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Thromboprophylaxis for medical patients with cancer: what do the guidelines say?

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Practice Points

- Hospitalized medically ill cancer patients should receive parenteral thromboprophylaxis for the duration of the hospital stay if there are no bleeding risks or other contraindications to anticoagulation.
- Mechanical thromboprophylaxis using intermittent pneumatic compression or graduated compression stockings are recommended when there is a contraindication to anticoagulation therapy.
- Ambulatory cancer patients receiving chemotherapy should be stratified according to their risk of venous thromboembolism (VTE; e.g., Khorana predictive model).
- Ambulatory patients at high risk for VTE who are receiving chemotherapy should be counselled on the signs and symptoms of VTE with instructions to seek medical attention if they occur.
- Parenteral thromboprophylaxis should not be used routinely in ambulatory cancer patients at high risk of VTE. In the absence of bleeding or other contraindications, parenteral thromboprophylaxis can be considered on a case-by-case basis accompanied by a discussion of the potential benefits and risks.

Venous thromboembolism (VTE) is frequent in cancer patients and is one of the leading causes of death in this population. Hospitalized cancer patients and those receiving chemotherapy are at the greatest risk of developing VTE. Many randomized controlled trials in a variety of patient populations have demonstrated that primary prophylaxis is effective in reducing the risk of VTE among cancer patients. Pharmacological thromboprophylaxis is recommended in all hospitalized medically ill cancer patients without a contraindication to anticoagulant therapy. Thromboprophylaxis in ambulatory patients undergoing chemotherapy is only considered in those at high risk of VTE. In this article, we evaluate the different clinical practice guideline recommendations for primary VTE prophylaxis in hospitalized medically ill patients with cancer and ambulatory patients undergoing chemotherapy.

Keywords: hemorrhage • heparin • low-molecular-weight • neoplasm • venous thromboembolism • venous thrombosis

Thromboprophylaxis in hospitalized medically ill cancer patients

Epidemiology

Venous thromboembolism (VTE) is an important complication in hospitalized cancer patients [1]. The incidence of VTE in this population varies according to the type of malignancy, and has been reported to be twice as high as in hospitalized patients without cancer [2]. A large retrospective cohort study reported a rate of VTE at 5.4% in hospitalized neutropenic cancer patients [1]. Discharge data of more than 1 million cancer patients showed that the rate of VTE increased from 3.6% per hospitalization in 1995–1996 to 4.6% in 2002–2003

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(p < 0.0001), while the rate of pulmonary embolism (PE) doubled from 0.8 to 1.5% (p < 0.0001) [3]. The prevalence of VTE in hospitalized cancer patients is also rising [3,4]. A retrospective cohort study of 66,329 cancer patients found a VTE prevalence of 12.3 per 1000 patients, which is much higher than that of the general population (two VTEs per 1000 patients) [5]. Moreover, VTE is a leading cause of death in hospitalized cancer patients [6]. In fact, compared with those without VTE, hospitalized patients with cancer have a twofold increased risk of death [7]. The probability of death within 183 days of initial hospitalization among patients with VTE and cancer or patients with VTE and no cancer was found to be 0.94 and 0.29 (p = 0.001), respectively [8]. A more recent study found that the mortality in hospitalized cancer patients who developed VTE and in similar patients who did not develop VTE was 16.3 and 6.3% (p < 0.0001), respectively [3]. In addition, it is estimated that one in every seven hospitalized cancer patients diagnosed with PE will have a fatal event [9].

Risk stratification scores

The Padua Prediction Score

Since VTE is a major cause of mortality and morbidity in hospitalized medical patients, multiple risk assessment models (RAMs) to identify those at increased risk have been proposed [10–17]. However, most of them have not been validated in prospective studies [10–12,15,16].

In a 2-year prospective cohort study, 1180 consecutive hospitalized medically ill patients were assigned points to 11 VTE risk factors [18]. Patients where then classified as having high or low risk of developing VTE. Approximately 20.0% of patients included in this study had active cancer. This predefined RAM score was modified after Kucher's empirical risk score [13]. Patients were followed after discharge for up to 90 days to assess the incidence of symptomatic VTE. According to the Padua Prediction Model, any cancer patients would be considered as having a high-risk of developing VTE if they have one or more of the following factors: elderly age (≥70 years), heart and/or respiratory failure, acute myocardial infarction or ischemic stroke, acute infection and/or rheumatologic disorder, obesity (BMI ≥30), ongoing hormonal treatment; or if they have recent (≤1 month) trauma and/or surgery; or if they have at least one of the following factors: previous VTE, reduced mobility for at least 3 days or thrombophilic condition [18].

Out of the 1180 recruited patients, 711 patients (60.3%) were categorized as low risk (score <4) and 469 patients (39.7%) were categorized as high risk (score ≥4). Among hospitalized patients who did not receive VTE prophylaxis, VTE occurred in 11.0% (31 out of 283) of high-risk patients and in 0.3% (2 out of 711) of low-risk patients, with a corresponding hazard ratio of 32.0 (95% CI: 4.1–251.0). Although the Padua Prediction Model seems promising, it has not been validated in independent cohorts and was not been derived from cancer patients. Therefore, the Padua Prediction model should be used carefully to stratify hospitalized medically ill cancer patients.

