Clinical practice guidelines for prophylaxis of venous thromboembolism in cancer patients

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Summary

Symptomatic venous thromboembolism (VTE) occurs 4-7 times more frequently in cancer patients as compared to non-cancer patients. A significant number of risk factors, which can be subcategorised as patient-, cancer- or treatment-related, have been shown to influence the risk of VTE during malignancy and further incorporated in risk-assessment models. Safe and efficient thromboprophylaxis regimens allow substantial decreased in VTE rates, since VTE is most often a largely preventable disease, but thromboprophylaxis remains underused in cancer compared to non-cancer patients. If thromboprophylaxis is warranted in cancer patients undergoing surgery or hospitalised for acute medical illness or with a lower mobility in the absence of contraindications to anticoagulants, its benefit remains controversial in outpatients and may be limited to locally advanced or metastatic pancreatic or lung cancer treated with chemotherapy. The International Initiative on Thrombosis and Cancer-CME free mobile app (ios and android), based on the International Clinical Practice Guidelines (CPG), facilitates their implementation and dissemination of knowledge worldwide so as to improve VTE treatment and prophylaxis in cancer patients.

Keywords

Venous thromboembolism, prophylaxis, anticoagulants, current clinical practice guidelines, risk assessment

Introduction

Venous thromboembolism (VTE), defined by deep-vein thrombosis (DVT), pulmonary embolism (PE) or central venous (CV) catheter-related thrombosis (CRT), is a frequent and major complication in cancer patients, at high cost for the patients and the health care system (1). Today, VTE has become the second-leading cause of death in the cancer patient population, due to recurrent VTE or anticoagulation-related bleedings (2). When analysing VTE-associated resource utilisation and real costs in US ambulatory patients initiating chemotherapy, the mean incremental of all-cause health-care overall costs for VTE were USD 30,538 per cancer patient (3). Large cancer registries and hospital discharge data sets reported cumulative incidence of VTE ranging from 1% to 8% depending on the cancer type and extension, the duration of patient follow-up, and the diagnostic methods to assess VTE events, with higher VTE rates among patients admitted to oncology departments or receiving chemotherapy (1). Most of these studies were focused on symptomatic VTE whereas autopsy series reported undiagnosed DVT or PE in up to 50% of cancer patients (4). The number of asymptomatic PE discovered during routine evaluation of cancer patients is around 2 to 3% according to studies, and increases with repeated multislice CT scan performed for cancer staging. Therefore, cancer-related-VTE rates have increased over recent years both in the surgical and the medical oncology setting (1). This increase can also be related to: i) the wider use of more effective systemic anticancer drugs, which are also more prothrombotic; ii) the increased number and the long-term use of CV catheters for chemotherapy and supportive care; iii) the aging cancer population with additional non cancer classical VTE risk factors (5).

Considering all the above, there is an important need to improve VTE prophylaxis in cancer patients, since VTE is a preventable disease when antithrombotic agents are appropriately used in well selected patients. Over the past ten years, many national clinical practice guidelines (CPG) have been issued for management of VTE in patients with cancer in Europe (6), Italy (7), France (8, 9, United Kingdom and Ireland (10, 11), and North America (12–25). These national CPG were based on heterogeneous clinical knowledge but few of them covered all questions, in particular thromboprophylaxis. For these reasons, an international multidisciplinary working group developed harmonised guidelines in 2013, using an up-to-date evidence based CPG development approach and the GRADE system (26, 27). The aim of this paper is to

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review the clinical evidences for VTE prophylaxis in cancer patients and to summarise the international CPG in this setting (▶Table 1).

Risk factors for VTE in cancer patients and risk assessment

VTE is a complex and multifactorial disease, which involves interactions between acquired and inherited risk factors for thrombosis (28). Many factors influencing the risk of VTE in cancer patients have been identified and extensively described (29, 30). These factors are summarised in ▶Table 2. Of note, the risk for VTE in cancer patients may vary throughout the disease course and should be periodically re-assessed in each patient.

