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Thromboprophylaxis Guidelines in Cancer with a Primary Focus on Ambulatory Patients Receiving Chemotherapy: A Review from the Southern Network on Adverse Reactions (SONAR)

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Abstract

Patients with cancer are at increased risk for venous thromboembolism (VTE). Factors related to cancer type, site, stage, duration, and extent of disease contribute to the oncology patient's risk of VTE. Patient-specific factors such as history of prior VTE and comorbidity are also contributory. The role of treatment-related factors, including chemotherapy regimen, has been a focus of recent investigation because most cases of VTE in the oncology setting occur in ambulatory patients. Thus, an emerging area of clinical research is primary VTE prophylaxis in the ambulatory cancer setting. Clinical guidelines currently recommend primary thromboprophylaxis in cancer patients who are undergoing surgery, who are hospitalized, and who are in a specific subset of high-risk ambulatory cancer patients. Validated risk stratification tools are essential for identification of patients who are at high risk of thrombosis. Emerging data from recently published clinical trials, as well as ongoing studies, are likely to advance our understanding of the potential utility of antithrombotic agents for primary prophylaxis in ambulatory patients with cancer and may influence future clinical guideline recommendations.

Keywords

anticoagulants; chemotherapy; cancer; venous thromboembolism; thromboprophylaxis

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Note

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Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication of cancer and is a leading cause of death among cancer patients.^{1–3} In a population-based case-control study of approximately 3000 patients with VTE, investigators found a sevenfold higher risk of VTE among patients with cancer than among those without cancer.⁴ Other studies have indicated that 20% to 29% of all VTEs occur in patients with cancer.^{5,6} VTE, a significant predictor of death among patients with cancer, is a leading cause of death among outpatients receiving chemotherapy^{1,7} and is associated with an estimated 47-fold increase in rate of death among these patients compared with the general population.² Herein, we review risk factors for VTE, risk stratification tools, clinical trials evaluating various anticoagulation regimens, and current clinical guideline recommendations for patients with malignancies. We focus on the outpatient setting, from which much of the data are currently emerging.

Risk Factors for VTE in Patients with Cancer

VTE risk factors in patients with cancer can be classified into three categories: patient-related factors, cancer-related factors, and treatment-related factors (Table 1).⁸ Patient-related risk factors may include thrombophilia and obesity.^{1,9,10} History of VTE is also a patient-related risk factor because recurrent VTE is more common among patients with cancer than in the general population. In a study of 842 patients with a first episode of symptomatic DVT, the 12-month cumulative incidence of recurrent VTE was 20.7% among those with cancer ($n = 181$) and 6.8% among those without cancer ($n = 661$), with a hazard ratio (HR) of 3.2 (95% confidence interval [CI] = 1.9 to 5.4).¹¹ Treatments known to increase this risk include conventional chemotherapy (e.g., cisplatin,¹² fluorouracil in combination with leucovorin¹³), the older antiangiogenic agents thalidomide or lenalidomide in combination with steroids or conventional chemotherapy agents,^{14,15} certain adjuvant chemotherapy and hormone therapy regimens,¹⁶ and some supportive therapies (e.g., erythropoiesis-stimulating agents).¹⁷ The newer antiangiogenic agent bevacizumab may be more thrombogenic than standard chemotherapy regimens according to a 2008 meta-analysis¹⁸; however, current data are inconclusive.¹⁹

Patients with malignancy may undergo routine computed tomography (CT) imaging for tumor staging and surveillance. Asymptomatic VTE is sometimes incidentally discovered during this routine imaging process. Patients with incidental VTE have a similar risk of recurrence, complications related to bleeding, and mortality as those with symptomatic VTE.²⁰ Among 1,921 cancer patients starting chemotherapy, 3.2% developed incidental VTE over a median treatment period of 8 months ($n = 62$),²¹ and this rate is similar to that of incidental PE in a large meta-analysis of 6,010 cancer patients (3.1%).²² A 4.4% rate ($n = 18$) of incidental PE was found in a smaller series of 407 oncology patients undergoing multidetector CT imaging.²³ Although these data imply that asymptomatic VTE is associated with morbidity and mortality, routine screening for asymptomatic VTE remains controversial.

