International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer

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Venous thromboembolism (VTE) is the second leading cause of death in patients with cancer. These patients are at an increased risk of developing VTE and are more likely to have a recurrence of VTE and bleeding while taking anticoagulants. Management of VTE in patients with cancer is a major therapeutic challenge and remains suboptimal worldwide. In 2013, the International Initiative on Thrombosis and Cancer (ITAC-CME), established to reduce the global burden of VTE in patients with cancer, published international guidelines for the treatment and prophylaxis of VTE and central venous catheter-associated thrombosis. The rapid global adoption of direct oral anticoagulants for management of VTE in patients with cancer is an emerging treatment trend that needs to be addressed based on the current level of evidence. In this Review, we provide an update of the ITAC-CME consensus recommendations based on a systematic review of the literature ranked according to the Grading of Recommendations Assessment, Development, and Evaluation scale. These guidelines aim to address in-hospital and outpatient cancer-associated VTE in specific subgroups of patients with cancer.

Introduction

Cancer is an independent major risk factor for venous thromboembolism (VTE), which is the second leading cause of death in medically and surgically treated patients with cancer.1 The incidence of symptomatic and asymptomatic VTE is steadily increasing in these patients2–4 who are at an increased risk of VTE recurrence and bleeding, and are more likely to use health-care resources.5–7 As an independent prognostic factor for cancer progression and death,13 it has been recommended that VTE occurrence becomes a secondary endpoint in oncological trials.4

The clinical presentation of VTE—defined as deep vein thrombosis, pulmonary embolism, or central venous catheter-associated thrombosis—poses major therapeutic challenges that are further complicated by multiple cancer-related risk factors and comorbidities, which influence the choice of anticoagulation.9–12 Despite the development of national clinical practice guidelines (CPGs) on VTE treatment,11–18 substantial knowledge gaps remain.9 Preconceptions about patient tolerance and quality of life with the recommended anticoagulants need to be addressed as they hinder global CPG implementation. The International Initiative on Thrombosis and Cancer (ITAC-CME) initially published the 2013 international CPGs.19–21 Evidence-based knowledge was translated into clinical practice with a free web-based mobile application (for iOS and Android), in English and French, to improve patient care. In 2015, direct oral anticoagulants (DOACs) were prescribed in 20% of patients with cancer in the US20 and worldwide21 despite an absence of direct evidence to support this shifting clinical practice.21 As a result, the ITAC-CME developed an update of the 2013 recommendations to address DOAC use in the treatment of VTE for patients with cancer. In this Review, we summarise those results, and provide the first evidence-based international guidelines on DOAC use in the treatment of VTE. Guidelines were developed by an independent working group of academic experts, reviewed by an expanded global advisory committee, and endorsed by the International Society on Thrombosis and Haemostasis.

Guideline development

Critical appraisal

After suitable articles were selected from the literature search, critical appraisal (appendix p 9) of the selected articles’ methodological strength and clinical relevance was done independently by the methodologists (DF and JD) and then approved by the working group. Data were extracted into evidence tables and identified discrepancies were resolved by the working group. Conclusion tables that summarised the evidence for each clinical question were assembled to guide the development of the recommendations. The tables included rankings of the quality of evidence based on the types of studies (low, medium, high); the degree of agreement between studies (consistency); and an assessment of the patient population (directness)—ie, patients with cancer versus an unselected study population, which was recorded as a study limitation.

The recommendations, developed during two consensus meetings, were formulated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) scale (panel 1).20,21,22 Additional economic considerations were taken into account during the development and ranking of the recommendations to offer treatment alternatives when possible that address potential economic barriers to treatment.

Review process

An independent medical education organisation—CME Solutions ULC (Montreal, QC, Canada), an organisation compliant with the Accreditation Council for Continuing Medical Education (ACCME), assisted in the development and promotion of the guidelines. CME Solutions ULC (Montreal, QC, Canada), an organisation compliant with the Accreditation Council for Continuing Medical Education (ACCME), assisted in the development and promotion of the guidelines.
for Continuing Medical Education for non-commercial interest in the USA and Canada—was appointed by the working group to impartially assemble the external global advisory committee. 56 experts from the global advisory committee were from relevant specialties and included national experts, international scientific societies and patient associations, three nurses, and two patient representatives (appendix p 78). They were identified on the basis of their knowledge, clinical expertise, publication record, and contributions to the field. Panel members were given an evaluation grid (nine point scale, from don't agree to agree [0–9]) to complete. Feedback was analysed by the working group and revisions were incorporated into this Review.

**Guideline recommendations for the treatment of established VTE**

Recommendations on the treatment of established VTE for patients with cancer and the international advisory panel rankings of the guidelines can be found in panel 2.25,26

**Initial treatment (first 10 days)**

As presented in the 2013 CPGs,20 data pooled from randomised and retrospective studies indicated that patients with cancer who were initially treated with unfractionated heparin or low-molecular-weight heparin (LMWH) followed by a vitamin K antagonist (VKA) have a high prevalence of VTE recurrence (10.0–38.0% for unfractionated heparin and 6.7–17.0% for LMWH) and major bleeding (6.3–35.0% and 2.9–16.9%, respectively).

With regard to recommendations for short-term LMWH versus short-term unfractionated heparin followed by VKA, the 2013 CPGs were based on several meta-analyses25–28 of subgroups of patients with cancer comparing short-term LMWH, unfractionated heparin, or fondaparinux in the initial treatment of VTE in the general population.

Since our previous recommendations, two meta-analyses29,30 have compared short-term LMWH with unfractionated heparin in patients with cancer. One meta-analysis31 progressively expanded the subgroups of patients with cancer (1016 patients in 2008,35 801 in 2011,18 1606 in 201424), and consistently reported that VTE recurrence was not statistically different between patients receiving LMWH and those receiving unfractionated heparin. However, mortality in these studies was significantly reduced by 29.0% with LMWH at 3-month follow-up (3 months; 801 patients with cancer, relative risk [RR] 0.71, 95% CI 0.52–0.98) compared with unfractionated heparin, which was not observed in patients without cancer. In the second meta-analysis,36 LMWH significantly reduced overall mortality compared with unfractionated heparin by the end of treatment (3–6 months; 3816 patients with cancer; odds ratio [OR] 0.53, 95% CI 0.33–0.85).

