel Deaconess Medical Center and Cleveland Clinic. Eligible patients were required to be at least 18 years of age; have a histologically confirmed diagnosis of solid tumor malignancy, lymphoma, or myeloma considered active (diagnoses or received cancer-direct therapy within the prior 6 months); life expectancy greater than 30 days; platelet count greater than $100 \times 10^9/L$, creatinine less than 1.5 mg/dL, or estimated creatinine clearance above 50 mL/min/1.73 m²; and weight between 50 and 130 kg. Eligible patients were also required to be considered high risk for VTE according to Padua risk score (score ≥ 4).¹⁸ Patients who received more than 48 hours of pharmacologic thromboprophylaxis during the current hospitalization were excluded. Patients were also excluded if they had an

allergy to heparin products, were actively bleeding or history of significant hemorrhage within the last 6 months, were receiving anticoagulants or dual antiplatelet therapy, or had uncontrolled hypertension.

The protocol was approved by the Institutional Review Boards at Beth Israel Deaconess Medical Center and Cleveland Clinic, and all patients provided written informed consent. The study was designed to accord with Good Clinical Practice guidelines and the Declaration of Helsinki.

Randomization and masking

Eligible patients were randomly assigned to receive enoxaparin 40 mg once daily or weight-adjusted enoxaparin at 1 mg/kg once daily (maximum dose, 100 mg daily). Double-blinding occurred through pharmacy, using a fixed-volume drug dispense (ie, syringes of enoxaparin were diluted to a uniform volume of 1 mL). Randomization was performed by permuted blocks with stratum, where strata were defined by hospital (Beth Israel Deaconess Medical Center and Cleveland Clinic). Study subjects were all at high risk using the Padua risk model, but this model was not developed specifically for cancer cohorts. To account for the influence of tumor type on thrombotic risk, patients were also stratified according to cancer type in the Khorana model: very high risk (stomach, pancreatic), high risk (lung, lymphoma, gynecologic, bladder, testicular), and standard risk (all others).¹⁹

Procedures

Enoxaparin was administered up to 14 days on-study during hospitalization only (Figure 1). Doses were held for estimated creatinine clearance lower than 30 mL/min/1.73 m² and reduced to 40 mg once daily for a creatinine clearance between 30 and 40 mL/min/1.73 m². Enoxaparin was similarly held for platelet counts lower than $50 \times 10^9/L$ and reduced to 40 mg fixed dose for platelet counts between $50 \times 10^9/L$ and $100 \times 10^9/L$. Adverse events were assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In the setting of a CTCAE grade 2 hemorrhage, enoxaparin doses were held until improvement (CTCAE \leq grade 1). Enoxaparin was discontinued for any CTCAE grade 3 or above hemorrhages or those considered major according to International Society of Thrombosis and Haemostasis definition.²⁰ Planned interim safety analyses were planned if the number of hemorrhages in the weight-adjusted enoxaparin arm was in excess of 3 greater than in the fixed-dose arm.

Participants who were rehospitalized before 14 days continued their prior treatment assignments. Physicians and participants were double-blinded during hospitalization and until the day 14 assessment ("off treatment"). The blinded off-treatment clinical assessment included an evaluation for clinical evidence of VTE or hemorrhage. Unblinding occurred after an off-treatment assessment. Those patients randomly assigned to fixed-dose enoxaparin subsequently underwent a bilateral lower extremity ultrasound to establish a point estimate of incidental deep vein thrombosis (DVT) in the fixed-dose enoxaparin cohort (between day 17 and day 25).

