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How to cite

FARGE, Dominique et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. In: Lancet oncology, 2016, vol. 17, n° 10, p. e452–e466. doi: 10.1016/S1470-2045(16)30369-2

This publication URL: https://archive-ouverte.unige.ch//unige:89098
Publication DOI: 10.1016/S1470-2045(16)30369-2

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.

Lancet Oncol 2016; 17: e452–66

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For more on **ITAC-CME web-based mobile application** see http://www.itacccme.com

See **Online** for appendix

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 patients[2–4] 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,[1,2] it has been recommended that VTE occurrence becomes a secondary endpoint in oncological trials.[8]

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,[13–18] substantial knowledge gaps remain.[19] 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.[20,21] 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 US[22] and worldwide[23] despite an absence of direct evidence to support this shifting clinical practice.[23] 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).[20,21,24] 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 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-analyses[27–35] 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-analyses[36,37] have compared short-term LMWH with unfractionated heparin in patients with cancer. One meta-analysis[35] progressively expanded the subgroups of patients with cancer (1016 patients in 2008,[35] 801 in 2011,[38] 1606 in 2014[36]), 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 trial[39] 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 trial[40] 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 study[41] examined in-hospital

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

Panel 2: Treatment of established venous thromboembolism

Initial treatment of established venous thromboembolism (VTE): first 10 days of anticoagulation

International Advisory Panel ranking: 8·75 out of 9·00

1 Low-molecular-weight heparin (LMWH) is recommended for the initial treatment of established VTE in patients with cancer (grade 1B).
Values and preferences: LMWH is easier to use than unfractionated heparin. A once-per-day regimen of LMWH is recommended, unless a twice-per-day regimen is required because of patient characteristics.

2 Fondaparinux and unfractionated heparin can also be used for the initial treatment of established VTE in patients with cancer (grade 2D).
Values and preferences: fondaparinux is easier to use than unfractionated heparin.

3 Thrombolysis in patients with cancer with established VTE should only be considered on a case-by-case basis, with specific attention paid to contraindications, especially bleeding risk—eg, specifically if brain metastasis (guidance, based on evidence of very low quality and the high bleeding risk of thrombolytic therapy).
Values and preferences: an expert opinion is recommended before using thrombolytics, and the procedure should be done in centres with health-care practitioners who have the appropriate expertise.

4 In the initial treatment of VTE, inferior vena cava filters can be considered in the case of contraindication for anticoagulant treatment or in the case of pulmonary embolism recurrence under optimal anticoagulation. Periodic reassessment of contraindications for anticoagulation is recommended, and anticoagulation should be resumed when safe (guidance, based on evidence of very low quality and an unknown balance between desirable and undesirable effects).

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

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

1 LMWHs are preferred over vitamin K antagonists (VKAs) for the treatment of VTE in patients with cancer (grade 1A).
Values and preferences: daily subcutaneous injection might be a burden for patients.

2 LMWH should be used for a minimum of 3 months to treat established VTE in patients with cancer (grade 1A).
Although the two largest studies[25,26] 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).

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

Seven randomised trials and eight meta-analyses have compared the benefit-to-risk ratio of LMWH versus 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,[25] CATCH,[26] LITE,[42] CANTHANOX,[43] ONCENOX[44]) and two in unselected patients with VTE,[45,46] some of whom had cancer (table 1). Four randomised trials[25,26,42,46] assessed VTE recurrence. Three[25,42,46] 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,[26] 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 proportion of patients with symptomatic deep vein thrombosis was significantly reduced in the long-term tinzaparin group (2·7% for long-term tinzaparin *vs* 5·3% for short-term tinzaparin followed by VKA; HR 0·48, 0·24–0·96; p=0·04), although this secondary outcome analysis was not adjusted for multiple comparisons. These results were not completely consistent with previous studies,[25,42–44] possibly because the patient population from the CATCH trial[26] had fewer thrombotic risk factors relative to other similar studies[25,42,43] and was at lower risk of recurrent VTE, as indicated by the lower than expected recurrence of VTE in the tinzaparin followed by the VKA group.