Data on the use of inferior vena cava filters for VTE in patients with cancer are scarce. The 2013 CPGs with regard to use of IVCFs were based on 14 retrospective cohort studies (29–308 patients). Since the 2013 CPGs were published, one new randomised trial39 has compared recurrence of pulmonary embolism in patients assigned to inferior vena cava filters plus anticoagulation (33 [16.5%] of 200 patients had active cancer) versus anticoagulant alone (29 [14.6%] of 199 patients had active cancer). The recurrence for pulmonary embolism was doubled with inferior vena cava filters compared with anticoagulant alone at 3-month and 6-month follow-ups, although not statistically significantly (3.0% for inferior vena cava filter and anticoagulant at 3-month follow-up vs 1.5% anticoagulant alone at 3-month follow-up). Symptomatic deep vein thrombosis, major bleeding, 3-month and 6-month mortality, or inferior vena cava filter complications were not different between patients assigned to inferior vena cava filters plus anticoagulation and those assigned to anticoagulation alone. Another new randomised trial40 compared inferior vena cava filters plus fondaparinux with fondaparinux alone in 64 patients with different types of cancer; a third had either lymphoma, ovarian cancer, or an undefined histology. No differences between treatment groups were reported for inferior vena cava filter complications, major or minor bleeding, or survival at 90-day end-of-treatment follow-up. One new retrospective multicentre study44 examined in-hospital

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**Panel 1: Grading of Recommendations Assessment, Development, and Evaluation scale and additional economic considerations**

**Levels of evidence**

- **High (A):** further research is very unlikely to change our confidence in the estimate of effect
- **Moderate (B):** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- **Low (C):** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- **Very low (D):** any estimate of effect is very uncertain

**Levels of recommendation**

- **Strong (grade 1):** the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects
- **Weak (grade 2):** the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but is not confident
- **Best clinical practice (guidance):** in the absence of any clear scientific evidence and because of the undetermined balance between desirable and undesirable effects, judgment was based on the professional experience and consensus of the international experts within the working group

**Additional economic considerations taken into account during the development and ranking of the recommendations**

- The price of a drug varies in different countries and in different regions of the world
- In the case of a strong recommendation, the benefit to the patient outweighs health economics considerations
- Costs of anticoagulants are negligible compared with the cost of cancer treatment
all-cause mortality in 318 115 patients with cancer and pulmonary embolism at discharge from short-stay hospitals in the USA between 1998 and 2009. Overall, 69 635 (21·9%) of 318 115 patients with cancer and pulmonary embolism received an inferior vena cava filter. Mortality was lower for patients with inferior vena cava filters who were older than 30 years than in those without inferior vena cava filters (RR 0·68, 95% CI 0·67–0·70). Case fatality rates associated with an inferior vena cava filter varied according to tumour type. The in-hospital all-cause case fatality rates were higher with inferior vena cava filters than without in patients with haematological malignancies (RR 1·14, 1·07–1·21), except in elderly patients (>80 years), and in the case of lymphoma, patients aged 71–80 years also had lower case fatality rates.

Early maintenance (10 days to 3 months) and long-term (beyond 3 months) treatment

Although the two largest studies15,16 in this setting treated patients for 6 months, the strength of the evidence for treatment up to 6 months is low (inconsistency). Values and preferences: daily subcutaneous injection might be a burden for patients.

3 Direct oral anticoagulants can be considered for VTE treatment of patients with stable cancer not receiving systemic anticancer therapy, and in cases where VKA is an acceptable, but not an available, treatment choice (guidance).

4 After 3–6 months, termination or continuation of anticoagulation (LMWH, VKA, or direct oral anticoagulants) should be based on individual assessment of the benefit-to-risk ratio, tolerability, drug availability, patient preference, and cancer activity (guidance, in the absence of data).

Treatment of VTE recurrence in patients with cancer given anticoagulant treatment

International Advisory Panel ranking: 8·48 out of 9·00

In the event of VTE recurrence, three options can be considered: (1) increase in LMWH dose (by 20–25%) in patients treated with LMWH; (2) switch from VKA to LMWH in patients treated with VKA; and (3) inferior vena cava filter insertion—with continued anticoagulant therapy, unless contraindicated (guidance, based on evidence of very low quality and an unknown balance between desirable and undesirable effects).

Values and preferences: individual decision.

Treatment of established catheter-related thrombosis

International Advisory Panel ranking: 8·79 out of 9·00

1 For the treatment of symptomatic catheter-related thrombosis in patients with cancer, anticoagulant treatment is recommended for a minimum of 3 months; in this setting, LMWHs are suggested. Direct comparisons between LMWHs and VKAs have not been made in this setting (guidance).

2 The central venous catheter can be kept in place if it is functional, well positioned, and non-infected with good resolution of symptoms under close surveillance; irrespective of whether the central venous catheter is kept or removed, no standard approach in terms of duration of anticoagulation is established (guidance).
short-term heparin followed by VKA in the early maintenance and long-term treatment of confirmed VTE. Five clinical trials were done in patients with cancer (CLOT, CATCH, LITE, CANTHANOX, ONCENOX) and two in unselected patients with VTE, some of whom had cancer (table 1). Four randomised trials assessed VTE recurrence. Three consistently reported a statistically significant 52.0–74.0% reduction in VTE with LMWH compared with heparin followed by VKA without increasing bleeds. In the CATCH study, long-term tinzaparin treatment was associated with a non-statistically significant reduction in a composite primary outcome measure of recurrent VTE (recurrent deep vein thrombosis, fatal or non-fatal pulmonary embolism, and incidental VTE), compared with short-term tinzaparin followed by VKA (7.2% with long-term tinzaparin vs 10.5% with short-term tinzaparin followed by VKA; hazard ratio [HR] 0.65, 95% CI 0.41–1.03; p=0.07).