Outcomes

The primary objectives were both to evaluate the safety of dose-adjusted enoxaparin and to establish a point estimate of the incidence of VTE with fixed-dose enoxaparin after lower-extremity ultrasound. The primary endpoint of VTE was defined as objectively

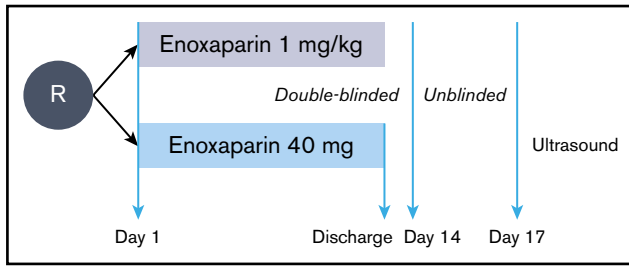


Figure 1. Schema of trial.

confirmed proximal or distal lower-extremity DVT (symptomatic or asymptomatic), subsegmental or larger pulmonary embolism (PE; symptomatic or asymptomatic), or fatal PE diagnosed by autopsy. All other venous or arterial events were to be analyzed as secondary endpoints (including any central venous catheter-associated DVT). Criteria for major hemorrhage were based on the International Society of Thrombosis and Haemostasis definition for major hemorrhage in nonsurgical populations.²⁰

Statistical analyses

The documented incidence of VTE in patients with cancer in randomized clinical trials ranges considerably (3%-17%) on pharmacologic thromboprophylaxis at fixed prophylactic dosing.¹³ Target enrollment was 50 patients with an assumed cumulative incidence of thrombosis at study completion of 12% in the fixed-dose enoxaparin arm (90% binomial confidence interval, 3.3%-28.2%). Point estimates of VTE and blinded enoxaparin allocation were analyzed with 90% exact binomial confidence intervals. All participants receiving at least 1 dose of enoxaparin were evaluated for toxicity and primary efficacy endpoints.

Results

A total of 50 patients were enrolled and randomized at the 2 hospitals. According to planned modified intention-to-treat analyses, 2 patients randomly assigned to fixed-dose enoxaparin and 1 patient in the weight-adjusted dose arm never received study medication and were not included in outcome analyses (Figure 2). Patients were stratified according to Khorana cancer site categories, as shown in Table 1, with approximately 60% of patients characterized as high-risk or very high risk disease sites. The most common cancer diagnoses were lymphoma in both fixed-dose and weight-adjusted arms (9 and 7 patients, respectively), followed by luminal gastrointestinal (4 patients on each arm) and 3 patients with pancreas and sarcoma in both arms (Table 2).

The median Padua score was 5 in the fixed-dose arm and 4 in the weight-adjusted arm (Mann-Whitney U , $P = .25$). There was no correlation between Padua score at time of hospitalization and Khorana score (Spearman $\rho = .01$; $P = .50$). Median duration of hospitalization was 5 days and 5.5 days on the fixed dose and weight-adjusted arms, respectively ($P = 0.25$). The median weight of patients enrolled in weight-adjusted enoxaparin arm was 76 kg (range, 63-124 kg), which equates to a median increase of 37 mg of enoxaparin (90% higher dose) in the weight-adjusted arm compared with fixed-dose enoxaparin.

There were no major hemorrhages reported in either arm. One patient randomly assigned to fixed-dose enoxaparin developed a grade 2 laryngeal bleed occurring several days after completing the last dose of enoxaparin.

During the blinded phase of the study, there were no symptomatic VTEs, but an incidental PE was diagnosed 6 days after stopping enoxaparin in the setting of a large mediastinal mass and large pericardial effusion in the weight-adjusted arm. Accordingly, the