Although it is difficult to predict bleeding risk in hospitalized cancer patients, it is important to develop and validate evidence-based bleeding risk assessment tools to identify those at high and low risks of bleeding during hospitalization as it will allow physicians to better individualize anticoagulant therapy duration for these patients and decide on whether to use mechanical or pharmacologic thromboprophylaxis. A recent large, multinational, observational study assessed records from the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) [19]. The authors reported on the incidence of in-hospital bleeding and identified 11 risk factors at admission associated with in-hospital bleeding risk in acutely ill medical patients [19]. 10.7% of the enrolled patients had active cancer, of them 1.4% experienced a major bleeding event within 14 days of admission. The strongest independent risk factors predictive of bleeding were active gastroduodenal ulcer (odds ratio [OR]: 4.15; 95% CI: 2.21–27.77), bleeding in the 3 months before admission (OR: 3.64; 95% CI: 2.21–25.99) and platelet count <50 × 10^9/l (OR: 3.37; 95% CI: 1.84–86.18). Some limitations of the IMPROVE study include the varied type and dosage of the received in-hospital VTE prophylaxis regimens and the small number of patients included with cancer. Therefore, decisions regarding the use of these risk factors to stratify the risk of bleeding in hospitalized cancer patients need to be made carefully. The risk–benefit analysis should be done on a case-by-case basis in this patient population.

Medical inpatients & thrombosis study score

A more recent study proposed two risk assessment models in medical inpatients, one using laboratory data available at admission and the other excluding laboratory data [20]. VTE complicated 7.6% of patients per 1000 admissions in the hematology/oncology services (95% CI: 5.2–10.0) [20]. Although the model specifically selected risk factors that could be easily assessed at admission, external validity of the model is needed.

Pharmacological thromboprophylaxis

Low-dose unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs) and fondaparinux are the most commonly used prophylactic anticoagulant regimens. They have been shown to be

effective in reducing the risk of symptomatic DVT and fatal PE with no major increases in bleeding events in hospitalized medically ill patients [21–23].

UFH

A mixed-treatment comparison meta-analysis of 16 trials that enrolled hospitalized nonsurgical patients compared UFH twice daily (b.i.d.), UFH three-times daily (t.i.d.) or LMWH to one another or to an inactive control. Results from these indirect comparisons suggest that UFH b.i.d. and UFH t.i.d. do not differ in reducing the risk of VTE and hemorrhagic complications. The risk ratio and 95% credible interval for UFH t.i.d. versus UFH b.i.d. for DVT, PE, death and major bleeding events were 1.56 (0.64–64.33), 1.67 (0.49–208.09), 1.17 (0.72–71.95) and 0.89 (0.08–7.05), respectively [24].

LMWH & fondaparinux

Data from trials in hospitalized patients with cancer are not available. The trials assessing the efficacy and safety of LMWH or fondaprinux included only a minority of patients with cancer and with little or no data on the rates of major bleeding events in the subgroups with malignancies [25–27]. Data used for practice guidelines came from subgroup analyses of these large trials. These trials that directly evaluated LMWHs or fondaparinux with placebo in hospitalized medically ill patients have reported a decrease of VTE events in patients receiving prophylactic anticoagulants [25–27]. The reported low rates of hemorrhagic complications from these trials justify the use of pharmacologic prophylaxis in hospital patients with cancer. Trials of anticoagulants for thromboprophylaxis in hospitalized medically ill patients are depicted in Table 1.

New oral anticoagulants

Rivaroxaban and apixaban were compared with enoxaparin for extended duration of thromboprophylaxis in the MAGELLAN [29] and ADOPT [30] trials, respectively (Table 1).

The MAGELLAN study was a multicenter, randomized controlled trial comparing extended prophylaxis with rivaroxaban and short-term prophylaxis with enoxaparin among patients 40 years of age or older hospitalized for acute medical illness [29]. A total of 8101 patients were randomized, of them 592 (7.3%) had active cancer, to receive enoxaparin 40 mg once daily for 10 days followed by placebo once daily for 35 days, or to receive placebo once daily for 10 days followed by rivaroxaban 10 mg once daily for 35 days. At day 10, rivaroxaban was found to be noninferior to enoxaparin for standard-duration thromboprophylaxis with an associated relative risk of 0.97 (95% CI: 0.71–71.31; $p = 0.003$). However, there were more major bleeding episodes with rivaroxaban than with enoxaparin ($p < 0.001$) [29]. In subgroup analyses, no statistical difference was found between extended thromboprophylaxis with rivaroxaban and short-term enoxaparin in patients with active malignancy on day 35 (relative risk ratio: 1.34; 95% CI: 0.71–72.54) [31].

In the ADOPT trial, 6528 hospitalized medically ill patients were randomly assigned to receive 2.5 mg apixaban twice daily for 30 days or 40 mg enoxaparin once daily for 6 to 14 days [30]. This double-blind, double-dummy, placebo-controlled trial reported that extended duration of thromboprophylaxis with apixaban was not superior to a short-term course of enoxaparin (relative risk: 0.87; 95% CI: 0.62–61.23; $p = 0.44$). Apixaban was associated with a higher incidence of bleeding events than was enoxaparin (relative risk: 2.58; 95% CI: 1.02–7.24; $p = 0.04$). Subgroup analyses in patients with cancer are not currently available [30]. Therefore, rivaroxaban or apixaban are currently not recommended as thromboprophylactic agent for cancer patients hospitalized with medical illness.