The updated search identified one study that assessed extended LMWH treatment in patients with cancer and residual VTE after an initial 6 months of nadroparin (97 IU/kg twice per day). Patients with residual VTE were randomly assigned to either 6-month anticoagulation continuation (119 patients) or immediate anticoagulant discontinuation (123 patients). Patients without residual VTE discontinued anticoagulation (105 patients).

### Table 1: Trials comparing LMWH with LMWH plus vitamin K antagonists in early maintenance and long-term treatment of venous thromboembolism

<table>
<thead>
<tr>
<th>Patients with cancer</th>
<th>Number of patients</th>
<th>LMWH Dosage and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOT, Lee et al (2003)</td>
<td>672</td>
<td>Dalteparin 200 IU/kg once per day for 1 month, 150 IU/kg per day for 5 months</td>
</tr>
<tr>
<td>CATCH, Lee et al (2015)</td>
<td>900</td>
<td>Tinzaparin 175 IU/kg once per day for 6 months</td>
</tr>
<tr>
<td>LITE, Hull et al (2006)</td>
<td>200</td>
<td>Tinzaparin 175 IU/kg once per day for 3 months</td>
</tr>
<tr>
<td>CANTHANOX, Meyer et al (2002)</td>
<td>146</td>
<td>Enoxaparin 1.5 mg/kg once per day for 3 months</td>
</tr>
<tr>
<td>ONCENOX, Deitcher et al (2005)</td>
<td>122</td>
<td>Enoxaparin 1 mg/kg twice per day for 5 days, 1.0 mg/kg or 1.5 mg/kg once per day for 6 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unselected patients</th>
<th>Number of patients</th>
<th>LMWH Dosage and duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez-Beret et al (2001)</td>
<td>158</td>
<td>Nadroparin 0.1 mL/10 kg twice per day for 3 to 6 months</td>
</tr>
<tr>
<td>Romera et al (2009)</td>
<td>241</td>
<td>Tinzaparin 175 IU/kg once per day for 6 months</td>
</tr>
</tbody>
</table>

Early maintenance was 10 days to 3 months. Long-term treatment was more than 3 months. LMWH=low-molecular-weight heparin.
(NCT02220725) and ciraparantag is under investigation as an antidote to all the DOACs (NCT01826266). Only protamine can be used to reverse the effects of LMWH, but this neutralisation is only partial.\(^5\) The protamine can be used to reverse the effects of LMWH, but this neutralisation is only partial. The \(\text{DOACs}\) group includes a thrombin inhibitor (dabigatran), and three factor Xa inhibitors: rivaroxaban, apixaban, and edoxaban (table 2). A fourth factor Xa inhibitor, betrixaban, is undergoing phase 3 trials.\(^5\) The DOACs and edoxaban (table 2). A fourth factor Xa inhibitor, betrixaban, is undergoing phase 3 trials.\(^5\) The DOACs include a thrombin inhibitor (dabigatran), and three factor Xa inhibitors: rivaroxaban, apixaban, and edoxaban (table 2). A fourth factor Xa inhibitor, betrixaban, is undergoing phase 3 trials.\(^5\) The DOACs include a thrombin inhibitor (dabigatran), and three factor Xa inhibitors: rivaroxaban, apixaban, and edoxaban (table 2). A fourth factor Xa inhibitor, betrixaban, is undergoing phase 3 trials.\(^5\) The DOACs include a thrombin inhibitor (dabigatran), and three factor Xa inhibitors: rivaroxaban, apixaban, and edoxaban (table 2). A fourth factor Xa inhibitor, betrixaban, is undergoing phase 3 trials.\(^5\) The DOACs include a thrombin inhibitor (dabigatran), and three factor Xa inhibitors: rivaroxaban, apixaban, and edoxaban (table 2). A fourth factor Xa inhibitor, betrixaban, is undergoing phase 3 trials.\(^5\)

<table>
<thead>
<tr>
<th>Target</th>
<th>Dabigatran</th>
<th>rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic dose</td>
<td>150 mg twice a day; 110 mg twice a day for ages &gt;80 years; 110 mg twice a day, following at least 5 days of parenteral anticoagulants for patients with high risk of bleeding</td>
<td>15 mg twice a day for 3 weeks followed by 20 mg once a day</td>
<td>10 mg twice a day for 7 days, followed by 5 mg twice a day</td>
<td>60 mg once a day following at least 5 days of parenteral anticoagulants</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>3–7%</td>
<td>10 mg dose: 100%; 20 mg dose: 100% when taken together with food; 66% under fasting conditions; interindividual variability: 30–40%</td>
<td>About 50%; interindividual variability: 30%</td>
<td>About 62%</td>
</tr>
<tr>
<td>Activity onset</td>
<td>1–3 h</td>
<td>2–4 h</td>
<td>3–4 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Half-life</td>
<td>12–18 h</td>
<td>5–13 h</td>
<td>12 h</td>
<td>10–14 h</td>
</tr>
<tr>
<td>Excretion (% of administered dose)</td>
<td>80% renal (unchanged), 20% liver</td>
<td>66% renal (half active drug unchanged and half inactive metabolites), 33% faeces (inactive metabolites)</td>
<td>25% renal, 75% faeces</td>
<td>50% renal (unchanged, 50% biliary or intestinal)</td>
</tr>
<tr>
<td>Considerations for renal insufficiency</td>
<td>Mild or moderate: dose adjustment recommended; severe: contraindicated if GFR &lt;30 mL/min</td>
<td>Moderate (GFR 30–49 mL/min): dose adjustment recommended; severe: not recommended if GFR &lt;30 mL/min</td>
<td>Mild or moderate, or if GFR &gt;25–30 mL/min: no dose adjustment required; severe: not recommended if GFR &lt;15 mL/min; no data available in patients with end-stage renal disease</td>
<td>Moderate (GFR 30–50 mL/min): dose adjustment recommended; severe: not recommended if GFR &lt;15 mL/min; no data available in patients with end-stage renal disease or on dialysis</td>
</tr>
<tr>
<td>Considerations for hepatic insufficiency</td>
<td>Liver enzymes twice normal limit or if acute liver diseases: not recommended</td>
<td>Moderate hepatic impairment: caution; hepatic disease with coagulopathy and clinically relevant bleeding risk: contraindicated</td>
<td>Mild or moderate hepatic impairment: caution, but no dose adjustment required; severe hepatic impairment: not recommended; hepatic disease with coagulopathy and clinical relevant bleeding risk: contraindicated</td>
<td>Mild hepatic impairment: no dose reduction; moderate or severe hepatic impairment: not recommended</td>
</tr>
<tr>
<td>Interaction</td>
<td>P-glycoprotein inducers or inhibitors</td>
<td>P-glycoprotein inducers or inhibitors; CYP3A4 and CYP2J2</td>
<td>P-glycoprotein inducers or inhibitors; CYP3A4</td>
<td>P-glycoprotein inducers or inhibitors; CYP3A4</td>
</tr>
<tr>
<td>Antidote</td>
<td>Idarucizumab</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 2: Characteristics of available direct-acting anticoagulants for venous thromboembolism treatment