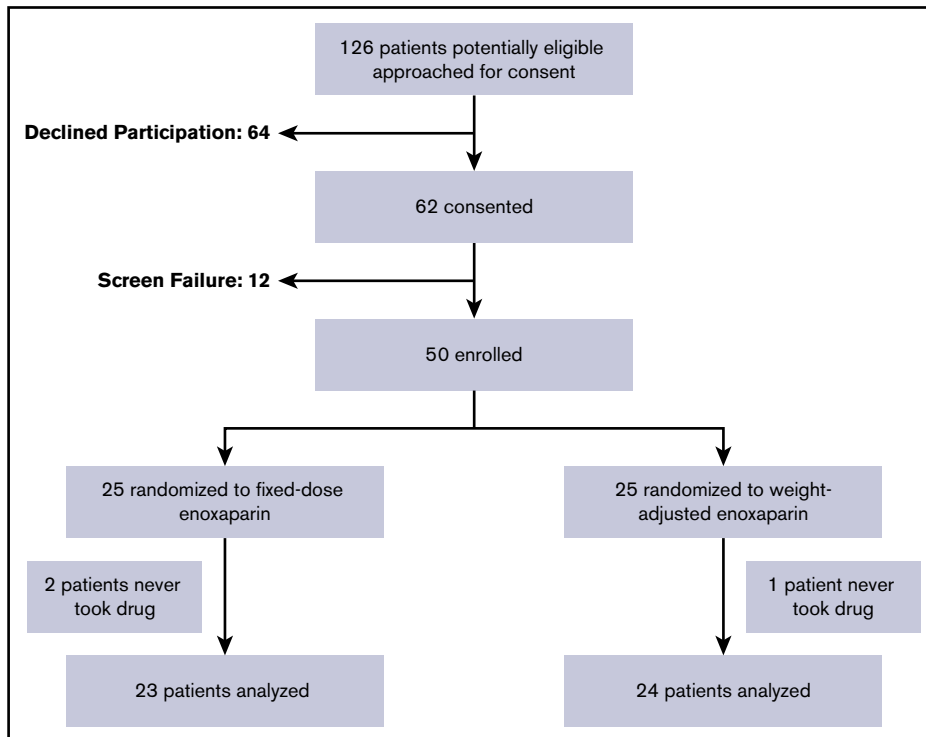


Figure 2. Consort diagram.

Table 1. Baseline demographics

Characteristic	Fixed-dose enoxaparin (n = 23)	Weight-adjusted enoxaparin (n = 24)
Female, n (%)	15 (65)	15 (62)
Age, median (range), y	60 (28-83)	61 (43-76)
Weight, median (range), kg	82 (53-109)	76 (61-124)
BMI, median (range), kg/m ²	30 (20-40)	30 (20-44)
Khorana site of cancer category, n (%)		
Very high risk	3 (13)	3 (13)
High risk	11 (48)	12 (50)
Standard risk	9 (39)	9 (38)
Padua score, n (%)		
4	9 (39)	14 (58)
5-7	12 (52)	8 (33)
>8	2 (8)	2 (8)
Tumor type, n (%)		
Lymphoma	9 (39)	7 (29)
Gastrointestinal	4 (17)	4 (17)
Pancreatic	3 (13)	3 (12)
Sarcoma	3 (13)	3 (12)
Breast	2 (9)	1 (4)
Glioblastoma	1 (4)	0 (0)
Myeloma	0 (0)	2 (8)
Other	1 (4)	4 (17)

cumulative incidence of VTE was 5.9% in the weight-adjusted arm at day 14 (90% binomial confidence interval, 0%-20.5%).

After unblinding, there were no symptomatic VTEs. The group randomly assigned to fixed-dose enoxaparin underwent a bilateral lower extremity ultrasound to evaluate for asymptomatic DVT. Among the 21 patients who underwent bilateral lower extremity ultrasounds, the cumulative incidence of DVT was 22% at day 25 (90% binomial confidence interval, 0%-51.3%). Ultrasounds were performed beyond day 25 in 4 patients (3 on day 28 and 1 on day 44), and none of these patients was diagnosed with a DVT. Notably, the 2 patients who were found to have DVT (both distal) in the fixed-dose arm had body mass indexes (BMIs; 40 kg/m² and 38 kg/m²) that exceeded those of patients enrolled who did not develop VTE (median BMI, 27 kg/m²; *P* = .025).

Discussion

The benefit of routine thromboprophylaxis with fixed-dose LMWH in hospitalized patients with cancer is not established. The available evidence suggests that the rate of VTE is high in patients with cancer despite receiving pharmacologic thromboprophylaxis. Considering that anticoagulant activity of LMWH is weight-dependent, dose adjustment of LMWH for high-risk patients with cancer is a rational approach to in-hospital thromboprophylaxis. To the best of our knowledge, this is the first randomized clinical trial of pharmacologic thromboprophylaxis conducted specifically in hospitalized patients with cancer.