Area of uncertainties

The risk of VTE among hospitalized medical patients is known to persist for weeks, even months, after hospital discharge [32]. Few studies have assessed the value of extending thromboprophylaxis in medical patients postdischarge and no such studies have been conducted in cancer patients (Table 1) [28–30].

Thromboprophylaxis following hospital discharge for patients with or without cancer is currently not recommended by practice guidelines. The National Comprehensive Cancer Network (NCCN) [33] recommends VTE prophylaxis following discharge for high-risk multiple myeloma patients undergoing antiangiogenic therapy only. The results from the EXCLAIM [28], MAGELLAN [29] and ADOPT [30] trials did not show a favorable risk–benefit ratio in administering VTE prophylaxis following hospital discharge and is currently not routinely recommended.

Summary of recommendations from the different guideline panels

The American Society of Clinical Oncology (ASCO) [34], the NCCN [33], the European Society of Medical Oncology (ESMO) [35], the Italian Association of Medical Oncology (AIOM) [36] and the American College of Chest Physicians (ACCP) [37] currently recommend UFH, LMWH, or fondaparinux as VTE prophylaxis for the duration of the hospital stay in medically ill patients with cancer when there is no bleeding risk or other contraindications. ESMO and AIOM restrict VTE prophylaxis to only hospitalized cancer patients

Table 1. Trials of anticoagulants for thromboprophylaxis in hospitalized medically ill patients.

Author (year); study name	Patients	Design	Number of patients/study intervention	Number of cancer patients/ study intervention	Primary outcome measure	Primary outcome/ conclusions	Bleeding events/ conclusions	Ref.
Samama *et al.* (1999); MEDENOX	Acutely ill medical patients >40 years	Double-blind RCT	371 placebo vs 364 enoxaparin 20 mg q.d. for 6–14 days or 267 enoxaparin 40 mg q.d. for 6–14 days	Total: 72 (12.4%) 41 placebo vs 31 enoxaparin 40 mg q.d. for 6–14 days	Symptomatic VTE	14.9 vs 15.0% (RR: 1.02; 95% CI: 0.70–1.51; p = 0.90) 14.9 vs 5.5% (RR: 0.37; 95% CI: 0.22–0.63; p < 0.001) Cancer subgroup: 19.5 vs 9.7% (RR: 0.50; 95% CI: 0.14–1.72; p = 0.40)	Major: 1.1 vs 0.3% Major: 1.1 vs 1.7% No difference	[25]
Leizorovicz *et al.* (2004); PREVENT	Acutely ill medical patients ≥40 years	Double-blind RCT	152 observation vs 160 dalteparin 5000 U daily for 14 days	Total: 137(3.7%) 72 placebo vs 65 dalteparin 5000 U daily for 14 days	Composite of symptomatic DVT, fatal or symptomatic nonfatal PE, sudden death and asymptomatic proximal DVT at day 21	5.0 vs 2.8% (RR: 0.55; 95% CI: 0.38–0.80; p = 0.0015) Cancer subgroup: 8.33 vs 3.08% (RR: 0.37; 95% CI: –)	Major: 0.16 vs 0.49% (p = 0.15)	[26]
Cohen *et al.* (2006); ARTEMIS	Acutely ill medical patients ≥60 years	Open RCT	152 observation vs 160 fondaparinux 2.5 mg q.d. for 6–14 days	Total: 131 (15.4%) 69 placebo vs 62 fondaparinux 2.5 mg q.d. for 6–14 days	Symptomatic and asymptomatic VTE for up to 15 days	10.5 vs 5.6% (RR: 0.47; 95% CI: 0.08–0.69; p = 0.029) Cancer subgroup: not available	Major: 0.2 vs 0.2%	[27]
Hull *et al.* (2010); EXCLAIM	Acutely ill medical patients ≥40 years	Open RCT	2988 placebo vs 2975 enoxaparin 40 mg q.d. for an additional 28 ± 4 days	Total 507 (8.5%) 272 placebo vs 235 enoxaparin 40 mg q.d. for an additional 28 ± 4 days	Composite of symptomatic and asymptomatic proximal DVT, symptomatic PE or fatal PE up to 28 days	4.0 vs 2.5% (AR difference: -1.53%; 95.8% CI: -2.54–0.52%) Cancer subgroup: not available	0.3 vs 0.8% (AR difference: 0.51%; 95% CI: 0.12–0.89%) Cancer subgroup: not available	[28]

AR: Absolute risk; DVT: Deep vein thrombosis; PE: Pulmonary embolism; q.d.: Once daily; RCT: Randomized controlled trial; RR: Relative risk; VTE: Venous thromboembolism.

Table 1. Trials of anticoagulants for thromboprophylaxis in hospitalized medically ill patients (cont.).