In order to identify those cancer patients at highest risk for VTE who might appropriately benefit from thromboprophylaxis, several risk assessment models (RAM) have been developed. The most frequently used is the Khorana risk score, based on a collection of readily available clinical (type of cancer, body mass index [BMI] ≥35) and biological parameters (platelet count >350,000/µl, leucocyte count >11,000/µl, haemoglobin <10 g/dl), each parameter being assigned a 1 or 2 value (31). This RAM was first developed in a prospective cohort of 2,701 ambulatory patients undergoing chemotherapy for cancer and it was then validated in an independent prospective cohort of 1,365 patients (31). Using Khorana predictive model, cancer patients were considered at VTE low-risk if they had a score of 0, at VTE intermediate-risk if they had a score of 1–2 and at VTE high-risk if they had a score ≥3 (31). This score was prospectively and independently validated in 819 patients with different malignancies included in the prospective Vienna Cancer and Thrombosis Study (CATS) (32). The predictability of developing VTE was considerably improved by adding two biomarkers, sP-selectin and D-dimers: cancer patients with a score ≥5 when using the expanded CATS model had a significantly higher cumulative probability of VTE within six months (35%) (32) as compared to those with the highest score when using the Korana model (6.7%) (31). Of note, RAM have yet only been validated for ambulatory cancer patients.

Table 1: International evidence-based clinical practice guidelines for prophylaxis of venous thromboembolism in cancer patients (International Consensus Group 2013 [26]).

<table>
<thead>
<tr>
<th>Surgical cancer patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of LMWH o. d. or low dose of UFH t. i. d. is recommended; pharmacological prophylaxis should be started 12–2 h preoperatively and continued for at least 7–10 days; there are no data allowing conclusion that one type of LMWH is superior to another [1A]</td>
</tr>
<tr>
<td>There is no evidence to support fondaparinux as an alternative to LMWH [2C]</td>
</tr>
<tr>
<td>Use of the highest prophylactic dose of LMWH is recommended [1A]</td>
</tr>
<tr>
<td>Extended prophylaxis (4 weeks) after major laparotomy may be indicated in cancer patients with a high risk of VTE and low risk of bleeding [2B]</td>
</tr>
<tr>
<td>The use of LMWH for VTE prevention in cancer patients undergoing laparoscopic surgery may be recommended as for laparotomy [Guidance]</td>
</tr>
<tr>
<td>Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated [2C]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospitalised medical patients with cancer and reduced mobility</th>
</tr>
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<tbody>
<tr>
<td>Prophylaxis with LMWH, UFH or fondaparinux [1B]</td>
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</table>

<table>
<thead>
<tr>
<th>Patients receiving chemotherapy</th>
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<tbody>
<tr>
<td>Prophylaxis is not recommended routinely [1B]</td>
</tr>
<tr>
<td>Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic [1B] or lung [2B] cancer treated with chemotherapy and having a low risk of bleeding</td>
</tr>
<tr>
<td>In patients treated with thalidomide or lenalidomide combined with steroids and/or chemotherapy, VTE prophylaxis is recommended; in this setting, VKA at low or therapeutic doses, LMWH at prophylactic doses and low-dose aspirin have shown similar effects; however, the efficacy of these regimens remains unclear [2C]</td>
</tr>
<tr>
<td>For children and adults with acute lymphocytic leukaemia treated with L-asparaginase, depending on local policy and patient characteristics, prophylaxis may be considered in some patients [Guidance]</td>
</tr>
</tbody>
</table>

LMWH, low-molecular-weight heparin; UFH, unfractionated; VKA, Vitamin K antagonists; VCF, Vena cava filters; CVC, central venous catheter; CRT, catheter related thrombosis. Recommendations were established based on these assessments and the corresponding levels of evidence, as well as the balance between desirable and undesirable effects, values and preferences, and costs. They were classified as Strong (Grade 1 Guideline) or Weak (Grade 2 Guideline) based on the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the international experts within the working group and defined as Best Clinical Practice [Guidance].
Table 2: Risk factors for venous thromboembolism in cancer patients.