This phase 2 trial demonstrates that weight-adjusted LMWH is feasible in high-risk hospitalized patients with cancer, and is well

Table 2. Outcome assessments according to enoxaparin randomization

	Fixed-dose enoxaparin (n = 23)	Weight-adjusted enoxaparin (n = 24)
Median number of days hospitalized (range)	5 (2-14)	6 (2-14)
Median study day numbers of ultrasounds (range)	18 (10-44)	Not applicable
Hemorrhages, no. of patients		
Major	0	0
Clinically relevant non-major	1	0
VTE: during blinded assessment period	0 symptomatic VTE	0 symptomatic VTE 1 incidentally identified filling defect within segmental branch of left pulmonary artery (asymptomatic)
VTE: end of study	0 symptomatic VTE 2 distal DVTs on surveillance ultrasound (asymptomatic)	0 symptomatic VTE

tolerated, without any major hemorrhages observed. These results are in keeping with a phase 3 study conducted in outpatients with pancreatic cancer. In the CONKO-004 trial, the administration of weight-adjusted enoxaparin at 1 mg/kg daily for 3 months resulted in an approximate 85% risk reduction in the incidence of VTE without an increase in major hemorrhage compared with no anticoagulation in ambulatory patients.²¹ Similarly, in an outpatient thromboprophylaxis trial, therapeutic dosing of weight-adjusted dalteparin for 3 months did not increase the risk for hemorrhage.²²

This phase 2 study was designed to align with real-world practice, as postdischarge thromboprophylaxis is not currently recommended.²³ In keeping with this clinical practice, thromboprophylaxis was not extended into the outpatient setting. Prior clinical trials have varied considerably in terms of timing and mode of imaging to identify asymptomatic DVT. Imaging for DVT was previously performed within 24 hours of the last dose of pharmacologic thromboprophylaxis,¹⁵ between days 6 and 14²⁴ or after day 21.²⁵ In the current study, a blinded clinical assessment of VTE was performed at day 14, and scheduled ultrasound examination performed between days 17 to 25. Considering thromboprophylaxis was not extended out of hospital, we cannot exclude the possibility that DVT developed in the posthospitalization period. However, even in this phase 2 trial, we observed a statistical difference in rates of DVT among those patients with BMI above 35 kg/m² receiving fixed-dose enoxaparin.

The observation that the BMI of those patients on the fixed-dose arm who developed a VTE was significantly greater than those without a VTE supports the fundamental rationale for the trial. In a retrospective study of 37 patients with acute lymphoblastic leukemia who received LMWH thromboprophylaxis, the rate of VTE was 43% among those who weighed more than 80 kg compared with 4.4% among those who weighed less.²⁶ Accordingly, in a postoperative cohort, the administration of 40 mg enoxaparin in patients with a weight greater than 80 kg resulted in peak factor Xa levels below prophylactic target of 0.3 to

0.5 IU/mL.¹⁷ These data further support weight-adjusted dosing of LMWH for thromboprophylaxis in high-risk populations.

Despite the development of direct oral anticoagulants, LMWH remains the preferred pharmacologic agent for thromboprophylaxis of hospitalized patients. Direct oral anticoagulants have been associated with an increased risk for hemorrhage relative to LMWH in cancer populations,²⁷⁻²⁹ and there is not a clear signal that low-dose direct oral anticoagulants offer any benefit relative to LMWH for the prevention of VTE in hospitalized patients with cancer. For instance, among the 405 patients with active cancer enrolled in the Magellan trial and randomly assigned to enoxaparin vs rivaroxaban, the rates of VTE were similar at day 35 (7.4% vs 9.9%, respectively; $P = 0.07$).²⁹ The US Food and Drug Administration recently approved rivaroxaban for extended prophylaxis after hospitalization, but specifically excluded patients with cancer because of concern about hemorrhage.³⁰