Author (year); study name	Patients	Design	Number of patients/study intervention	Number of cancer patients/ study intervention	Primary outcome measure	Primary outcome/ conclusions	Bleeding events/ conclusions	Ref.
Cohen *et al.* (2013); MAGELLAN	Acutely ill medical patients ≥40 years	Double-blind RCT	4051 enoxaparin 40 mg q.d. for 10 ± 4 days + placebo q.d. for 35 ± 4 days vs 4050 placebo q.d. for 10 ± 4 days days + rivaroxaban 10 mg q.d. for 35 ± 4 days	Total: 592 (7.3%) 296 in both arms	Composite of symptomatic and asymptomatic VTE at days 10 and 35	Major VTE (day 10): 2.7 vs 2.7% (RR: 0.97; 95% CI: 0.71–1.33; p = 0.003) Major VTE (day 35): 5.7 vs 4.4% (RR: 0.77; 95% CI: 0.62–0.96; p = 0.02) Cancer subgroup (day 35): 1.7 vs 5.4% (RR: 1.34; 95% CI: 0.71–72.54)	Clinically relevant Day 10: 1.2 vs 2.8% (p < 0.0001) Day 35: 1.7 vs 4.1% (p < 0.0001) Cancer subgroup: not available	[29]
Goldhaber *et al.* (2011); ADOPT	Acutely ill medical patients ≥40 years	Double-blind RCT	3255 apixaban 2.5 mg twice daily for 30 days vs 3273 enoxaparin 40 mg q.d. during for a minimum of 6 days	Total active cancer: 211 (3.2%) 113 Apixaban 2.5 mg twice daily for 30 days vs 98 enoxaparin 40 mg q.d. for a minimum of 6 days	Composite of symptomatic and asymptomatic VTE at days 30	Total VTE: 2.7 vs 3.1% (RR: 0.87; 95% CI: 0.62–1.23) Cancer subgroup: not available	Major: 0.5 vs 0.2% (RR: 2.58; 95% CI: 1.02–7.24) Cancer subgroup: not available	[30]

AR: Absolute risk; DVT: Deep vein thrombosis; PE: Pulmonary embolism; q.d.: Once daily; RCT: Randomized controlled trial; RR: Relative risk; VTE: Venous thromboembolism.

confined to bed. Intermittent pneumatic compression or graduated compression stockings are recommended when there is a contraindication to such therapy [35,36]. Practice recommendations for VTE prophylaxis in medically ill hospitalized patients with cancer from the different guidelines panels are summarized in Table 2.

Thromboprophylaxis in ambulatory patients undergoing chemotherapy

Epidemiology

Patients with cancer who are receiving active therapy are at high risk of developing VTE [42]. In a population-based case–control study, cancer alone was associated with a 4.1-fold increased risk of thrombosis, whereas the use of cytotoxic or immunosuppressive chemotherapy increased the risk to 6.5-fold [39]. The annual incidence of symptomatic VTE among cancer patients on chemotherapy is 10.9% [38]. A retrospective cohort study comparing the incidence of VTE in cancer inpatients versus outpatients reported that the majority of VTE events occur in the outpatient setting (78.3 vs 21.7%; p < 0.0001) [40]. Moreover, VTE is a significant independent predictor of early all-cause mortality during chemotherapy (HR: 4.50; 95% CI: 1.61–12.53; p = 0.004) [41]. The annual death rate of VTE in cancer outpatients receiving systemic chemotherapy was reported to be 47-times higher than that of the general population (95% CI: 6–89; p = 0.03) [43].

Risk stratification

A risk assessment score for chemotherapy-associated VTE in ambulatory cancer patients was derived and validated [42]. The model identified two clinical (site of cancer and BMI) and three laboratory (platelet

count, hemoglobin level and/or use of erythropoiesis-stimulating agents, and leukocyte count) predictive variables to assess the risk of symptomatic VTE in patients initiating chemotherapy, and stratifies patients into three categories. The rates of VTE in the development and validation groups were 0.8 and 0.3% in the low-risk cohort (score = 0), 1.8 and 2.0% in the intermediate-risk cohort (score = 1–2), and 7.1 and 6.7% in the high-risk cohort (score ≥3), respectively [42].

The risk assessment score was first validated using data from the Vienna Cancer and Thrombosis Study [44]. The Khorana model has been expanded by incorporating two additional biomarkers, soluble P-selectin and D-dimer. A prospective observational cohort study of 819 cancer patients was conducted to assess the expanded risk model [44]. The 6-month cumulative VTE probabilities in the original and expanded risk model were 17.7 and 35.0% in the high-risk group, 9.6 and 10.3% in the intermediate-risk group, and 1.5 and 1.0% in the low-risk group, respectively. Furthermore, compared with patients with the lowest-risk score (score = 0), the hazard ratio for VTE among those with the highest-risk score (score ≥5) was 25.9 (95% CI: 8.0–84.6) [44]. Although the addition of biomarkers seems to improve the predictability of the model, the expanded risk score needs to be further validated to be widely accepted. The lack of standardization of assays, the availability of tests and cost are barriers to incorporating them into existing VTE prediction models [45].