Thromboprophylaxis in Hospitalized Cancer Patients

Consensus guidelines recommend the use of anticoagulant therapies for thromboprophylaxis in hospitalized patients with cancer and patients undergoing cancer surgery.^{1,8,24–26} Current data suggest that these medications may be underused in the oncology setting. In one study, among approximately 250,000 cancer patients undergoing major oncologic surgery, only 46% received anticoagulation therapy for VTE prophylaxis, and this rate varied from 38.8% in low-volume hospitals to 53.1% in high-volume hospitals.²⁷ Another observational study found that 73.5% of 200 hospitalized cancer patients with multiple risk factors for VTE who had discharge diagnoses of DVT or PE had not previously received any VTE prophylaxis.²⁸ Reasons for underuse of anticoagulants in these patients are unclear but may include practitioners' uncertainty of VTE risk or clinical contraindications to anticoagulant therapy, lack of familiarity with evidence-based VTE prophylaxis guidelines, lack of familiarity with risk assessment tools, cost concerns, and, potentially most common, clinician concern for drug-induced bleeding complications.^{27–29}

According to the National Comprehensive Cancer Network (NCCN) guidelines, contraindications to pharmacologic prophylaxis of VTE using anticoagulant medications include clinically significant active or chronic bleeding, lesions of the central nervous system that are at high risk for bleeding, recent surgery with a high bleeding risk, spinal anesthesia/lumbar puncture, a high risk for falls, thrombocytopenia or platelet dysfunction, and systemic coagulopathy.¹ Interestingly, not only are cancer patients at an increased risk of thrombosis but they also have a significantly higher risk of bleeding events related to anticoagulation therapy than the general population.^{1,30} Other less common risks associated with anticoagulation therapy include osteoporosis and heparin-induced thrombocytopenia (in patients receiving heparin products or low-molecular-weight heparin [LMWH]).³¹ Precautions regarding drug–food and drug–drug interactions are very important considerations in patients receiving oral anticoagulants.¹

VTE Risk in the Outpatient Setting—An Emerging Area of Investigation

Clinical practice guidelines recommend assessing and stratifying ambulatory cancer patients at risk for VTE and considering administration of primary thromboprophylaxis in selected patients—usually patients receiving highly thrombogenic regimens, including thalidomide or lenalidomide, or myeloma patients at high risk for VTE.^{1,24} To assist with the risk assessment process, Khorana and colleagues⁹ evaluated multiple factors known to be associated with VTE in the development of a predictive model for chemotherapy-associated VTE to identify high-risk ambulatory cancer patients who would be appropriate candidates for thromboprophylaxis. These investigators evaluated baseline clinical and laboratory values for their association with VTE in 4,066 out-patients who were enrolled in a multicenter, prospective, observational study and were starting chemotherapy for a variety of malignancies.⁹ Five factors were associated with development of symptomatic VTE, including cancer site, pre-chemotherapy platelet count $< 350 \times 10^9/L$, hemoglobin < 10 g/dL, and/or use of erythropoiesis-stimulating agents, prechemotherapy leukocyte count $> 11 \times 10^9/L$, and body mass index < 35 kg/m². These factors were used to develop a risk score for predicting the likelihood of chemotherapy-associated VTE: 0 (low risk), 1–2

(intermediate risk), or 3 (high risk) for each patient. Scoring was validated in a separate cohort of patients, and risk categories corresponded well with the observed rates of VTE in the cohort of patients initially used to develop the model.⁹

Ay and colleagues³² expanded the model to include two biomarkers found to be associated with an increased risk of VTE, including the cell adhesion molecule soluble P-selectin and the fibrin degradation product D-dimer. When all seven factors were evaluated in a population of 819 patients with a variety of malignancies who were either receiving no treatment or were being treated with chemotherapy, surgery, or radiotherapy, risk stratification improved compared with the original Khorana risk assessment tool. The expanded tool uses risk scores between 1 and 5, with higher scores being associated with a higher risk of VTE. In the study, this expanded risk assessment tool was associated with a difference in HR for VTE in high-risk versus low-risk groups of 25.9 (95% CI = 8.0 to 84.6), and higher scores in the expanded risk assessment model were significantly associated with higher VTE rates (Fig. 1).³² This expanded risk model enables a more precise identification of outpatients at very high risk of VTE.³²

A streamlined and potentially more objective approach to risk stratification has been explored as well. In an observational study³³ in approximately 1,000 patients with different forms of cancer, the predictive value of thrombin generation as a reflection of the net effect of multiple influences on coagulation capacity was investigated. Results showed that patients with elevated peak thrombin levels ≥ 611 nM had a greater than twofold increase in risk of developing VTE after 6 months compared with patients with lower peak thrombin levels.³³ Although these risk assessment tools are available and validated in observational studies, their use is not yet recommended in clinical guidelines for risk stratification and evaluation of ambulatory cancer patients' candidacy for primary VTE prophylaxis because they have not yet been validated in randomized clinical trials.¹