Rivaroxaban was administered at 15 mg twice a day for 3 weeks, followed by 20 mg once a day for the long-term treatment phase. Patients with a glomerular filtration rate of less than 30 mL/min were excluded. A prespecified pooled analysis of the two trials examined safety and efficacy outcomes in 597 patients with active cancer (430 at inclusion, 167 diagnosed during the study).\(^6\) At the end of treatment (approximately 200 days), rivaroxaban was non-inferior to short-term LMWH followed by VKA with regard to VTE recurrence (5·1% with rivaroxaban vs 7·1% with short-term LMWH followed by VKA; HR 0·69, 95% CI 0·36–1·33), major bleeding (2·8% vs 5·0%; HR 0·53, 95% CI 0·23–1·23), and in a composite of clinically relevant non-major and major bleeding (15·2% vs 15·8%; HR 0·93, 0·62–1·33), and in a composite of clinically relevant non-major and major bleeding (15·2% vs 15·8%; HR 0·93, 0·62–1·33). Two randomised phase 3 clinical trials compared dabigatran with VKA in acute VTE treatment for more than 6 months (RE-COVER [1273 patients treated with dabigatran vs 1266 patients treated with VKA];\(^7\) RE-COVER II [1280 patients treated with dabigatran vs 1288 patients treated with VKA]\(^8\)). Patients with a glomerular filtration rate of less than 30 mL/min were excluded. Participants initially received LMWH or
unfractionated heparin for at least 5 days, followed by 6 months of dabigatran at 150 mg twice a day or a VKA. 335 (6-6%) of 5107 study participants across both RECOVER trials combined had an active cancer (221 at baseline, 114 diagnosed during the study). The dabigatran treatment group had a recurrence of VTE that was similar to VKA for both cancer at baseline (HR 0.75, 95% CI 0.20–2.8) and cancer diagnosed during the study (HR 0.63, 0.20–2.0), with no differences in major and clinically relevant non-major bleeding (cancer at baseline: HR 1.48, 0.64–3.4; cancer diagnosis during study: HR 0.65, 0.27–1.6). These data are from a pooled analysis of both RECOVER trials.69

The AMPLIFY trial50 (5400 patients) compared apixaban (10 mg twice a day for 7 days, then 5 mg twice a day) with LMWH followed by a VKA for acute VTE treatment for 6 months. Patients with a glomerular filtration rate of less than 25 mL/min were excluded. In 534 patients with cancer (169 with active cancer; 365 with a history of cancer), VTE recurrence (RR 0.45, 0.08–2.46) were similar in both treatment groups. In patients with a history of cancer only, VTE recurrence was significantly reduced with apixaban compared with LMWH plus VKA (1-1% vs 6-3%; RR 0.17, 0.04–0.78), with no significant differences in major bleeding (0.5% vs 2.8%; RR 0.20, 0.02–1.65).71

The HOKUSAI-VTE phase 3 trial72 randomised 8292 participants to edoxaban or a VKA for 3–12 months. Patients with a 30–50 mL/min glomerular filtration rate received a 50% dose of edoxaban, and those with a glomerular filtration rate of less than 30 mL/min were excluded. A post-hoc analysis assessed the safety and efficacy of edoxaban in 771 patients with active cancer or a history of cancer (9-3% of the study population).72,73 In 208 patients with active cancer, VTE recurrence was similar between treatment groups (HR 0.55, 95% CI 0.20–1.35; p=0.80). DOACs versus VKA had comparable recurrence (HR 0.66, 0.39–1.11). No significant differences in major bleeding were observed; compared with VKA, LMWH was associated with a non-significant increase in major bleeding and DOACs were associated with a non-significant reduction (LMWH: RR 1.06, 0.5–2.23; DOAC: RR 0.78, 0.42–1.44). An indirect network meta-analysis estimated the relative efficacy and safety of DOACs compared with LMWH. Preliminary pairwise comparisons indicated that the risk of VTE recurrence was significantly reduced with LMWH compared with VKA (RR 0.60, 95% CI 0.45–0.79; p=0.001), without increasing risk of major bleeding (RR 1.07, 0.66–1.73; p=0.80). DOACs versus VKA had comparable recurrence of VTE (RR 0.65, 0.38–1.09; p=0.10) and major bleeding (RR 0.72, 0.39–1.35; p=0.31). The indirect network meta-analysis, which used VKA as the common comparator, showed that the risk of recurrent VTE (RR 1.08, 0.59–1.95; p=0.81) and major bleeding (RR 0.67, 0.31–1.46; p=0.31) might be similar between LMWH and DOAC.