<table>
<thead>
<tr>
<th>Patient-related factors</th>
<th>Cancer-related factors</th>
<th>Treatment-related factors</th>
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<tbody>
<tr>
<td>• Older age</td>
<td>• Primary tumour site</td>
<td>• Recent major surgery</td>
</tr>
<tr>
<td>• Gender (Female)</td>
<td>(pancreatic, ovarian,</td>
<td>• Hospitalisation</td>
</tr>
<tr>
<td>• Ethnic origin (higher</td>
<td>kidney, lung, gastric,</td>
<td>• Central venous catheters</td>
</tr>
<tr>
<td>in African Americans;</td>
<td>brain, and haemato</td>
<td>• Chemotherapy</td>
</tr>
<tr>
<td>lower in Asian-Pacific</td>
<td>logic)</td>
<td>• Antiangiogenic agents</td>
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<tr>
<td>Islanders)</td>
<td></td>
<td>(bevacizumab, sunitinib,</td>
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<tr>
<td></td>
<td></td>
<td>sorafenib)</td>
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<td></td>
<td></td>
<td>• Immonomodulatory drugs</td>
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<td></td>
<td></td>
<td>(thalidomide, lenalidomide)</td>
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<tr>
<td></td>
<td></td>
<td>• Hormonal therapy</td>
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<tr>
<td></td>
<td></td>
<td>(tamoxifen)</td>
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<td></td>
<td></td>
<td>• Erythropoietin</td>
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<td></td>
<td></td>
<td>• Transfusions (platelets,</td>
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<td></td>
<td></td>
<td>red blood cells)</td>
</tr>
</tbody>
</table>

**Prophylaxis of VTE in surgical cancer patients**

The benefit of prophylactic anticoagulation in surgical oncology patients is unquestionable. Cancer patients undergoing surgical procedures carry a two- to three-fold higher risk to develop a postoperative VTE (33) and a two- to three-fold higher risk of fatal PE (34) compared to their relative non-cancer counterparts. A recent retrospective study conducted in 2,508,916 patients undergoing major cancer surgery demonstrated that VTE remains a major complication since the in-hospital VTE rate was 1.3% (35). The risk for VTE varies depending on the type and the duration of surgical intervention. Whereas breast cancer surgery is considered to be at lower risk of VTE, other interventions lasting more than 30 minutes (min) in cancer patients such as laparotomy, laparoscopy, thoracotomy and brain surgery are considered to be at the highest risk of VTE. Recently, the association between surgical duration and VTE was shown to increase in a stepwise fashion (36).

Early meta-analysis analysed the benefit of prophylactic anticoagulation with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) to either placebo or no prophylaxis in the surgical setting: one focused on surgical cancer patients in 2007 (37) and the other on general surgical patients, which included a subgroup of cancer patients, in 2001 (38). Both LMWH and UFH were superior to either placebo or no prophylaxis in preventing postoperative VTE, with a VTE rate reduction ranging from 42% to 75% in the overall population (37, 38).