Guideline Recommendations for Thromboprophylaxis in Ambulatory Cancer Patients

Several publications outline recommendations for VTE prophylaxis in medical patients with cancer; these include the American Society of Clinical Oncology (ASCO),⁸ the NCCN,¹ and the American College of Chest Physicians (ACCP) (Table 2).^{24,25} Current clinical guidelines^{1,8,24,26} recommend use of thromboprophylaxis in cancer patients undergoing surgery, in hospitalized patients with cancer, and in some ambulatory patients at high risk for VTE. The 2007 ASCO guidelines recommend against routine primary VTE prophylaxis in ambulatory cancer patients receiving chemotherapy, except in high-risk patients—specifically myeloma patients receiving thalidomide or lenalidomide with chemotherapy or dexamethasone.⁸ Until recently, recommendations regarding routine use of anticoagulants for thromboprophylaxis in the ambulatory cancer setting were limited to this very specific group of myeloma patients.^{8,34} This limitation was perhaps due to concerns that cancer patients at low risk for VTE might be placed at unnecessary risk of bleeding events if routinely given anticoagulant prophylaxis. More recent guidelines expand the recommendations for thromboprophylaxis in certain categories of outpatients with cancer.^{1,24} The ACCP guidelines provide a Grade 2B recommendation for primary VTE

prophylaxis with anticoagulants in ambulatory patients with solid tumors, additional VTE risk factors (prior VTE, immobilization, hormonal therapy, and angiogenesis inhibitor therapy), and low bleeding risk.²⁴ The NCCN guidelines also suggest optional consideration of primary pharmacologic VTE prophylaxis in ambulatory cancer patients based on the presence of risk factors for VTE.¹

Clinical Studies of Pharmacologic Agents for Primary Prevention of Thrombosis in Ambulatory Patients with Cancer

We searched the PubMed database of English language publications to investigate the use of antithrombotic agents for the primary prevention of thrombosis in ambulatory medical patients with cancer who are receiving chemotherapy. The initial search strategy captured clinical studies carrying the MeSH terms *venous thromboembolism AND neoplasms*. A total of 433 citations were found, and titles and/or abstracts for these citations were reviewed to identify full-text articles of relevance to the stated topic. Studies focusing specifically on prevention of central venous catheter–related thrombosis were excluded. The subsequent review yielded eight publications describing nine studies that evaluated the use of primary VTE prophylaxis in ambulatory cancer patients receiving chemotherapy (Table 3).^{35–42} The nine studies evaluated the use of parenteral anticoagulants, including two U.S. Food and Drug Administration (FDA) –approved LMWHs, enoxaparin and dalteparin, two non-FDA-approved LMWHs, nadroparin and certoparin, and an investigational ultra-LMWH agent, semuloparin. Studies evaluating the efficacy of two oral agents, the antiplatelet agent aspirin, and the vitamin K antagonist warfarin were also identified. It should be noted that none of these agents are currently FDA approved for routine use in the primary prevention of VTE in ambulatory patients with cancer.

Of the nine identified trials, eight compared a single antithrombotic agent with placebo or no antithrombotic treatment^{35,37–42} and one included three active treatment groups but no placebo group.³⁶ In five of the eight placebo-controlled studies, pharmacologic thromboprophylaxis resulted in statistically significant reductions of thromboembolic events, with no statistically significant increase in bleeding events.^{35,40,41} The only studies in which there was no statistically significant reduction in the incidence of VTE with a prophylactic regimen were the study by Perry and colleagues,³⁹ evaluating the use of dalteparin in patients with malignant glioma and the TOPIC-1 and TOPIC-2 studies by Haas and colleagues,⁴² evaluating use of certoparin in patients with metastatic breast cancer or late-stage lung cancer. It is important to note that the negative results from these three studies are inconclusive because none of them met statistical power owing to low VTE event rates and low recruitment rates. Thus, further study is needed to evaluate the use of these agents in the specific populations. With regard to survival benefit from anticoagulant use for primary prophylaxis in cancer patients receiving chemotherapy, of the four published studies described in Table 4, some showed a small, statistically significant survival benefit with anticoagulant use, whereas others did not.^{43–46} Additional investigation is warranted, and the clinical significance of this possible survival benefit needs to be further explored, with continued evaluation of the risks and benefits of primary prophylaxis in this population.⁴⁷

Ongoing and Recently Completed Studies

Searches of the U.S. National Institutes of Health clinical study registry (<http://www.clinicaltrials.gov>) (search phrases *anticoagulants in patients with cancer* and *thromboembolism in patients with cancer*) identified 10 ongoing clinical trials and 8 completed clinical trials for which full results are not yet published. The trials evaluating anticoagulant therapy for VTE prophylaxis in medical patients with cancer who are receiving chemotherapy are listed in Tables 5 and 6.