Despite representing a key contributor to in-hospital mortality, symptomatic VTE during hospitalization is a rare event, such that the absence of apparent benefit with dose-adjusted enoxaparin was not an unexpected finding. In phase 3 trials, the rate of symptomatic VTE is typically less than 2%,^{24,29} and in recent retrospective analyses of high-risk hospitalized patients with cancer, the rate of clinically apparent VTE was approximately 5%.³¹ There is equipoise regarding the inclusion of asymptomatic screen-detected VTE as an endpoint in thromboprophylaxis trials. Inclusion of asymptomatic VTE (assessed via imaging of the veins of the lower extremities using bilateral venography or ultrasonography) is the standard endpoint by which all inpatient anticoagulants have been evaluated,^{15,24,25,32,33} and we believe that screen-detected VTEs are especially relevant when assessing benefit in hospitalized cancer populations. Distal DVT portends a similar prognosis as more proximal thrombi in patients with cancer.^{34,35} VTEs are often detected in patients with cancer incidentally based on imaging performed as part of routine cancer care, and such VTEs in cancer convey the same rates of recurrence as symptomatic events.³⁶ Current guidelines recommend similar anticoagulant management to symptomatic VTE.^{37,38} Furthermore, there are emerging data that asymptomatic DVT diagnosed during hospitalization are clinically relevant, as they are associated with a three- to eightfold increased risk for short-term mortality after hospitalization relative to those patients not diagnosed with a DVT.^{39,40}

Strengths of this phase 2 study include a double-blinded, randomized, multicenter design. This study was sponsored by the National Institutes of Health, which enabled comparison of dosing regimens for a generic drug. However, because of budget limitations, only those patients randomly assigned to fixed-dose enoxaparin underwent end-of-study lower extremity ultrasound to diagnose incidental DVT. Considering this trial was not powered for efficacy, we acknowledge that we cannot conclude that weight-adjusted enoxaparin is more efficacious than fixed-dose enoxaparin. However, these data provide valuable affirmation of feasibility along with a reassuring signal of safety.

References

1. Lau BD, Haut ER. Practices to prevent venous thromboembolism: a brief review. *BMJ Qual Saf.* 2014;23(3):187-195.
2. Landrigan CP, Parry GJ, Bones CB, Hackbarth AD, Goldmann DA, Sharek PJ. Temporal trends in rates of patient harm resulting from medical care. *N Engl J Med.* 2010;363(22):2124-2134.
3. Cohen AT, Agnelli G, Anderson FA, et al; VTE Impact Assessment Group in Europe (VITAE). Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost.* 2007;98(4):756-764.

Appropriate thromboprophylaxis of hospitalized patients with cancer is a recognized knowledge gap in the field. In the recently published guidelines from the American Society of Hematology, the “optimal dosing of parenteral anticoagulation” in high-risk hospitalized patients was identified as a key research question.²³ On the basis of the results of this phase 2 trial, weight-adjusted enoxaparin is well tolerated and warrants further investigation in hospitalized patients with cancer.

Acknowledgments

This study was funded by the National Institutes of Health, National Heart, Lung, and Blood Institute (R34HL127156). J.I.Z. and A.A.K. receive salary support from Consortium Linking Oncology with Thrombosis (U01HL143365 and U01HL143402 from the National Institutes of Health, National Heart, Lung, and Blood Institute) and A.A.K. acknowledges additional research support from the Sondra and Stephen Hardis Chair in Oncology.

Authorship

Contribution: J.I.Z. and A.A.K. conceived of the project and participated in all aspects of trial design, conduct, and reporting; J.R., B.L.S., A.S., D.P., R.J., B.B., and K.A.B. participated in trial conduct; M.P. and D.N. performed data analyses; and all authors reviewed and approved of the manuscript.