VTE recurrence in patients with cancer on anticoagulation medication

Studies assessing therapeutic strategies for VTE recurrence are scarce. The 2013 international CPGs relied on one retrospective cohort study in 70 patients with cancer and recurrent VTE undergoing anticoagulation treatment. Several retrospective or prospective cohort studies have analysed the use of inferior vena cava filters in the prevention of VTE recurrence, including one systematic review of 6834 patients (number with cancer unspecified) that was not identified in the 2013 guidelines, with inconsistent findings.
Treatment of established central venous catheter-associated thrombosis

Symptomatic catheter-associated thrombosis occurs in 3·0–5·0% of patients with cancer requiring venous access, which increases to as much as 30·0% when including asymptomatic cases.21

Since 2013, one new retrospective study88 assessed LMWH for symptomatic catheter-associated thrombosis in 99 patients with cancer. 72 (72·7%) patients received full-dose LMWH for 1 month followed by an intermediate dose for 3, 6, or 12 months, with no recurrence. In the 13 patients receiving a preventive dose of LMWH after 3, 6, or 12 months at full or intermediate doses, two (15·4%) had VTE recurrence. A second retrospective study89 in 35 patients with acute leukaemia reported that 17 (81·0%) of 21 patients had VTE resolution with high-dose or low-dose enoxaparin, compared with six (42·9%) of 14 patients not on anticoagulants (p=0·11). The prevalence of mortality was 33·3% for patients treated with enoxaparin versus 71·4% for patients who did not receive anticoagulation (HR 0·32, 95% CI 0·12–0·85).

One meta-analysis90 assessed the benefit-to-risk ratio of different anticoagulants in 2564 patients with catheter-associated thrombosis. LMWH or unfractionated heparin at prophylactic doses significantly reduced symptomatic deep vein thrombosis by 50% compared with no heparin, with no differences in major or minor bleeding, mortality, or thrombocytopenia. A similar safety and efficacy profile to LMWH and unfractionated heparin was found for VKA, but quality of this evidence was ranked as low.

The reported prevalence of incidental VTE varies between 2·0% and 7·3% depending on VTE site and cancer type.86,87 Some studies suggest that as many as 5·9% of patients with cancer undergoing surgery. 220 patients with cancer undergoing gastric surgery. 17 (7·2%) of 237 patients undergoing inferior vena cava filter placement for VTE recurrence. Five (25·0%) of these 20 patients had VTE recurrence with an inferior vena cava filter (effective period of filter placement between 4 weeks before and 6 weeks after the primary cytoreductive surgery), compared with a VTE recurrence of 5·9% of 17 patients receiving inferior vena cava filters for a non-VTE indication. 17 (7·2%) of 237 patients without an inferior vena cava filter developed VTE. The cumulative risk of metastasis or disease progression was 45·2% with an inferior vena cava filter versus 13·6% for those without an inferior vena cava filter (HR 4·35, 95% CI 2·04–9·25; p<0·001). Median survival was 5·7 months with an inferior vena cava filter versus 15·3 months without (p<0·001).

Guideline recommendations for VTE prophylaxis in patients with cancer

Recommendations for VTE prophylaxis in patients with cancer and the corresponding international advisory panel rankings can be found in panel 3. VTE risk-assessment models are provided to guide anticoagulant-treatment decisions (panel 4).22–26

Patients with cancer undergoing surgery

A systematic review27 of 14 randomised trials that was not in the 2013 CPGs has been identified. The review compares VTE prophylaxis with placebo or no intervention in women undergoing benign or oncological gynaecological surgery. VTE prevalence ranged 0·0–34·6% in patients with cancer without prophylaxis, compared with 0·0–14·8% in oncology patients receiving prophylaxis.

One meta-analysis93 compared LMWH with unfractionated heparin in perioperative VTE prophylaxis across 16 randomised controlled trials (12 890 patients with cancer). Consistent with an earlier version of this meta-analysis90 and a meta-analysis in general surgery,96 perioperative prophylaxis with LMWH once a day produced effects on symptomatic and asymptomatic deep vein thrombosis that were similar to those with unfractionated heparin three times a day (RR 0·78, 95% CI 0·53–1·15), and superior to unfractionated heparin twice a day (RR 0·66, 0·44–0·99). The search did not identify any new studies that compared different anticoagulants or different doses of LMWH in patients with cancer undergoing surgery.

Two randomised clinical trials assessed extended-duration prophylaxis in patients with cancer after major abdominal or pelvic surgery, and reported a decrease in VTE without increasing major or minor bleeding (626 patients;96 225 patients).97 The latest randomised study98 compared LMWH prophylaxis (group A) with extended-duration prophylaxis (group B, an additional 3 weeks) after laparoscopic cancer surgery. Extended-duration prophylaxis reduced VTE occurrence at the end of treatment (28 days [SD 2]); 9·7% in group A vs 0·0% in group B; p=0·001) and at 3 months after surgery, with no differences in bleeding.

One new prospective study99 assessed perioperative inferior vena cava filter use for primary cytoreductive surgery in 274 patients with ovarian, fallopian tube, or primary peritoneal cancer receiving LMWH. Of the 38 patients with an inferior vena cava filter, 20 underwent filter placement for VTE. Five (25·0%) of these 20 patients had VTE recurrence with an inferior vena cava filter (effective period of filter placement between 4 weeks before and 6 weeks after the primary cytoreductive surgery), compared with a VTE recurrence of one (5·9%) of 17 patients receiving inferior vena cava filters for a non-VTE indication. 17 (7·2%) of 237 patients without an inferior vena cava filter developed VTE. The cumulative risk of metastasis or disease progression was 45·2% with an inferior vena cava filter versus 13·6% for those without an inferior vena cava filter (HR 4·35, 95% CI 2·04–9·25; p<0·001). Median survival was 5·7 months with an inferior vena cava filter versus 15·3 months without (p<0·001).