Conclusions

Patients with cancer are at increased risk for VTE, and VTE is a major cause of death in this population.^{1,2} Patient-related, cancer-related, and treatment-related factors are important predictors of VTE incidence in patients with malignancy.⁸ Guidelines for VTE prophylaxis recommend the use of pharmacologic anticoagulants for hospitalized cancer patients and some high-risk ambulatory cancer patients such as those receiving thalidomide or lenalidomide with chemotherapy or dexamethasone or those with several VTE risk factors who are at low bleeding risk.^{1,8,24,26} The recommendation to consider the option of primary VTE prophylaxis in patients with multiple risk factors for VTE may be difficult to implement currently because practitioners await data from ongoing, prospective studies to validate the use of VTE risk stratification tools in cancer patients. To date, 13 randomized trials of anticoagulant therapy in ambulatory patients receiving chemotherapy have been published, with 9 of these evaluating efficacy and safety and 4 evaluating patient survival. Overall, these studies appear to suggest a favorable efficacy and safety profile for use of anticoagulants in outpatient populations of patients with cancer receiving chemotherapy. Results from 18 other studies (10 ongoing and 8 completed but not yet published) are expected to become available during the next few years. The data regarding survival benefit with use of anticoagulants in cancer patients suggest that anticoagulants may confer a small survival benefit when used for primary prophylaxis in some outpatients with cancer who are receiving chemotherapy. The results of forthcoming studies may be used to shape recommendations for VTE prophylaxis in ambulatory cancer patients receiving chemotherapy in future clinical guideline updates.

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References

1. Streiff MB, Bockenstedt PL, Cataland SR, et al. Venous thromboembolic disease. J Natl Compr Canc Netw. 2011; 9(7):714–777. [PubMed: 21715723]

2. Khorana AA, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost.* 2007; 5(3):632–634. [PubMed: 17319909]
3. Khorana AA, Francis CW, Culakova E, Fisher RI, Kuderer NM, Lyman GH. Thromboembolism in hospitalized neutropenic cancer patients. *J Clin Oncol.* 2006; 24(3):484–490. [PubMed: 16421425]
4. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA.* 2005; 293(6):715–722. [PubMed: 15701913]
5. Spencer FA, Lessard D, Emery C, Reed G, Goldberg RJ. Venous thromboembolism in the outpatient setting. *Arch Intern Med.* 2007; 167(14):1471–1475. [PubMed: 17646600]
6. Imberti D, Agnelli G, Ageno W, et al. Clinical characteristics and management of cancer-associated acute venous thromboembolism: findings from the MASTER Registry. *Haematologica.* 2008; 93(2): 273–278. [PubMed: 18223291]
7. Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med.* 2006; 166(4):458–464. [PubMed: 16505267]
8. Lyman GH, Khorana AA, Falanga A, et al. 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. [PubMed: 17968019]
9. 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. [PubMed: 18216292]
10. Sood SL. Cancer-associated thrombosis. *Curr Opin Hematol.* 2009; 16(5):378–385. [PubMed: 19606029]
11. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood.* 2002; 100(10):3484–3488. [PubMed: 12393647]
12. Moore RA, Adel N, Riedel E, et al. High incidence of thromboembolic events in patients treated with cisplatin-based chemotherapy: a large retrospective analysis. *J Clin Oncol.* 2011; 29(25): 3466–3473. [PubMed: 21810688]
13. Otten HM, Mathijssen J, ten Cate H, et al. Symptomatic venous thromboembolism in cancer patients treated with chemotherapy: an underestimated phenomenon. *Arch Intern Med.* 2004; 164(2):190–194. [PubMed: 14744843]
14. Bennett CL, Schumock GT, Desai AA, et al. Thalidomide-associated deep vein thrombosis and pulmonary embolism. *Am J Med.* 2002; 113(7):603–606. [PubMed: 12459408]
15. Bennett CL, Angelotta C, Yarnold PR, et al. Thalidomide- and lenalidomide-associated thromboembolism among patients with cancer. *JAMA.* 2006; 296(21):2558–2560. [PubMed: 17148721]
16. Deitcher SR, Gomes MP. The risk of venous thromboembolic disease associated with adjuvant hormone therapy for breast carcinoma: a systematic review. *Cancer.* 2004; 101(3):439–449. [PubMed: 15274057]
17. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *JAMA.* 2008; 299(8):914–924. [PubMed: 18314434]
18. Nalluri SR, Chu D, Keresztes R, Zhu X, Wu S. Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis. *JAMA.* 2008; 300(19): 2277–2285. [PubMed: 19017914]
19. Hurwitz HI, Saltz LB, Van Cutsem E, et al. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. *J Clin Oncol.* 2011; 29(13):1757–1764. [PubMed: 21422411]
20. 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. [PubMed: 21555690]