Conflict-of-interest disclosure: J.I.Z. reports receiving research funding from Incyte and Quercogen; consultancy for Sanofi, CSL, and Parexel; and honoraria/advisory boards for Pfizer/BMS, Portola, and Daiichi. A.K.K. reports receiving honoraria from Janssen Pharmaceuticals, Halozyne, Pfizer, Bayer AG, AngioDynamics, and Pharmacyte Biotech; performing a consulting or advisory role for Janssen Pharmaceuticals, Halozyne, Bayer AG, Pfizer, Pharmacyte Biotech, Pharmacyclics, and Seattle Genetics Research; receiving institutional funding from Merck, Array BioPharma, Bristol-Myers Squibb, and Leap Oncology; and receiving funding for travel, accommodations, and expenses from Janssen Pharmaceuticals, Pfizer, and Bayer AG. K.A.B. reports consultancy with Janssen. B.B. reports research funding from Nanoview Bioscience and travel expenses from Erytech Pharma. The remaining authors declare no competing financial interests.

ORCID profiles: J.I.Z., 0000-0001-5810-6893; B.L.S., 0000-0002-1529-3278; R.J., 0000-0002-7251-8082; B.B., 0000-0002-9162-1560; D.N., 0000-0003-2566-3145; A.A.K., 0000-0002-9509-0998.

Correspondence: Jeffrey I. Zwicker, Division of Hematology, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215; e-mail: jzwicker@bidmc.harvard.edu.

4. Cohoon KP, Leibson CL, Ransom JE, et al. Costs of venous thromboembolism associated with hospitalization for medical illness. *Am J Manag Care*. 2015;21(4):e255-e263.
5. Shojania KG, Duncan BW, McDonald KM, Wachter RM, Markowitz AJ. Making health care safer: a critical analysis of patient safety practices. *Evid Rep Technol Assess (Summ)*. 2001;(43):i-x, 1-668.
6. The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism. In: Office of the Surgeon General; National Heart, Lung, and Blood Institute ed. Rockville, MD; 2008.
7. The Joint Commission. Venous thromboembolism. <https://www.jointcommission.org/en/measurement/measures/venous-thromboembolism/>. Accessed 1 May 2020.
8. National Institute for Health Care Excellence. *Venous Thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE guideline*. UK: National Institute for Health and Care Excellence London; 2018 [NG89].
9. Lyman GH, Khorana AA, Falanga A, et al; American Society of Clinical Oncology. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol*. 2007;25(34):5490-5505.
10. Lyman GH, Khorana AA, Kuderer NM, et al; American Society of Clinical Oncology Clinical Practice. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2013;31(17):2189-2204.
11. Mandalà M, Falanga A, Roila F; ESMO Guidelines Working Group. Management of venous thromboembolism in cancer patients: ESMO clinical recommendations. *Ann Oncol*. 2008;19(Suppl 2):ii126-ii127.
12. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e195S-226S.
13. Carrier M, Khorana AA, Moretto P, Le Gal G, Karp R, Zwicker JI. Lack of evidence to support thromboprophylaxis in hospitalized medical patients with cancer. *Am J Med*. 2014;127(1):82-6.e1.
14. Alikhan R, Cohen AT, Combe S, et al. Prevention of venous thromboembolism in medical patients with enoxaparin: a subgroup analysis of the MEDENOX study. *Blood Coagul Fibrinolysis*. 2003;14(4):341-346.
15. Cohen AT, Davidson BL, Gallus AS, et al; ARTEMIS Investigators. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ*. 2006;332(7537):325-329.
16. Figueroa R, Alfonso A, López-Picazo J, et al. Insights into venous thromboembolism prevention in hospitalized cancer patients: Lessons from a prospective study. *PLoS One*. 2018;13(8):e0200220.
17. Pannucci CJ, Fleming KI, Holyoya K, Moulton L, Prazak AM, Varghese TK Jr. Enoxaparin 40 mg per day is inadequate for venous thromboembolism prophylaxis after thoracic surgical procedure. *Ann Thorac Surg*. 2018;106(2):404-411.
18. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost*. 2010;8(11):2450-2457.
19. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111(10):4902-4907.
20. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.
21. Pelzer U, Opitz B, Deutschnoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 Trial. *J Clin Oncol*. 2015;33(18):2028-2034.
22. Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. *Eur J Cancer*. 2012;48(9):1283-1292.
23. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv*. 2018;2(22):3198-3225.
24. Samama MM, Cohen AT, Darmon JY, et al; Prophylaxis in Medical Patients with Enoxaparin Study Group. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med*. 1999;341(11):793-800.
25. Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Vaitkus PT, Goldhaber SZ; PREVENT Medical Thromboprophylaxis Study Group. Randomized, placebo-controlled trial of dalteparin for the prevention of venous thromboembolism in acutely ill medical patients. *Circulation*. 2004;110(7):874-879.
26. Sibai H, Seki JT, Wang TQ, et al. Venous thromboembolism prevention during asparaginase-based therapy for acute lymphoblastic leukemia. *Curr Oncol*. 2016;23(4):e355-e361.
27. Raskob GE, van Es N, Verhamme P, et al; Hokusai VTE Cancer Investigators. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378(7):615-624.
28. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017-2023.
29. Cohen AT, Spiro TE, Büller HR, et al; MAGELLAN Investigators. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368(6):513-523.
30. U.S. FDA Approves XARELTO® (rivaroxaban) to Help Prevent Blood Clots in Acutely Ill Medical Patients. <https://www.jnj.com/u-s-fda-approves-xarelto-rivaroxaban-to-help-prevent-blood-clots-in-acutely-ill-medical-patients>. Accessed 1 May 2020.