Since the 2013 CPGs, one randomised study99 assessed the safety and efficacy of external compression devices in 220 patients with cancer undergoing gastric surgery. External compression devices plus LMWH was associated with reduced VTE incidence and significant increased risk of bleeding compared with the use of an external compression device alone.
Medically treated patients with cancer

The 2013 CPGs were based on findings from the general medically ill patient population admitted to hospital, 5·0–15·0% of whom had cancer. The updated search identified one randomised trial (CERTIFY) of 274 patients with cancer that found similar VTE prevalence between patients who received 3000 IU certoparin once a day and those who received 5000 IU unfractionated heparin three times a day (4·5% with certoparin vs 6·0% with unfractionated heparin; OR 0·73, 95% CI 0·23–2·39). The occurrence of major bleeds was similar between groups, with a non-significant increase in minor bleeding in the unfractionated heparin group. Since 2013, one meta-analysis assessed LMWH prophylaxis in 307 patients with cancer from three placebo-controlled randomised trials (including 5134 hospital-admitted medical patients). By contrast with the general medically ill, hospital-admitted population, 40 mg enoxaparin, 5000 IU dalteparin, or 2·5 mg fondaparinux once a day did not significantly

Panel 3: Prophylaxis in venous thromboembolism in patients with cancer

Prophylaxis of venous thromboembolism (VTE) in surgically treated patients with cancer

International Advisory Panel ranking: 8·60 out of 9·00

1 Use of low-molecular-weight heparin (LMWH) once per day or low-dose unfractionated heparin (UFH) three times per day is recommended to prevent postoperative VTE in patients with cancer; pharmacological prophylaxis should be started 12–2 h preoperatively and continued for at least 7–10 days; no data are available to allow conclusions regarding the superiority of one type of LMWH over another (grade 1A).

Values and preferences: LMWH once per day is more convenient.

2 Evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer is insufficient (grade 2C).

Values and preferences: similar.

3 Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in patients with cancer is recommended (grade 1A).

Values and preferences: equal (no preferences).

4 Extended prophylaxis (4 weeks) with LMWH to prevent postoperative VTE after major laparotomy in patients with cancer is indicated in patients with a high VTE risk and low bleeding risk (grade 1B).

Values and preferences: longer duration of injections.

5 Extended prophylaxis (4 weeks) with LMWH for the prevention of VTE in patients with cancer undergoing laparoscopic surgery is recommended in the same way as for laparotomy (grade 2C).

Values and preferences: daily injections.

Costs: in some countries, the price of LMWH might influence the choice.

6 Mechanical methods are not recommended as monotherapy, except when pharmacological methods are contraindicated (grade 2B).

Values and preferences: no injection.

7 Inferior vena cava filters are not recommended for routine prophylaxis (grade 1A).

Prophylaxis of VTE in medically treated patients with cancer

International Advisory Panel ranking: 8·54 out of 9·00

1 We recommend prophylaxis with LMWH, UFH, or fondaparinux in medically treated patients with cancer and reduced mobility who are admitted to hospital (grade 1B). In this setting, direct oral anticoagulants are not recommended routinely (guidance).

Values and preferences: subcutaneous injections.

Costs: in some countries price differences between LMWH, UFH, or fondaparinux might influence the choice.

2 Primary prophylaxis with LMWH, vitamin K antagonists, or direct oral anticoagulants in patients receiving systemic anticancer therapy is not recommended routinely (grade 1B).

Values and preferences: subcutaneous injections.

3 Primary pharmacological prophylaxis of VTE with LMWH is indicated in patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low bleeding risk (grade 1B).

Values and preferences: subcutaneous injections.

4 Primary pharmacological prophylaxis of VTE might be indicated in patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy and who have a low bleeding risk (grade 2C).

Values and preferences: subcutaneous injections.

5 In patients treated with thalidomide and lenalidomide combined with steroids or other systemic anticancer therapies, or both, VTE primary pharmacological prophylaxis is recommended (grade 1A); in this setting, vitamin K antagonists at low or therapeutic doses, LMWH at prophylactic doses, and low-dose aspirin can be used and have shown similar effects with regard to preventing VTE (grade 2C).

Values and preferences: subcutaneous injections.

Prophylaxis of catheter-related thrombosis

International Advisory Panel ranking: 8·45 out of 9·00

1 Use of anticoagulation for routine prophylaxis of CRT is not recommended (grade 1A).

Values and preferences: bleeding risk anticoagulants.

2 Catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium (grade 1B).
reduce the VTE relative risk compared with placebo in hospital-admitted patients with cancer (RR 0·91, 95% CI 0·81–1·02; P = 0·68%).

The MAGELLAN trial assessed rivaroxaban for VTE prophylaxis in 8101 hospital-admitted, medically ill patients, including 592 (7·3%) patients with active cancer. Rivaroxaban (10 mg once a day) was compared with enoxaparin (40 mg) for the first 10 days. Patients receiving rivaroxaban were maintained on the same regimen for an additional 35 days, whereas the enoxaparin group received a placebo after day 10. In patients with active cancer, VTE prevalence was similar between rivaroxaban and enoxaparin (9·9% for rivaroxaban vs 7·4% for enoxaparin). Similar to the results reported in the whole study population, rivaroxaban increased the risk of clinically relevant bleeding in patients with active cancer compared with enoxaparin (5·4% for rivaroxaban vs 1·7% for enoxaparin).