21. Di Nisio M, Ferrante N, De Tursi M, et al. Incidental venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Thromb Haemost.* 2010; 104(5):1049–1054. [PubMed: 20806119]
22. Dentali F, Ageno W, Becattini C, et al. Prevalence and clinical history of incidental, asymptomatic pulmonary embolism: a meta-analysis. *Thromb Res.* 2010; 125(6):518–522. [PubMed: 20451960]
23. Browne AM, Cronin CG, English C, Ni Mhuirheartaigh J, Murphy JM, Bruzzi JF. Unsuspected pulmonary emboli in oncology patients undergoing routine computed tomography imaging. *J Thorac Oncol.* 2010; 5(6):798–803. [PubMed: 20421822]
24. 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–e226S. [PubMed: 22315261]
25. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012; 141(2 Suppl):e227S–e277S. [PubMed: 22315263]
26. Mandalà M, Falanga A, Roila F. ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2011; 22(Suppl 6):vi85–vi92. [PubMed: 21908511]
27. Wright JD, Lewin SN, Shah M, et al. Quality of venous thromboembolism prophylaxis in patients undergoing oncologic surgery. *Ann Surg.* 2011; 253(6):1140–1146. [PubMed: 21394015]
28. Abdel-Razeq H, Albadainah F, Hijawi S, Mansour A, Treish I. Venous thromboembolism (VTE) in hospitalized cancer patients: prophylaxis failure or failure to prophylax! *J Thromb Thrombolysis.* 2011; 31(1):107–112. [PubMed: 20686822]
29. Kucher N, Spirk D, Baumgartner I, et al. Lack of prophylaxis before the onset of acute venous thromboembolism among hospitalized cancer patients: the SWISS Venous ThromboEmbolic Registry (SWIVTER). *Ann Oncol.* 2010; 21(5):931–935. [PubMed: 19828560]
30. Trujillo-Santos J, Nieto JA, Ruíz-Gamietea A, et al. Bleeding complications associated with anticoagulant therapy in patients with cancer. *Thromb Res.* 2010; 125(Suppl 2):S58–S61. [PubMed: 20434007]
31. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012; 141(2 Suppl):e24S–e43S. [PubMed: 22315264]
32. Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood.* 2010; 116(24):5377–5382. [PubMed: 20829374]
33. Ay C, Dunkler D, Simanek R, et al. Prediction of venous thromboembolism in patients with cancer by measuring thrombin generation: results from the Vienna Cancer and Thrombosis Study. *J Clin Oncol.* 2011; 29(15):2099–2103. [PubMed: 21464402]
34. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). *Chest.* 2008; 133(6 Suppl):381S–453S. [PubMed: 18574271]
35. Levine M, Hirsh J, Gent M, et al. Double-blind randomised trial of a very-low-dose warfarin for prevention of thromboembolism in stage IV breast cancer. *Lancet.* 1994; 343(8902):886–889. [PubMed: 7908358]
36. Palumbo A, Cavo M, Bringhen S, et al. Aspirin, warfarin, or enoxaparin thromboprophylaxis in patients with multiple myeloma treated with thalidomide: a phase III, open-label, randomized trial. *J Clin Oncol.* 2011; 29(8):986–993. [PubMed: 21282540]
37. Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc.* 2005; 80(12):1568–1574. [PubMed: 16342649]
38. 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. [PubMed: 22100906]

39. Perry JR, Julian JA, Laperriere NJ, et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. *J Thromb Haemost.* 2010; 8(9):1959–1965. [PubMed: 20598077]
40. Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol.* 2009; 10(10):943–949. [PubMed: 19726226]
41. Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med.* 2012; 366(7):601–609. [PubMed: 22335737]
42. Haas SK, Freund M, Heigener D, et al. Low-molecular-weight heparin versus placebo for the prevention of venous thromboembolism in metastatic breast cancer or stage III/IV lung cancer. *Clin Appl Thromb Hemost.* 2012; 18(2):159–165. [PubMed: 22275397]
43. Lebeau B, Chastang C, Brechot JM, et al. Subcutaneous heparin treatment increases survival in small cell lung cancer. “Petites Cellules” Group. *Cancer.* 1994; 74(1):38–45. [PubMed: 8004580]
44. Altinbas M, Coskun HS, Er O, et al. A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer. *J Thromb Haemost.* 2004; 2(8):1266–1271. [PubMed: 15304029]
45. Kakkar AK, Levine MN, Kadziola Z, et al. Low molecular weight heparin, therapy with dalteparin, and survival in advanced cancer: the Fragmin advanced malignancy outcome study (FAMOUS). *J Clin Oncol.* 2004; 22(10):1944–1948. [PubMed: 15143088]
46. Sideras K, Schaefer PL, Okuno SH, et al. Low-molecular-weight heparin in patients with advanced cancer: a phase 3 clinical trial. *Mayo Clin Proc.* 2006; 81(6):758–767. [PubMed: 16770976]
47. Akl EA, Schünemann HJ. Routine heparin for patients with cancer? One answer, more questions. *N Engl J Med.* 2012; 366(7):661–662. [PubMed: 22335745]