Numerous randomised clinical trials (RCTs) compared the safety and efficacy of LMWH to UFH for VTE prophylaxis in cancer patients. In the Enoxaparin and Cancer (ENOXACAN) trial, enoxaparin 40 mg once daily given 2 hours (h) preoperatively and for 10 ± 2 days post surgery was as effective as UFH 5000 IU three times daily for reducing the incidence of postoperative VTE in cancer patients after curative abdominal or pelvic surgery (VTE rates 14.7% vs 18.2%, respectively; 95% CI for the difference, −9.2−2.3) with no significant difference in bleedings (18.7% vs 17.1%, respectively) (39). A recent meta-analysis computed 16 RCTs comparing the safety and efficacy of LMWH to UFH (40). UFH three times daily was found to be as effective as LMWH once daily, but LMWH once daily appeared to be superior to UFH twice daily (40). One double-blind RCT with a large effect size (67% of cancer patients) demonstrated that a high dosage of LMWH (Dalteparin 5000 IU once daily) was superior to a low dosage of LMWH (Dalteparin 2500 IU once daily) in preventing postoperative VTE after major elective abdominal surgery (VTE rates 8.5% vs 3.6%, respectively, p<0.001) with a comparable safety (41). There are no sufficient data yet allowing to conclude or not on the superiority of one type of LMWH over another one, nor to support fondaparinux as an alternative to LMWH since direct comparison of drugs found no difference between these drugs. The duration of VTE prophylaxis in cancer patients after surgery is generally 7–10 days, but some results suggest that extended prophylaxis should be considered when appropriate. For example, in the ENOXACAN II trial (42), extended use of enoxaparin at 40 mg once daily prophylaxis for four weeks as compared with the standard seven days prophylactic regimen allowed a significant decrease in VTE in patients undergoing major abdominal surgery for cancer (VTE rates 4.8% vs 12.0%, respectively; p=0.02) (42). Two recent studies analysed the benefit of extended-duration prophylaxis after major
abdominal or pelvic cancer surgery (43, 44) and showed a reduced rate of VTE in the extended-duration arm compared to the control arm with similar rates of bleedings (43, 44). Of note, these results were observed for extended prophylaxis (4 weeks) after laparoscopy surgery for colorectal cancer (44).

Based on these data, the 2013 international CPG (26) released several recommendations concerning thromboprophylaxis in surgical cancer patients:

- The use of LMWH once daily or of a low dose of UFH three times daily (but LMWH once a day appeared to be more convenient) to be started 12–24 h preoperatively and continued for at least 7–10 days is recommended. No data allow conclusions regarding the superiority of one type of LMWH over another (Grade 1A) (26).

- The use of the highest prophylactic dose of LMWH is recommended (Grade 1A) (26). There is yet no evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in cancer patients (Grade 2C) (26).

- After major laparotomy, extended prophylaxis (4 weeks) may be indicated in cancer patients with a high risk of VTE and a low risk of bleeding risk (Grade 2B) (26).

- The use of LMWH for the prevention of VTE in cancer patients undergoing laparoscopic surgery may be recommended in the same way as for laparotomy considering that the risk for VTE could be higher in cancer patients than in non-cancer patients, even in the case of laparoscopic procedures [Best clinical practice, based on a balance between desirable and undesirable effects indicating an increased bleeding] (26).

- Mechanical compression methods are not recommended as monotherapy in surgical cancer patients except when pharmacological methods are contraindicated (Grade 2C) (26).

**Prophylaxis of VTE in medical cancer patients**

**Hospitalised cancer patients**

Until now, no specific study has been conducted in hospitalised medical cancer patients. Data on the efficacy and safety of pharmacologic thromboprophylaxis in this setting are almost exclusively based on extrapolation or post-hoc analysis from large RCTs conducted in unspecified hospitalised patients admitted for acute illness or with reduced mobility. Three main RCTs (MEDENOX, PREVENT and ARTEMIS) compared VTE prophylaxis with LMWH (enoxaparin 40 mg once-daily, dalteparin 5000 IU once-daily) or fondaparinux (fondaparinux 2.5 mg once-daily) with placebo (45–47). Only 5–15% of patients with malignancy were included in these trials. Pharmacological thromboprophylaxis was found to significantly decrease the risk of VTE in the overall population (relative risk [RR], 0.37; 95% confidence interval [CI] 0.22–0.63; RR, 0.55; 95% CI, 0.38–0.80 and RR, 0.47; 95% CI, 0.08–0.69, respectively, in MEDENOX, PREVENT and ARTEMIS studies). No difference was reported between non-cancer and cancer patients. However, a recent meta-analysis focused on the subgroup of cancer patients of these three studies found no statistical reduction in the overall incidence of VTE (RR, 0.91; 95% CI 0.21–4.0) (48). This recent finding has to be interpreted with caution due to the large between-study heterogeneity (I²=68%) and the small number of cancer patients included (n=307 cancer patients/5,134 total patients) (48).