The updated search identified one study[47] that assessed extended LMWH treatment in patients with cancer and residual VTE after an initial 6 months of nadroparin (97 IU/kg twice a 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). No differences were observed in major bleeding between all three groups. Patients with residual VTE were at higher risk of VTE recurrence than were those with no residual VTE, irrespective of whether they received 6 months of extended LMWH prophylaxis or not. In a prospective multicentre cohort study,[48] the proportion of patients with fatal recurrent pulmonary embolism and those patients with fatal bleeding were similar during the first 3 months of anticoagulation in the patients with cancer. After 3 months, case fatality rates associated with recurrent pulmonary embolism decreased, whereas fatal bleeds did not.

One prospective study published since 2013 compared VTE recurrence and major bleeding in 78 patients who received fondaparinux (six [7·7%] had 2·5 mg daily; 17 [21·8%] had 5 mg daily; 51 [65·4%] had 7·5 mg daily; four [5·1%] had 10 mg daily) with 3928 patients with LMWH (189 IU/kg [SD 65] daily) and found no differences in 3-month outcomes.[49]

DOACs have an easier route of administration (oral) compared with anticoagulants that are administered by parenteral injection, and have fixed-dose regimens with predictable anticoagulant effects,[50] but their absorption might be affected by vomiting, which occurs in up to 50·0% of patients with cancer.[51] Drug interactions between DOACs and chemotherapy agents and antiangiogenic therapies are a risk. P-glycoprotein transport and CYP3A4 metabolic pathways are inhibited by tyrosine-kinase inhibitors and hormonal therapies, and are induced by doxorubicin, vinblastine, and dexamethasone,[52] which might result in reduced responses to chemotherapy and an increased risk of bleeding by altering the serum concentration of DOACs. LMWH is not associated with risk of interaction with chemotherapy, nor does it rely on oral intake or gastrointestinal absorption.[50] However, it does have a more onerous route of administration, since it requires weight adjustment of the dose, and can be associated with heparin-induced thrombocytopenia. Before 2015, there were no antidotes to immediately reverse the actions of the DOACs in case of bleeding.[53] However, idarucizumab has become available as an antidote to dabigatran.[54] Two other antidotes are under different stages of development: andexanet alfa is undergoing phase 3 trials as an antidote for the factor Xa inhibitors

	Number of patients	LMWH	Dosage and duration
Patients with cancer			
CLOT; Lee et al (2003)[25]	672	Dalteparin	200 IU/kg once per day for 1 month, 150 IU/kg per day for 5 months
CATCH; Lee et al (2015)[26]	900	Tinzaparin	175 IU/kg once per day for 6 months
LITE; Hull et al (2006)[42]	200	Tinzaparin	175 IU/kg once per day for 3 months
CANTHANOX; Meyer et al (2002)[43]	146	Enoxaparin	1·5 mg/kg once per day for 3 months
ONCENOX; Deitcher et al (2006)[44]	122	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
Unselected patients			
Lopez-Beret et al (2001)[45]	158	Nadroparin	0·1 mL/10 kg twice per day for 3 to 6 months
Romera et al (2009)[46]	241	Tinzaparin	175 IU/kg once per day for 6 months

Early maintenance was 10 days to 3 months. Long-term treatment was more than 3 months. LMWH=low-molecular-weight heparin.

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

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

FIIa=thrombin. FXa=factor Xa. GFR=glomerular filtration rate.

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

(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.[55] The available 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.[56,57] The DOACs are target specific and bind coagulation factor catalytic sites in a dose-dependent manner, which results in a rapid onset of activity (<4 h) that precludes the need for parenteral anticoagulation. LMWH inhibits factor Xa indirectly by activating and accelerating antithrombin action. Several phase 3 clinical trials[58–63] have assessed DOACs in the treatment and prevention of VTE in general patient populations. Many of these studies included small subgroups of patients with cancer (2·0–10·0%) that might not reflect the overall population of patients with cancer because stringent inclusion criteria were used. Additionally, consistent with recommended treatment for VTE in the general population, the comparator in these studies was a VKA.