The Khorana predictive model has now been evaluated and validated in over 10,000 cancer patients in prospective and retrospective studies and is ready to be used to determine the need for thromboprophylaxis in outpatients undergoing active therapy [44,46–50]. In a multivariate analysis of 1412 patients enrolled in Phase I studies, the Khorana score was the only predictor of VTE [47]. The score was also found to be predictive of VTE in both a subgroup analysis of the SAVE-ONCO study [51] and a *post-hoc* subgroup analysis of the PROTECHT trial [52].

Pharmacological thromboprophylaxis

LMWHs

A summary of the trials of anticoagulants for thromboprophylaxis in ambulatory patients with cancer undergoing chemotherapy is provided in Table 3.

The SAVE-ONCO trial evaluated the use of ultra-LMWH semuloparin in patients with locally advanced or metastatic lung, pancreas, stomach, colorectal, bladder or ovary cancer [51]. A total of 3200 patients were randomized to either semuloparin or placebo. The incidence of symptomatic VTE in the semuloparin arm and placebo arm was 1.2 and 3.4%, respectively. When compared with placebo, patients on prophylactic semuloparin had a 64% relative risk reduction of VTE with a corresponding hazard ratio of 0.36 (95% CI: 0.21–20.60; p < 0.0001). The risk of bleeding between both groups was not statistically significant (HR: 1.05; 95% CI: 0.55–51.99) [51].

Another study assessing thromboprophylaxis in ambulatory patients with locally advanced or metastatic mixed solid tumors receiving chemotherapy was the PROTECHT trial [52]. The efficacy of the LMWH nadroparin was evaluated among 1150 patients with lung, gastrointestinal, pancreatic, breast, ovarian or head and neck cancer. The incidence of thromboembolic event was 2.0% in the LMWH group and 3.9% in the placebo group (single-sided 95% CI: 0.30; p < 0.02). The rates of major bleeding events between both arms were not statistically significant (two-sided p = 0.18) [52].

The Phase IIb FRAGEM trial [56] focused on pancreatic cancer only. Patients were randomized to gemcitabine with full therapeutic dose of dalteparin versus gemcitabine alone for up to 12 weeks. All-type VTE during a treatment period of <100 days from randomization was reduced from 23 to 3.4% (p = 0.002) with a corresponding risk ratio of 0.15 (95% CI: 0.035–30.61) and a risk reduction of 85%. The incidence of all-type VTE throughout the whole follow-up period was reduced from 28 to 12% (p = 0.039), with a risk ratio of 0.42 (95% CI: 0.19–10.94), representing a 58% risk reduction [56]. Similarly, a more recently presented randomized controlled trial has also reported a 75% relative risk in reduction in the incidence of VTE in ambulatory patients with locally advanced or metastatic pancreatic cancer receiving dalteparin while undergoing chemotherapy treatment [59]. Finally, the PROSPECT-CONKO 004 study [60] reported a significant 65% relative risk reduction of symptomatic VTE with the high-dose enoxaparin compared with no thromboprophylaxis in 312 patients with advanced pancreatic cancer (14.5 vs 5.0%: p < 0.01, and RR: 0.35; 95% CI: 0.16–10.75; p = 0.007) [54].

Two double-blind placebo-controlled trials were conducted in ambulatory patients with metastatic breast carcinoma (TOPIC 1) or stage III/IV non-small-cell lung cancer (TOPIC 2) [53]. Patients were randomized to receive either LMWH certoparin 3000 IU or placebo for 6 months for the prevention of chemotherapy-associated VTE. TOPIC-1 failed to show superiority of LMWH over placebo. Rates of VTE during 6 months of treatment were 4.0% in both groups, whereas rates of major bleeding events were 1.7% in the LMWH arm and 0% in the placebo arm. In TOPIC-2, the risk-reduction of VTE was not statistically significant. VTE rates

occurred in 4.5% of patients randomized to LMWH and 8.3% randomized to placebo ($p < 0.07$). The rates of major bleeding were 3.7% in the LMWH group and 2.2% in the placebo group. In a *post-hoc* analysis, LMWH significantly reduced the rate of VTE among stage IV lung cancer patients (3.5 vs 10.2%; $p < 0.0032$) with no increase in bleeding complications (Table 1) [53].

In a combined *post-hoc* analysis of stage III or IV lung cancer patients who received chemotherapy from PROTECHT [57] and TOPIC-2 [53], LMWH was associated with a relative risk reduction of symptomatic VTE of 0.58 (95% CI: 0.28–21.06) [61]. Furthermore, a relative risk reduction of both symptomatic and asymptomatic VTE of 0.54 (95% CI: 0.31–30.95) was found in favor of LMWH [61].

A Cochrane review comparing the efficacy and safety of oral or parenteral anticoagulants with placebo or no thromboprophylaxis in ambulatory cancer patients undergoing chemotherapy was undertaken [62]. Compared to inactive control, LMWH reduced the incidence of symptomatic VTE (RR: 0.62; 95% CI: 0.41–40.93) in the pooled analysis of 2400

Table 2. Practice recommendations for venous thromboembolism prophylaxis in medically ill hospitalized patients with cancer and ambulatory patients receiving chemotherapy by the different guidelines panels.