Concerning the choice of anticoagulation, LMWH and UFH showed similar efficacy in preventing VTE in hospitalised medical patients, but the use of LMWH was overall associated with a lower rate of bleeding. A post-hoc analysis of the recent CERTIFY study (certoparin 3000 IU once-daily vs UFH 5000 IU once-daily) focusing on the subgroup of cancer patients (n=274) showed a similar efficacy but a non significant increased in minor bleeding with UFH (49).

Although specific data concerning hospitalised medical cancer patients as compared to non-cancer patients are still lacking, adequate use of pharmacological thromboprophylaxis is of major importance in these patients given their high risk of VTE. Thromboprophylaxis should be used cautiously in cancer patients with a higher bleeding risk according to the cancer specific features, the chemotherapy induced-thrombocytopenia, the effect of systemic anti-cancer therapies and other comorbidities.

A specific case is represented by children with acute lymphocytic leukaemia (ALL). A meta-analysis of 17 prospective studies comprising 1,752 paediatric patients found a 5.2% (95% CI: 4.2–6.4) rate of venous thrombosis in this population (50). A multicentre cohort study using a risk assessment model to identify high-risk patients for thromboembolism further demonstrated the benefit of LMWH prophylaxis in this high VTE risk group of patients (51).

Based on these data, the international CPG recommend:

- For hospitalised medical patients with cancer and reduced mobility, prophylaxis with LMWH, UFH or fondaparinux [Grade 1B] (26).

- For children with ALL treated with L-asparaginase, depending on local policy and individual patient characteristics (platelet count, kidney function, fibrinogen and antithrombin levels), prophylaxis may be considered in some patients; the same therapeutic option can be considered for adults [Best clinical practice] (26).