31. Patel R, Rybicki L, McCrae KR, Khorana AA. Predicting risk of venous thromboembolism in hospitalized cancer patients: Utility of a risk assessment tool. *Am J Hematol*. 2017;92(6):501-507.
32. Cohen AT, Harrington RA, Goldhaber SZ, et al; APEX Investigators. Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients. *N Engl J Med*. 2016;375(6):534-544.
33. Cohen AT, Spiro TE, Spyropoulos AC; MAGELLAN Steering Committee. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. *N Engl J Med*. 2013;368(20):1945-1946.
34. Galanaud JP, Sevestre MA, Pernod G, et al. Long-term outcomes of cancer-related isolated distal deep vein thrombosis: the OPTIMEV study. *J Thromb Haemost*. 2017;15(5):907-916.
35. Poudel SK, Park DY, Jia X, et al. Clinical outcomes of isolated distal deep vein thrombosis versus proximal venous thromboembolism in cancer patients: The Cleveland Clinic experience. *J Thromb Haemost*. 2020;18(3):651-659.
36. Kraaijpoel N, Bleker SM, Meyer G, et al; UPE investigators. Treatment and long-term clinical outcomes of incidental pulmonary embolism in patients with cancer: an international prospective cohort study. *J Clin Oncol*. 2019;37(20):1713-1720.
37. van der Hulle T, den Exter PL, Planquette B, et al. Risk of recurrent venous thromboembolism and major hemorrhage in cancer-associated incidental pulmonary embolism among treated and untreated patients: a pooled analysis of 926 patients. *J Thromb Haemost*. 2016;14(1):105-113.
38. den Exter PL, Hooijer J, Dekkers OM, Huisman MV. Risk of recurrent venous thromboembolism and mortality in patients with cancer incidentally diagnosed with pulmonary embolism: a comparison with symptomatic patients. *J Clin Oncol*. 2011;29(17):2405-2409.
39. Kalayci A, Gibson CM, Chi G, et al. Asymptomatic deep vein thrombosis is associated with an increased risk of death: insights from the APEX Trial. *Thromb Haemost*. 2018;118(12):2046-2052.
40. Vaitkus PT, Leizorovicz A, Cohen AT, Turpie AG, Olsson CG, Goldhaber SZ; PREVENT Medical Thromboprophylaxis Study Group. Mortality rates and risk factors for asymptomatic deep vein thrombosis in medical patients. *Thromb Haemost*. 2005;93(1):76-79.