Question	ASCO [38]	ACCP [23]	NCCN [39]	AIOM/ESMO [40,41]	ISTH Guidelines [77]
Should medically ill hospitalized patients with cancer receive anticoagulant prophylactic therapy?	• Hospitalized cancer patients with medical illness or reduced mobility should receive prophylactic anticoagulation in the absence of contraindications • Hospitalized patients with cancer should be considered for prophylactic anticoagulation in the absence of contraindications • Hospitalized patients with cancer without additional risk factors may be considered for prophylactic anticoagulation in the absence contraindications • Anticoagulation therapy in patients admitted for minor procedures/short chemotherapy infusion/ undergoing stem-cell/bone marrow transplantation cannot be recommended • LMWH, UFH or fondaparinux	• Recommends prophylactic anticoagulation therapy for all patients at increased risk • Recommends against the use of pharmacologic or mechanical prophylaxis in low-risk patients • Suggests the use of mechanical prophylaxis in patients at increased risk of VTE with contraindications to pharmacologic prophylaxis • Suggests pharmacologic prophylaxis when contraindication resolves • Suggests against extending the duration of primary prophylaxis beyond the period of hospitalization • LMWH, UFH or fondaparinux	• Recommends prophylactic anticoagulation therapy for all hospitalized patients with cancer in the absence of contraindications • Recommends administration of prophylactic anticoagulation throughout the duration of hospitalization • Recommends against extending the duration of primary prophylaxis beyond the period of hospitalization • Recommends extending the duration of primary prophylaxis in the outpatient setting in multiple myeloma patients receiving thalidomide-/ lenalidomide-based combination therapies • LMWH, UFH or fondaparinux	• Recommends prophylactic anticoagulation in immobilized hospitalized cancer patients with an acute medical illness • LMWH/UFH, LMWH or fondaparinux	• Recommends prophylactic anticoagulation in hospitalized medical patients with malignancy and reduced mobility • LMWH, UFH or fondaparinux

ACCP: American College of Chest Physicians; AIOM: Italian Association of Medical Oncology; ASA: Acetylsalicylic acid; ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; INR: International normalized ratio; ISTH: International Society on Thrombosis and Haemostasis; LMWH: Low-molecular-weight heparin; NCCN: National Comprehensive Cancer Network; UFH: Unfractionated heparin; VTE: Venous thromboembolism.

Table 2. Practice recommendations for venous thromboembolism prophylaxis in medically ill hospitalized patients with cancer and ambulatory patients receiving chemotherapy by the different guidelines panels (cont.).

Question	ASCO [38]	ACCP [23]	NCCN [39]	AIOM/ESMO [40,41]	ISTH Guidelines [77]
Should ambulatory patients with cancer receive anticoagulant prophylactic therapy during chemotherapy?	• Prophylactic anticoagulation therapy is not recommended • Prophylaxis with LMWH may be considered on a case-by-case basis in high-risk outpatients with solid tumors receiving chemotherapy, accompanied by a discussion regarding the uncertainty of benefits and harms, dose and duration • Patients with multiple myeloma receiving thalidomide- or lenalidomide-based combination therapies should receive prophylactic anticoagulation • ASA or LMWH for low risk patients and LMWH for higher-risk patients	• Suggests against prophylaxis with LMWH or UFH in those with no additional risk factors (history of VTE, immobilization and cancer therapy) • Suggests prophylaxis with LMWH or UFH in outpatients with solid tumors and additional risk factors for VTE in the absence of contraindications	• Patients with malignancy at high risk for VTE (based on Khorana risk assessment score ≥3) could be considered for outpatient pharmacologic prophylaxis on a case-by-case basis, and a discussion regarding the uncertainty of benefits and harms is recommended	AIOM: • Prophylactic anticoagulation therapy is not recommended • Prophylactic anticoagulation during adjuvant chemotherapy and/or hormone therapy is not recommended • Prophylactic anticoagulation therapy is not recommended, but may be considered for those at high risk ESMO: • Suggests considering the use of LMWH, ASA or warfarin (INR: 1.5) in multiple myeloma patients receiving thalidomide- or lenalidomide-based combination therapies • Prophylactic anticoagulation during adjuvant chemotherapy and/or hormone therapy is not recommended	• Prophylactic anticoagulation therapy is not recommended • Prophylaxis with LMWH or UFH may be indicated in patients with locally advanced or metastatic pancreatic cancer in the absence of contraindications

ACCP: American College of Chest Physicians; AIOM: Italian Association of Medical Oncology; ASA: Acetylsalicylic acid; ASCO: American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; INR: International normalized ratio; ISTH: International Society on Thrombosis and Haemostasis; LMWH: Low-molecular-weight heparin; NCCN: National Comprehensive Cancer Network; UFH: Unfractionated heparin; VTE: Venous thromboembolism.

patients. However, there was no statistically significant difference in the rates of symptomatic PE, asymptomatic VTE and 1-year mortality between the two groups. The estimated number to treat to prevent one symptomatic VTE was 60. There was no significant effect on major bleeding (RR: 1.57; 95% CI: 0.69–3.60) [62].