**Ambulatory cancer patients**

In recent years, VTE prophylaxis in ambulatory cancer patients has become an emerging area of interest. Indeed substantial proportion of VTE events (up to 74%) occur in the outpatient setting (52). Patients receiving chemotherapy, hormonal therapy, or several targeted agents were shown to be at seven-fold increased risk for VTE as compared to the general non cancer population (53). Supportive care measures commonly used in ambulatory cancer patients, such as the administration of erythroid-stimulating agents and of blood transfusions, were also shown to increase the risk of VTE (54, 55). Nonetheless, the benefit of thromboprophylaxis in ambulatory cancer patients has yet not been clearly established and its use in this setting is still under debate. The paucity of data still limits the ability to provide a concise recommendation regarding when and how to prevent VTE. The evidences...
supporting prophylaxis in selected cancer patients is derived from RCTs and meta-analysis of RCTs comparing anticoagulant prophylaxis to either placebo or no prophylaxis in ambulatory patients receiving systemic anti-cancer therapies. The main studies assessing the efficacy and safety of thromboprophylaxis are summarised in Table 3 (56-62). Two recent meta-analysis demonstrated a benefit from thromboprophylaxis (63, 64). The first one (n=6,809 participants) showed that heparin therapy, using either UFH or LMWH, was associated with a significant reduction in VTE (RR 0.56; 95% CI 0.42 to 0.74) without increase in major bleeding (RR 1.14; 95% CI 0.70 to 1.85) (63). The second one found that the use of LMWH (n=1,829) significantly reduced the incidence of symptomatic VTE (RR 0.53, 95% CI 0.38 to 0.75) as compared to control without prophylaxis (n=1,427) with similar rates of major bleeding events (RR 1.30, 95% CI 0.75 to 2.23. (64) Nonetheless, a careful review of the literature suggest that this benefit may be limited to certain types of cancer. Indeed, two large RCTs including patients with different cancer types, namely the Prophylaxis of Venous Thromboembolism during Chemotherapy Trial (PROTECHT) (58) and the Evaluation of Semuloparin in the Prevention of Venous Thromboembolism in Cancer Patients Undergoing Chemotherapy trial (SAVE-ONCO) (57) found a significant reduction in the relative risk of VTE, but with small difference in the respective absolute risk: 2.0% for the nadroparin arm vs 3.9% for the placebo arm in the PROTECHT study (58), and 1.2% for the semuloparin arm vs 3.4% for the placebo arm in the SAVE-ONCO study (57). More robust benefits from anticoagulant VTE prophylaxis are reported in the pancreatic and lung cancer ambulatory patients. The largest absolute rates of VTE as well as the largest difference in absolute risk were observed in advanced pancreatic cancer (APC) patients. In APC patients, the use of LMWH reduced VTE rate from 28% to 12% (RR, 0.42; 95% CI, 0.19–0.94; p=0.039) in the FRAGEM study (59) and from 15.1% to 6.4% (hazard ratio [HR], 0.40; 95% CI, 0.19–0.83; p=0.01) corresponding to a 88% relative risk reduction in the PROSPECT-CONKO 004 study (58). More recently, in the FRAGMATIC trial, dalteparin added to standard therapy reduced the risk of VTE from 9.7% to 5.5% (HR, 0.57; 95% CI, 0.42–0.79; p=0.001) in lung cancer patients (n=2,202), but increased a composite criteria of major plus clinically relevant non-major bleedings (62).

The benefits from anticoagulation prophylaxis were also evidenced in multiple myeloma patients receiving thalidomide- or lenalidomide-based combination regimens, particularly when combined with steroids or doxorubicin, or with the use of multi agent chemotherapy regimens. A prospective randomised trial compared prophylactic doses of LMWH or aspirin (ASA 100 mg/day) or warfarin and showed no significant difference in the rate of VTE. Another randomised sub-study of a phase III trial including