Ambulatory patients treated with systemic anticancer therapy

The updated search identified eight meta-analyses (1669–9861 patients) and six randomised clinical trials comparing anticoagulant prophylaxis with no intervention or placebo in ambulatory patients receiving systemic anticancer therapy. Overall, a significant 45% reduction in VTE occurrence was reported across the six meta-analyses assessing the safety and efficacy of LMWH compared with no intervention or placebo. Specific cancer subgroup analyses across the meta-analyses showed that LMWH significantly reduced the VTE prevalence compared with no treatment or placebo by 67·9–71·2% in patients with pancreatic cancer (range of 430–748 patients) and by 50·3–53·6% in patients with lung cancer (range of 1926–2075 patients). Five of six meta-analyses reported no significant increase in major bleeding with LMWH (13·0–30·0% of patients received LMWH and had major bleeding) compared with no prophylaxis. The sixth study reported that patients were 65% more likely to experience a bleeding event with LMWH (7875 patients in the total population across the II studies; OR 1·65, 95% CI 1·12–2·44) compared with no prophylaxis (appendix p 46). The likelihood of bleeding on LMWH decreased when the analysis was limited to studies with a low risk of bias (41·0% compared with 65·0%), or when the analysis was limited to studies not limited to a single type of cancer (57·0% compared with 65·0%), and these odds ratios were not statistically significant. Three studies of 855–6884 patients with cancer assessed bleeding with LMWH versus placebo or no intervention. All studies reported a significant increase in minor bleeding in the LMWH prophylaxis group. No significant difference in 1-year mortality was reported by any of the meta-analyses.

The effects of VTE prophylaxis in pancreatic and lung cancer subgroup meta-analyses suggest a more robust anticoagulant benefit-to-risk ratio in these populations. The FRAGEM randomised controlled trial compared gemcitabine plus weight-adjusted dalteparin (200 IU/kg once a day for 4 weeks, then 150 IU/kg for a further 8 weeks) with gemcitabine alone in 123 patients with advanced pancreatic cancer. Prevalence of VTE was 23·0% in the control group versus 3·4% with anticoagulation treatment after treatment for less than 100 days (RR 0·145, 95% CI 0·02–1·05).

Panel 4: Risk stratification schemes for prophylaxis of venous thromboembolism in patients with cancer

Clinical parameters

Patients with cancer are at increased risk of venous thromboembolism (VTE) as a result of the presence of multiple simultaneous risk factors.

- VTE risk factors associated with malignancy: neoplasm characteristics (site, histology, stage); the need for surgery or hospital admission, or both; central venous catheter use; and systemic anticancer therapy, including chemotherapy, and treatment with immunomodulatory drugs or erythropoiesis-stimulating agents.
- General individual VTE risk factors: age, weight (body-mass index [BMI]), mobility, comorbidities, sepsis, compliance with prophylaxis.

Patients with cancer and VTE are also more prone to bleeding complications compared with patients without cancer, and this risk is exacerbated by anticoagulant drugs used for VTE prophylaxis.

Emerging biomarkers

- Blood-count parameters (ie, neutrophils, platelets)
- Markers of blood-clotting activation (soluble P-selectin)
- D-dimers
- Microparticle-associated tissue factor (MP-TF) activity: increased MP-TF activity in patients with cancer is associated with increased risk of VTE. Additional research is needed to quantify microparticles according to their origin (ie, endothelial, platelets, tumour) and to establish their clinical use as predictors of VTE.

Khorana predictive model for chemotherapy-associated VTE

Developed for VTE risk assessment in patients who are receiving chemotherapy, the model uses five readily available clinical and laboratory parameters: site of cancer; platelet count; haemoglobin or use of erythropoiesis-stimulating agents, or both; leucocyte count; and BMI. The risk score for VTE was derived from a US development cohort of 2701 patients and then validated in an independent cohort of 1365 patients from a prospective registry. This model has now been externally validated by the Vienna CATS study in 819 patients with cancer in Austria. Several other retrospective and prospective studies have further validated this risk score, although rates vary between studies.

Extended Vienna CATS score

The Vienna group described an expansion of the original Khorana risk score with the inclusion of two additional biomarkers—D-dimer and soluble P-selectin—because of their predictive value. Patients with a score of ≥5 have a 35% risk of developing VTE within 6 months after diagnosis of cancer. Biomarker tests might further refine the predictive use of such risk-assessment models, as has been achieved with D-dimer in patients without cancer.

PROTECHT score

This score is an expansion of the Khorana risk score, which includes platinum-based and gemcitabine-based chemotherapy to the predictive variables. The International Myeloma Working Group is validating a proposed risk-assessment model to categorise VTE risk among patients with myeloma treated with thalidomide or lenalidomide.
95% CI 0.035–0.612; p=0.002), and was 28·0% versus 12·0%, respectively, during follow-up (>100 days; RR 0.419, 0.387–0.935; p=0.039). The prospective, open-label, randomised, multicentre CONKO-004 trial assessed 312 patients with advanced pancreatic cancer receiving first-line chemotherapy in an outpatient setting, with or without enoxaparin (1 mg/kg per day for 3 months, 40 mg per day thereafter). Prevalence of symptomatic VTE was 1·3% in the enoxaparin group versus 9·9% without enoxaparin (1 mg/kg per day for 3 months, or no (0-0%) patients in the apixaban group (32 in the 5 mg group, 29 in the 10 mg group, and 32 in the 20 mg group). No major bleeding incidents were reported with either a 5 mg or 10 mg dose of apixaban, but two (6·3%) of 32 patients had a major bleed in the 20 mg group.

Since the 2013 CPGs, one new meta-analysis of 1669 patients assessed the effects of VKAs versus placebo or no intervention in primary VTE prophylaxis. A non-significant decrease in VTE in patients on VKA was reported (RR 0.15, 95% CI 0.02–1.2; p=0.074), with a significant sizeable increase in major bleeding (RR 4.24, 1.86–9.65) and minor bleeding (RR 3.19, 1.83–5.55).

A phase 2 dose-finding, double-blind, randomised study (ADVOCATE) assessed the safety and tolerability of apixaban prophylaxis in 125 ambulatory patients with advanced or metastatic cancer receiving chemotherapy. Apixaban prophylaxis was started within 4 weeks of initiating chemotherapy and lasted for 12 weeks. The proportion of patients with VTE was three (10·3%) of 29 patients in the placebo group, and no (0-0%) patients in the apixaban group (32 in the 5 mg group, 29 in the 10 mg group, and 32 in the 20 mg group). No major bleeding incidents were reported with either a 5 mg or 10 mg dose of apixaban, but two (6·3%) of 32 patients had a major bleed in the 20 mg group.