New oral anticoagulants

A Phase II pilot study has evaluated the oral factor Xa inhibitor, apixaban, in outpatients with advanced or metastatic tumors lung, breast, gastrointestinal, bladder, ovarian or prostate cancer, tumors of unknown origin, myeloma or selected lymphomas receiving chemotherapy. Subjects were randomized to one of three doses of apixaban or placebo for 12 weeks [63]. The rate of major bleeding among the 93 patients who received apixaban was 2.2% (95% CI: 0.26–25.5). Although the authors concluded that the use of apixaban could be safe and feasible in patients with advanced cancer on chemotherapy, it has not shown reduction in the

Table 3. Trials of anticoagulants for thromboprophylaxis in ambulatory patients with cancer undergoing chemotherapy.

Study (year); study name	Tumor types	Design	Number of patients/study intervention	Primary outcome measure	Primary outcome/ conclusions	Bleeding events/ conclusions	Survival outcome/ conclusions	Ref.
Haas *et al.* (2012); TOPIC-I and TOPIC-II	• Metastatic breast cancer • Stages III or IV of non-small-cell lung carcinoma	Double-blind RCT	• 177 observation vs 174 certoparin 3000 U q.d. • 268 observation vs 264 certoparin 3000 U q.d.	Symptomatic and asymptomatic VTE	• 4.0 vs 4.0% No difference (p = 1.00) • 8.3 vs 4.5% No difference (p = 0.078)	• 1.7 vs 5.2% No difference (p = 0.084) • 7.3 vs 13.6% Significant difference (p = 0.024)	• 6-month mortality: 6.7 vs 8.6% No difference • 6-month mortality: 21.6 vs 20.2% No difference	[53]
Riess *et al.* (2009); PROSPECT-CONKO 004	• Advanced pancreatic cancer	Open RCT	• 152 observation vs 160 enoxaparin 1 mg/kg daily for 3 months, then 40 mg	Symptomatic VTE	• 15.3 vs 5.0% Significant difference (favors enoxaparin) (p < 0.01)	• 9.9 vs 6.3% No difference (p-value n.s.)	• Median survival: 8.15 vs 7.92 months No difference (p = 0.054)	[54,55]
Maraveyas *et al.* (2012); FRAGEM	• Advanced pancreatic adenocarcinoma	Open RCT	• 62 observation vs 59 dalteparin 200 U/kg daily for 1 month, then 150 U/kg daily for 3 months	All type VTE	• 28.0 vs 12.0% Significant difference (favors dalreparin) (p = 0.039)	• Severe 3.0 vs 3.0% No difference	• 100-day mortality: 11.0 vs 7.0% No difference (p = 0.388)	[56]
Agnelli *et al.* (2009); PROTECHT	• Locally advanced or metastatic lung, GI, pancreatic, breast, ovary, head and neck tumors	Double-blind RCT	• 381 placebo vs 769 nadroparin, 3800 U daily up to 4 months	Composite of symptomatic venous or arterial thrombosis.	• 3.9 vs 2.0% Significant difference (favors nadroparin) (p = 0.02)	• Major: 0 vs 0.7% No difference (p = 0.18)	• Not available	[57]
Perry *et al.* (2010); PRODIGE	• Grade III or IV malignant glioma	Double-blind RCT	• 87 placebo vs 99 dalteparin 5000 U OD for 6–12 months	Symptomatic VTE	• 14.9 vs 9.1% No difference (p = 0.29)	• Major: 1.1 vs 5.1% No difference HR_{adj} = 4.2, 95% CI: 0.48–36	• 6-month mortality: 12.6 vs 18.2% No difference HR_{adj} = 1.4, 95% CI: 0.60–3.2	[58]
Agnelli *et al.* (2012); SAVE-ONCO	• Locally advanced or metastatic lung, pancreatic, stomach, colon, bladder, ovary tumors	Double-blind RCT	• 1604 placebo vs 1608 semuloparin 20 mg daily for at least 3 months	Composite of symptomatic DVT, nonfatal PE or VTE-related death	• 3.4 vs 1.2% (p < 0.0001) Significant difference (favors semuloparin) Fatal VTE: 0.6 vs 0.4%	• Major: 1.1 vs 1.2% No difference	• Death rate: 44.5 vs 43.3% No difference (p = 0.40)	[51]

DVT: Deep vein thrombosis; GI: Gastrointestinal; HR_{adj}: Adjusted hazard ratio; n.s.: Not significant; OD: Once daily; PE: Pulmonary embolism; q.d.: Once daily; RCT: Randomized controlled trial; VTE: Venous thromboembolism.

rates of fatal VTE [63]. At this time, apixaban should not be recommended for cancer outpatients undergoing active treatment. Furthermore, Phase III clinical studies in cancer patients are therefore needed to assess the role of novel oral anticoagulants before recommending these agents for primary thromboprophylaxis in this population.

Areas of controversies

Although both SAVE-ONCO [51] and PROTECHT [57] have demonstrated that outpatient thromboprophylaxis is effective and safe among patients with a variety of solid tumors, current guidelines do not recommend prophylaxis among cancer patients, due in part to the low event rates observed in these studies. In SAVE-ONCO trial, there is no evidence that semuloparin reduced the incidence of VTE-related deaths. Furthermore, semuloparin is not available and its clinical development has been withdrawn worldwide in 2012 [60].

The PROSPECT-CONKO 004 [54,55] and FRAGEM [56] studies showed that very high VTE rates occur among pancreatic patients and that pharmacological thromboprophylaxis can be effectively and safely used to prevent these events in this specific cancer subgroup. However, the FRAGEM trial [56] failed to show statistically significant reduction of fatal VTE events ($p = 0.057$).