Table 3: Main studies evaluating LMWH or ULMWH vs placebo for thromboprophylaxis in ambulatory cancer patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of cancer, Stage</th>
<th>Interventional arm</th>
<th>n</th>
<th>Treatment duration</th>
<th>Incidence of VTE</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAMOUS</td>
<td>Mixed, III-IV</td>
<td>Dalteparin 5000 IU o. d.</td>
<td>374</td>
<td>1 year</td>
<td>Placebo arm : 3.3%</td>
<td>(56)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>LMWH arm : 2.4%</td>
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<tr>
<td>SAVE-ONCO</td>
<td>Mixed, III-IV</td>
<td>Semuolparin 20 mg o. d.</td>
<td>3212</td>
<td>3.5 months</td>
<td>Placebo arm : 3.4%</td>
<td>(57)</td>
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<td></td>
<td></td>
<td>LMWH arm : 1.2%</td>
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<td></td>
<td>RR,0.36; 95% CI, 0.21–0.60</td>
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<tr>
<td>PROTECHT</td>
<td>Mixed, III-IV</td>
<td>Nadroparin 3800 IU o. d.</td>
<td>1150</td>
<td>4 months</td>
<td>Placebo arm : 3.9%</td>
<td>(58)</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>LMWH arm : 2%</td>
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<td></td>
<td></td>
<td></td>
<td>p=0.02</td>
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<tr>
<td>FRAGEM-UK</td>
<td>APC</td>
<td>Dalteparin 200IU/kg o. d. for 4 weeks followed by 150 IU/kg o. d. for 8 weeks</td>
<td>123</td>
<td>3 months</td>
<td>Placebo arm : 28%</td>
<td>(59)</td>
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<tr>
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<td>LMWH arm : 12%</td>
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<td></td>
<td>RR,0.419; 95% CI, 0.187–0.935</td>
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<tr>
<td>CONKO-04</td>
<td>APC</td>
<td>Enoxaparin 1 mg/Kg o. d.</td>
<td>312</td>
<td>3 months</td>
<td>Placebo arm :15.1%</td>
<td>(60)</td>
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<td></td>
<td></td>
<td>LMWH arm : 6.4%</td>
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<td></td>
<td>HR,0.40; 95% CI, 0.19–0.83; p=0.01</td>
<td></td>
</tr>
<tr>
<td>TOPIC-1</td>
<td>Breast</td>
<td>Certoparin 3000 IU o. d.</td>
<td>351</td>
<td>6 months</td>
<td>Placebo arm : 4%</td>
<td>(61)</td>
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<td></td>
<td>LMWH arm : 4%</td>
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<td></td>
<td>OR,1.02; 95% CI, 0.30–3.48</td>
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<tr>
<td>TOPIC-2</td>
<td>NSCLC, III-IV</td>
<td>Certoparin 3000 IU o. d.</td>
<td>532</td>
<td>6 months</td>
<td>Placebo arm :8.3%</td>
<td>(61)</td>
</tr>
<tr>
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<td>LMWH arm : 4.5%</td>
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<td></td>
<td></td>
<td>OR,0.52; 95% CI, 0.23–1.12;</td>
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</tr>
<tr>
<td>FRAGMATIC</td>
<td>Lung cancer, any stage and histology</td>
<td>Dalteparin 5000 IU o. d.</td>
<td>2202</td>
<td>24 weeks</td>
<td>Placebo arm :9.7%</td>
<td>(62)</td>
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<td></td>
<td></td>
<td>LMWH arm : 5.5%</td>
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<td></td>
<td>HR,0.57; 95% CI, 0.42–0.79; p=0.001</td>
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LMWH, low-molecular-weight heparin; ULMWH, ultra low molecular weight heparin; APC, Advanced pancreatic cancer; o. d., once daily; NSCLC, non small cells lung cancer.
342 patients with newly diagnosed multiple myeloma treated with lenalidomide compared thromboprophylaxis with low-dose ASA or LMWH with regard to preventing VTE (incidence of VTE 2.27% in the ASA group and 1.20% in the LMWH group) (65, 66). The efficacy of such regimen remains however unclear. Based on these data, the international CPG (26) specify that:

- Prophylaxis is not recommended routinely [Grade 1B] (26).
- Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic [Grade 1B] or lung [Grade 2B] cancer treated with chemotherapy and having a low risk of bleeding (26).
- In patients treated with thalidomide or lenalidomide combined with steroids and/or chemotherapy, VTE prophylaxis is recommended; in this setting, VKA at low or therapeutic doses, LMWH at prophylactic doses and low-dose aspirin have shown similar effects; however, the efficacy of these regimens remains unclear [Grade 2C] (26).

Interestingly, increasing data underline the need to well assess and stratify ambulatory cancer patients at risk for VTE who should benefit from primary thromboprophylaxis and all recent updated CPG encourage the use of RAMS (16, 24).