Fig. 1.

Kaplan–Meier estimates of the risk of VTE in the expanded risk scoring model including sP-selectin and D-dimer developed by Ay and colleagues. VTE, venous thromboembolism.

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Table 1

Risk factors for VTE in patients with cancer

Patient-related	Cancer-related	Treatment-related
<ul style="list-style-type: none"> • Older age • African American race • Comorbid conditions • History of VTE • Elevated prechemotherapy platelet count • Heritable prothrombotic mutations 	<ul style="list-style-type: none"> • Primary site of cancer (higher risk in GI, brain, lung, gynecologic, renal, and hematologic cancers) • Initial 3–6 months after diagnosis • Current metastatic disease 	<ul style="list-style-type: none"> • Recent major surgery • Current hospitalization • Active chemotherapy • Active hormonal therapy • Current or recent antiangiogenic therapy • Current erythropoiesis-stimulating agents • Presence of CVCs

Abbreviations: CVC, central venous catheter; GI, gastrointestinal; VTE, venous thromboembolism.

Source: Adapted from Lyman et al.⁸ ©2007 American Society of Clinical Oncology. All rights reserved.

Table 2

Summary of guideline recommendations for VTE prophylaxis in ambulatory patients with cancer: ASCO, NCCN, and ACCP

Society	Recommendations
ASCO ⁸ (2007)	<ul style="list-style-type: none"> Routine prophylaxis with an antithrombotic agent is not recommended for ambulatory patients with cancer during systemic chemotherapy Ambulatory patients with myeloma receiving thalidomide or lenalidomide with chemotherapy or dexamethasone are at high risk for thrombosis and warrant prophylaxis. LMWH or adjusted-dose warfarin (international normalized ratio 1.5) is recommended in myeloma patients receiving thalidomide or lenalidomide plus chemotherapy or dexamethasone
NCCN ¹ (2011)	<ul style="list-style-type: none"> Despite a lack of consistent evidence supporting extended outpatient prophylaxis in most populations of ambulatory medical oncology patients, this practice is recommended for patients with multiple myeloma receiving highly thrombogenic combination chemotherapy regimens based on limited data With respect to other ambulatory cancer outpatients, the option of prophylaxis should be considered in individuals who are at risk for VTE based on an assessment of VTE risk factors
ACCP ²⁴ (2012)	<ul style="list-style-type: none"> In outpatients with cancer who have no additional risk factors for VTE, the ACCP guidelines suggest against routine prophylaxis with LMWH or LDUH, and recommended against prophylactic use of vitamin K antagonists In outpatients with solid tumors who have additional risk factors for VTE and have a low risk of bleeding, prophylaxis with LMWH or LDUH is suggested (risk factors for VTE include prior VTE, immobilization, hormone therapy, and angiogenesis inhibitors, thalidomide, and lenalidomide)

Abbreviations: ACCP, American College of Chest Physicians; ASCO, American Society of Clinical Oncology; LDUH, low-dose unfractionated heparin; LMWH, low molecular weight heparin; NCCN, National Comprehensive Cancer Network; VTE, venous thromboembolism.

Table 3
Summary of trials of VTE prophylaxis in ambulatory cancer patients receiving chemotherapy