One retrospective analysis of the PROTECHT trial, which was not identified in the 2013 CPGs, assessed the benefit to risk of LMWH thromboprophylaxis in 1150 patients with initiation of chemotherapy for a maximum of 120 days. Nadroparin (3800 anti-Xa IU once a day) reduced VTE risk by 68·0% in patients receiving gemcitabine alone and by 78·0% when combined with a platinum-based agent.

Two randomised studies (with 342 patients and 991 patients) and one meta-analysis (6632 patients) that were not identified in the 2013 CPGs compared LMWH thromboprophylaxis with aspirin or warfarin in patients treated with thalidomide or lenalidomide with multiple myeloma. Overall, these studies indicated that prophylactic doses of LMWH, aspirin (100 mg per day), or warfarin reduced the risk of VTE in patients with myeloma treated with lenalidomide or thalidomide without increasing bleeding complications. None of the studies included a placebo group.

**Prophylaxis of central venous catheter-associated thrombosis**

One new meta-analysis, which pooled the effect of different anticoagulants, reported a reduction in symptomatic catheter-associated thrombosis in patients with cancer and a central venous catheter (RR 0.61, 95% CI 0.42–0.88; 3018 patients in total). Another new meta-analysis assessed VTE prophylaxis in paediatric patients with cancer with tunneled central venous catheters. Treatment with LMWH (n=134); low-dose warfarin (n=31); antithrombin (n=37); cryoprecipitate or fresh frozen plasma, or both (n=240); or antithrombin plus LMWH (n=41) produced a similar proportion of VTE occurrences to no intervention. However, concomitant LMWH and antithrombin supplementation reduced symptomatic VTE without an increase in bleeding. Since 2013, one new meta-analysis reported that peripherally
inserted central venous catheters are associated with a higher risk of deep vein thrombosis compared with other central venous catheters, particularly in critically ill patients or patients with cancer.

VTE treatment in special clinical situations

Recommendations on VTE treatment for patients in special clinical situations can be found in panel 5.

Patients with brain tumours

One new retrospective study assessed the risk of intracranial haemorrhage associated with VTE anticoagulation in 293 patients with cancer with brain metastases. Therapeutic doses of enoxaparin did not increase intracranial haemorrhage, including in patients with melanoma and renal-cell carcinoma, who in control cohorts had a four times increased risk of intracranial haemorrhage relative to other types of cancer.

One randomised, placebo-controlled, double-blind clinical trial (186 patients with brain tumours) assessed VTE prophylaxis with dalteparin treatment (5000 IU once a day). LMWH was not associated with a significant reduction in VTE occurrence or in mortality. Major bleeding was not significantly increased, but the CI was large (HR 4.2, 95% CI 0.48–36), and all major bleeds were intracranial. Since 2013, one meta-analysis reported that the proportion of patients with VTE was 4.3% with bevacizumab alone, 4.2% when co-administered with chemotherapy, and 7.5% with the addition of radiotherapy, although these results were not statistically significant. However, severe CNS bleeding was considerably more prevalent in patients receiving anticoagulation (8.2% with anticoagulation vs 0.6% without anticoagulation; p<0.001).

One new meta-analysis since the 2013 CPGs assessed LMWH, unfractionated heparin, and mechanical prophylaxis in 1558 patients who underwent craniotomy. Similar to earlier studies, the use of prophylaxis in patients with neuro-oncological conditions undergoing surgery reduced the occurrence of VTE without increasing bleeding risk (OR 0.24; 95% CI 0.08–0.75; p=0.01). Use of intermittent pneumatic compression devices and LMWH further reduced the VTE occurrence compared with mechanical compression alone (OR 0.57, 0.39–0.82; p=0.002). The addition of LMWH was associated with a non-significant increase in major bleeding.

Thrombocytopenia

Since the 2013 CPGs, one prospective study has assessed low-dose dalteparin (100 U/kg daily for 6 months) in 93 patients with thrombocytopenia versus a standard dose (200 U/kg daily for 1 month, followed by 150 U/kg daily for 5 months) in patients with mild to no thrombocytopenia. The proportions of patients with residual VTE, VTE recurrence, and overall bleeding were similar between groups. In a second prospective study (24401 patients), the incidence of thrombocytopenia was significantly greater with unfractionated heparin (1.4%) than with LMWH (0.5%). Another retrospective study reported outcomes associated with concomitant VTE and thrombocytopenia in 74 patients with inoperable, advanced pancreatic cancer receiving first-line chemotherapy. Standard anticoagulation significantly reduced the occurrence of VTE (OR 0.13, 95% CI 0.03–0.58) without increasing bleeds, but this reduction was not observed with reduced anticoagulation doses or when administered for less than 3 months.

Renal failure

One prospective study investigated the impact of renal insufficiency on the safety and efficacy of anticoagulant therapy by comparing the risks of recurrent VTE and bleeding in 1279 patients with cancer with and without chronic kidney disease. Risk of major bleeds and fatal bleeds increased with the stage of chronic kidney disease.
Conclusion
Most new data from patients with cancer address VTE prophylaxis with LMWH and the effects of DOACs in VTE treatment. LMWH for the treatment and management of established VTE in patients with cancer is well demonstrated, with strong evidence for at least a 3-month treatment duration. Primary thromboprophylaxis with LMWH is also well defined in cancer surgery. The evidence is less clear in medically treated patients with cancer, particularly those receiving ambulatory systemic anticancer therapy. Trials assessing anticoagulants in this population need to be stratified according to VTE and bleeding risks, which vary widely across cancer types and patients. Analysis of patients with cancer from large pivotal trials (containing 169–597 patients) suggest that DOACs are non-inferior to VKAs in the treatment of VTE in this population. Direct data on the safety and efficacy of DOACs in cancer are missing, with the need for dose-finding studies and more research into potential anticoagulant drug interactions. More than 35 clinical trials are underway to compare DOACs with LMWH.

Declaration of interests
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References
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