In addition to the negative findings from TOPIC 1 and TOPIC 2 studies [53], the PRODIGE study [58], which evaluated postsurgical prophylactic dose of dalteparin versus placebo in patients with grade III/IV malignant glioma, did not show any significant difference in symptomatic VTE for patients receiving thromboprophylaxis.

The conflicting evidence makes it difficult to recommend prophylaxis with LMWH for ambulatory patients with solid tumors receiving chemotherapy and controversy still remains as to which subgroup of patients should be selected for thromboprophylaxis. Thus, it is essential to use tools to better stratify patients at high risk of VTE that could benefit from prophylaxis with LMWH. Ongoing trials are specifically assessing thromboprophylaxis in high-risk patients identified using the Khorana model. The PHACS study, evaluating the efficacy and safety of dalteparin administered for 12 weeks compared with placebo, is currently enrolling patients considered at high risk of VTE (based on the Khorana score) [64]. This study will hopefully provide a better understanding of the potential role of primary prophylaxis in a subpopulation of ambulatory patients with cancer which may in turn influence future practice guideline recommendations.

Effect of primary thromboprophylaxis on survival

Tumor cells express tissue factor, the physiologic initiator of hemostasis, which is released into the circulation. Levels of the microparticles can be detected in cancer patients [65]. Anticoagulants may have an antitumor effect and thus act as anticancer agents. Inhibiting the hemostatic system with heparins (UFH or LMWH) may change the biology of cancers resulting in improved survival [66]. Many studies have evaluated the effect of anticoagulants of cancer patients' survival.

Warfarin

Three trials evaluating the effect of warfarin anticoagulation on survival among cancer patients without VTE observed no improvement in overall survival when warfarin was used [67–69]. A Cochrane review evaluating survival with warfarin in patients with cancer who have no therapeutic or prophylactic indication for anticoagulation was published. Warfarin did not show a statistical significant reduction in mortality at 6 months, 1 year and 2 years compared with placebo or no intervention. Furthermore, warfarin was associated with increased risks of both major and minor bleeding events [70].

UFH

The Cochrane review by Akl *et al.* reported that heparin was not associated with a decreased mortality at 1 year (RR: 0.93; 95% CI: 0.85–81.02), and its effect was statistically significant at 2 years (RR: 0.92; 95% CI: 0.88–80.97) when compared with placebo [70].

LMWH

Many randomized trials have evaluated the effect of LMWH on survival in patients with cancer. While many studies reported improvements in survival in certain cancer populations [71–74], others did not [75,76]. A meta-analysis of the impact of anticoagulants on survival and safety in cancer patients without venous thromboembolism identified 11 RCTs [76]. LMWH were found to significantly improve overall survival while increasing the risk for bleeding complications [76].

Although it appears that the use of anticoagulants, especially LMWHs, in cancer patients without VTE improves survival, it is important to note, however, that the available data has major limitations that include the use of analysis not specified *a priori*, heterogeneous patient populations included, the use of different doses given for different durations and the small sample size. More studies are therefore needed to study the association between anticoagulants and survival by different tumor sites and stage.

Summary of recommendations from the different guideline panels

Currently, outpatient prophylaxis is only recommended by ASCO [34], ACCP [37], NCCN [33], AIOM [36] and ESMO [35] for high-risk myeloma patients receiving thrombogenic thalidomide- or lenalidomide-based combination chemotherapy regimens. Regarding other high-risk ambulatory patients receiving chemotherapy in the absence of bleeding or other contraindications, ACCP [37], ASCO [34] and NCCN [33] guidelines suggest considering thromboprophylaxis on a case-by case basis, accompanied by a discussion of the potential benefits and risks. The International Society on Thrombosis and Haemostasis guidelines suggest that primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic or lung cancer treated with chemotherapy and having a low bleeding risk [77]. Practice recommendations for VTE prophylaxis in ambulatory patients receiving chemotherapy by the different guidelines panels are summarized in Table 2.

Conclusion & future perspective

The primary prevention of VTE in patients with cancer is still a major area of research with many unanswered questions. Limited evidence is available on pharmacological thromboprophylaxis in cancer patients admitted to the hospital for medical illness. However, the majority of hospitalized cancer patients are already at moderate to high risk of VTE and pharmacologic thromboprophylaxis should therefore at least be considered for these patients. The role of primary thromboprophylaxis in ambulatory cancer patients is less certain due in fact to inconsistent evidence and varying cancer and treatment-related factors. Pharmacological prophylaxis should only be considered for high-risk patients.

The significant gaps in the evidence regarding pharmacological thromboprophylaxis in the oncology setting limit the scope of guideline recommendations. To better understand the clinical benefits of primary prophylaxis in cancer patients, future trials should target those who have the greatest risk of VTE and therefore include homogenous populations with the same tumor site, stage of disease and chemotherapy regimens. In addition, further studies assessing the use of biomarkers (e.g., soluble P-selectin and D-dimer) are desperately needed and could potentially help identifying appropriate candidates for primary thromboprophylaxis in patients with cancer.

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