Agent(s)	Patient population	N	Main efficacy and safety result(s)	Reference
Warfarin (very low dose)	Metastatic breast cancer (Stage IV)	N = 311: very low-dose warfarin, n = 152; placebo, n = 159	<ul style="list-style-type: none"> Thromboembolic events occurred in 1 patient in the warfarin group (0.1%) and 7 (4.4%) in the placebo group (RRR = 85% for warfarin vs. placebo; $p = 0.03$) Bleeding occurred in 8 patients (5.3%) in the warfarin group and 5 (3.1%) in the placebo group ($p = 0.4$) 	Levine et al, 1994 ³⁵
Aspirin, warfarin, enoxaparin	Multiple myeloma treated with thalidomide-based regimen	N = 659: aspirin, n = 220; warfarin, n = 220; enoxaparin, n = 219	<ul style="list-style-type: none"> Thromboembolic events occurred in 13 patients (5.9%) receiving aspirin, 18 (8.2%) receiving warfarin, and 7 (3.2%) receiving enoxaparin (absolute differences were not significant between the aspirin and enoxaparin groups [$p = 0.17$], but the event rate was significantly higher in the warfarin vs. enoxaparin group [$p = 0.024$]) Bleeding occurred in 9 patients (4.1%) in the aspirin group, 1 patient (0.5%) in the warfarin group, and 3 patients (1.4%) in the enoxaparin group (between-group differences were not significant) 	Palumbo et al, 2011 ³⁶
Aspirin	Multiple myeloma	N = 103: aspirin, n = 84; no aspirin, n = 19	<ul style="list-style-type: none"> Thromboembolic events occurred in 15 patients (18%) who received aspirin and in 11 (58%) who did not (HR = 0.22; 95% CI = 0.10–0.47; $p < 0.001$) No significant bleeding occurred in patients who received aspirin 	Baz et al, 2005 ³⁷
Dalteparin	Pancreatic cancer treated with gemcitabine	N = 123: dalteparin, n = 62; no dalteparin (control arm), n = 59	<ul style="list-style-type: none"> Thromboembolic events occurred in 14 patients (23%) in the control group and 2 (3%) in the dalteparin group (RR = 0.145; 95% CI = 0.035–0.612; $p = 0.002$) The incidence of severe bleeding was 3% in both treatment groups 	Maraveyas et al, 2011 ³⁸
	Malignant glioma	N = 186: dalteparin, n = 99; no dalteparin (control arm), n = 87	<ul style="list-style-type: none"> Thromboembolic events occurred in 13 patients (15%) in the control group and in 9 patients (9%) in the dalteparin group (HR = 0.51 [0.19–1.41]; $p = 0.29$); Of note, the study was underpowered due to low recruitment rates. Five patients (5.1%) in the dalteparin group and 1 (1.2%) in the placebo group experienced bleeding ($p = 0.22$) 	Perry et al, 2010 ³⁹
Nadroparin (not available in the United States)	Metastatic or locally advanced solid tumors	N = 1,150: nadroparin, n = 769; placebo, n = 381	<ul style="list-style-type: none"> Thromboembolic events occurred in 15 patients (2.0%) in the nadroparin group and 15 (3.9%) in the placebo group ($p = 0.02$) Major bleeding occurred in 5 patients (0.7%) in the nadroparin group and in no patient in the placebo group ($p = 0.18$), and minor bleeding occurred in 57 patients (7.4%) in the nadroparin group and 30 patients (7.9%) in the placebo group 	Agnelli et al, 2009 ⁴⁰

Agent(s)	Patient population	N	Main efficacy and safety result(s)	Reference
Semuloparin (investigational agent)	Metastatic or locally advanced lung, pancreatic, stomach, colon, rectal, bladder, or ovarian cancer	N = 3,212; semuloparin, n = 1,608; placebo, n = 1,604	<ul style="list-style-type: none"> VTE or VTE-related death occurred in 20 patients (1.2%) in the semuloparin group and in 55 (3.4%) in the placebo group (HR = 0.36; 95% CI = 0.21–0.60; $p < 0.001$) Clinically relevant bleeding occurred in 45 patients (2.8%) in the semuloparin group and 32 (2.0%) in the placebo group (HR = 1.40; 95% CI = 0.89–2.21) 	Agnelli et al, 2012 ⁴¹
Certoparin (not available in the United States)	Metastatic breast cancer (TOPIC-1) or late-stage (III/IV) lung cancer (TOPIC-2)	TOPIC-1 (N = 351): certoparin, n = 174; placebo, n = 177 TOPIC-2 (N = 532): certoparin, n = 268; placebo, n = 264	TOPIC-1: <ul style="list-style-type: none"> VTE occurred in 7 patients (4.0%) who received certoparin and in 7 patients (4.0%) who received placebo ($p = 1.0$); notably, the study was underpowered due to low event rates Bleeding events occurred in 9 patients (5.2%) receiving certoparin and 3 patients (1.7%) receiving placebo ($p = 0.08$) TOPIC-2: <ul style="list-style-type: none"> VTE occurred in 12 patients (4.5%) in the certoparin group and 22 patients (8.3%) in the placebo group ($p = 0.078$); notably, the study was underpowered due to low event rates Bleeding events occurred in 37 patients (13.6%) in the certoparin group and 20 patients (7.3%) in the placebo group ($p = 0.02$) 	Haas et al, 2012 ⁴²

Abbreviations: CI, confidence interval; HR, hazard ratio; RR, risk ratio; RRR, relative risk reduction; VTE, venous thromboembolism.