**Thromboprophylaxis underuse**

VTE thromboprophylaxis is still largely underused, although there is strong epidemiological evidence for a high risk of VTE in patients with malignancies. Several studies addressed the use of pharmacological thromboprophylaxis in hospitalised cancer patients despite existing GCP guidelines and incentives from healthcare agencies. The overall adherence rates to CPG in daily practice has remained low, ranging from 18-56% (5). The Fundamental Research in Oncology and Thrombosis (FRONTLINE) survey in 2001 was the first study to specifically collect data related to VTE in cancer patients when analysing the prescription practices from 3,891 healthcare practitioners. FRONTLINE results showed that pharmacological thromboprophylaxis was adequately used in only 52% of surgical cancer patients and in less of 5% of medical patients (67). Similarly, the Canadian multicentre chart audit of 29 hospitals and 1,894 medical inpatients reported that patients admitted for cancer were significantly less likely to receive any form of VTE prophylaxis than other medical patients (odds ratio [OR], 0.40; 95% CI, 0.24–0.68; p=0.0007) (68). The IMPROVE registry analysing 15,156 hospitalised medical patients from 12 countries later reported that only 40% in the subgroup of cancer patients received LMWH or UFH (69). Similar findings were observed in the multicentre Swiss SWIVTER registry both in the surgical and the medical setting when prophylactic regimen were analysed (70). Only 49% of cancer patients had received pharmacological thromboprophylaxis within the 30 days prior to a VTE event (70). A more recent prospective cross-sectional study of 775 hospitalised cancer patients assessed use of thromboprophylaxis in five US academic medical centres (71). Patients admitted for cancer therapy were significantly less likely to receive anticoagulation prophylaxis as compared to those admitted for other causes (OR, 0.37; 95% CI, 0.22–0.61; p=0.001). Patients suffering from non-haematologic malignancies were more likely to receive anticoagulants as compared to those with haematologic malignancies (OR, 2.34; 95% CI, 1.43–3.82; p=0.007). Prior history of VTE was the strongest predictor for adequate prophylaxis prescription (OR, 0.37; 95% CI, 1.96–17.18; p=0.02) (71). Of importance, only 58.8% of the cancer patients estimated at high risk of VTE did not receive thromboprophylaxis (71). Few data have been obtained concerning practice assessment for VTE prophylaxis in ambulatory cancer patients. A recent single-centre prospective study among 1,108 cancer patients receiving ambulatory chemotherapy reported that previous history of VTE, intercurrent hospitalisation, and gastrointestinal or gynaecologic cancer were the main factors influencing the effective VTE thromboprophylaxis use. In this study, outpatient prophylaxis was associated with a lower risk of VTE during follow up (OR, 0.30; 95% CI, 0.10–0.95) (72).

**Direct oral anticoagulants**

The use of direct oral anticoagulants (DOAC) is not recommended routinely in cancer patients due to insufficient data concerning their use in the cancer setting. A single Phase III clinical trial (MAGELLAN) assessed the efficacy and safety of rivaroxaban in acutely ill hospitalised medical patients (73). The trial was designed in two consecutive phases. The first phase compared rivaroxaban (10 mg once-daily) vs enoxaparin (40 mg once-daily) given for 10 days. The second phase compared an extended treatment with rivaroxaban (35 days) versus placebo. The post hoc analysis of the subgroup of patients with active cancer showed a non-significant trend for lower efficacy of VTE prophylaxis in cancer patients treated with rivaroxaban (9.9% of VTE at day 35) compared with enoxaparin (7.4% of VTE at day 35) as well as a non-significantly higher bleeding risk (5.4% vs 1.7%; RR,1.34; 95% CI, 0.71–2.54) (73). A single Phase II pilot study (ADVOCATE) evaluated the efficacy and safety of apixaban in cancer patients receiving chemotherapy. Patients (n=125) were randomised to receive once-daily doses of apixaban 5 mg, 10 mg, 20 mg, or placebo. No subject in any of the three doses of apixaban groups and three patients in the placebo group (10.3%) developed symptomatic VTE but these findings should be interpreted cautiously due to the study limits (74). Further studies assessing the use of DOACs in cancer patients are needed.

**Conclusion**

The benefit of adequate VTE prophylaxis is well documented in cancer patients undergoing surgery or hospitalised for acute medical illness or with a lower mobility, in the absence of contraindication to anticoagulation. In ambulatory cancer patients, increased evidences suggest that the benefit from pharmacological prophylaxis may be limited to certain cancer types, such as presently evidenced in the subgroup of cancer patients with locally advanced or...
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References