Table 4

Summary of randomized trials of survival in ambulatory cancer patients receiving chemotherapy and VTE prophylaxis

Agent(s)	Patient population	N	Main efficacy and safety result(s)	Reference
Unfractionated heparin (UFH)	Small cell lung cancer; receiving chemotherapy	N = 277: UFH, n = 138; no UFH (control arm), n = 139	<ul style="list-style-type: none"> Thromboembolic events rates were not reported in this study Chemotherapeutic response occurred in 23% of patients in the control group and 37% of patients in the UFH group ($p = 0.004$) Median survival was 261 days in the control group and 317 days in the UFH group ($p = 0.01$) No important bleeding was related to UFH treatment 	Lebeau et al, 1994 ⁴³
Dalteparin	Small cell lung cancer; receiving chemotherapy	N = 84: dalteparin, n = 42; no dalteparin (control arm), n = 42	<ul style="list-style-type: none"> A thromboembolic event occurred in one patient (2.4%) in the control group and in none of the dalteparin group patients Median overall survival was 8 months in the control group and 13 months in the dalteparin group ($p = 0.01$) Bleeding events occurred in one patient (2.4%) in the dalteparin group and in none of the control group patients 	Altinbas et al, 2004 ⁴⁴
	Advanced breast, GI tract, lung, genitourinary tract, pancreas, liver, ovary, or uterine cancer; 31% of placebo and 34% of dalteparin groups received chemotherapy	N = 385	<ul style="list-style-type: none"> Thromboembolic events occurred in five patients (3.3%) in the placebo group and in four (2.4%) in the dalteparin group Median survival was 24.3 months (95% CI = 22.4–41.5 months) in the placebo group and 43.5 months in the dalteparin group (95% CI = 33–52.3 months) Bleeding events occurred in nine patients (4.7%) in the dalteparin group and in five patients (2.7%) in the placebo group 	Kakkar et al, 2004 ⁴⁵
	Advanced breast, colon, lung, and prostate cancer; receiving chemotherapy	N = 138: dalteparin, n = 68; no dalteparin (control arm), n = 70	<ul style="list-style-type: none"> Thromboembolic events occurred in five patients (7%) in the control group and four (6%) in the dalteparin group Median overall survival was 10.5 months in the control group and 7.3 months in the dalteparin group ($p = 0.46$) Bleeding events occurred in two patients (3%) in the dalteparin group and five (7%) in the control group 	Sideras et al, 2006 ⁴⁶

Abbreviations: CI, confidence interval; GI, gastrointestinal; UFH, unfractionated heparin.

Table 5

Ongoing trials of thromboprophylaxis in medical patients with cancer receiving chemotherapy (as of March 2012, www.clinicaltrials.gov)

Agent	Cancer type	Phase	Trial number
Enoxaparin	Gastric/gastroesophageal cancer	III	NCT00718354
	Small cell lung cancer	III	NCT00717938
	Non-small cell lung cancer	III	NCT00771563
Dalteparin	High-risk, ambulatory cancer	III	NCT00876915
	Pancreatic cancer	IV	NCT00966277
	Lung cancer	III	NCT00519805
	Metastatic pancreatic cancer	III	NCT00662688
	Metastatic renal cell carcinoma	I/II	NCT01061411
Fondaparinux	Non-small cell lung cancer	I	NCT00476216
Warfarin	Advanced solid tumors	I	NCT00091299

Table 6

Recently completed trials of thromboprophylaxis in medical patients with cancer receiving chemotherapy (as of March 2012, www.clinicaltrials.gov)

Agent	Cancer type	Phase	Trial number
Apixaban	Advanced cancer	II	NCT00320255
Dalteparin	Unresectable or metastatic pancreatic cancer	III	NCT00031837
	Multiple types; chemotherapy infused via CVC	III	NCT00006083
	Advanced breast, lung, colorectal, or prostate cancer	III	NCT00003674
Enoxaparin	Pancreatic cancer	II/III	NCT00785421
Nadroparin	Non–small cell lung, pancreas, or prostate cancer	III	NCT00312013
Aspirin, clopidogrel	Recurrent/metastatic head and neck cancer	II	NCT00020189
Warfarin	Prostate cancer	II	NCT00014352

Abbreviation: CVC, central venous catheter.