The EINSTEIN trials (3449 patients in EINSTEIN-DVT;[64] 4832 patients in EINSTEIN-PE[65]) compared rivaroxaban with initial enoxaparin followed by VKA. 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).[66] 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, 0·23–1·23), and in a composite of clinically relevant non-major and major bleeding (15·2% *vs* 15·8%; HR 0·93, 0·62–1·41).

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];[67] RE-COVER II [1280 patients treated with dabigatran *vs* 1288 patients treated with VKA][68]). 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 trial[70] (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 0·56, 95% CI 0·13–2·37) and major bleeding (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 trial[72] randomised 8292 participants to edoxaban or a VKA for 3–12 months. Patients with a 30–50 mL/min glomerular filtration rate received a 50·0% 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 0·16–1·85), with no significant differences in major and clinically relevant non-major bleeding (HR 0·72, 0·40–1·30). In all 771 patients with cancer, VTE recurrence was similar between treatments (HR 0·53, 0·28–1·00), and clinically relevant bleeding was significantly lower with edoxaban than with a VKA (HR 0·64, 0·45–0·92). A randomised study directly comparing edoxaban with LMWH in the secondary prevention of VTE in patients with cancer is underway (NCT02073682).

Seven meta-analyses[74–80] have examined the role of DOACs in the treatment and secondary prevention of acute VTE since 2013. When including six randomised DOAC trials with a documented cancer subgroup,[64,65,67,68,70,72] VTE recurrence was 3·9% (23 of 595 patients) with DOAC versus 6·0% (32 of 537 patients) with VKA in 1132 patients with cancer.[74] The proportion of patients who had VTE while on DOAC treatment was reduced by approximately 35·0% compared with that in the VKA group, although not significantly (OR 0·63, 95% CI 0·37–1·10). The proportion of patients with major bleeding (3·2% in the DOAC group *vs* 4·2% in the heparin followed by VKA group; OR 0·77, 0·41–1·44) and minor bleeding (14·5% *vs* 16·5%; OR 0·85, 0·62–1·18) were similar between the two treatment groups. Another meta-analysis[75] of these trials reported consistent findings. When analysing the same six clinical trials, but with a broader inclusion of 1581 patients with cancer, the composite efficacy endpoint combining recurrent VTE and VTE-related death was significantly reduced with a DOAC (27 [3·4%] of 805 patients with a DOAC *vs* 46 [5·9%] of 776 patients with a VKA; RR 0·57, 0·36–0·91) with no differences in major bleeding between treatments (RR 0·77, 0·44–1·33).[76] Meta-analyses that were limited to fewer phase 3 trials reported similar findings.[77,78]

In the absence of studies that compared DOACs with LMWH in patients with cancer, one pairwise meta-analysis included nine prospective studies of patients with cancer with acute symptomatic deep vein thrombosis or pulmonary embolism, or both, randomly assigned to receive LMWH alone, a DOAC, or a VKA.[79] Although LMWH was associated with reduced VTE recurrence versus VKA (RR 0·52, 95% CI 0·36–0·74), DOACs had a similar VTE recurrence to VKA (RR 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[80] 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[81] 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,[20] including one systematic review[82] 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 study[83] 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 study[84] 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-analysis[85] 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 half of cancer-related VTEs are incidentally diagnosed,[86] partly owing to differences in CT technology and clinical criteria (ie, when retrospectively analysed, half of the incidental pulmonary embolism cases were symptomatic). However, data on the clinical implications of incidental VTE in cancer are scarce. One pooled analysis[88] of individual patient data from 11 observational studies and ongoing registries (926 patients) supported LMWH over VKA for incidental pulmonary embolism treatment; although VTE recurrence was similar between LMWH and VKA, a higher risk of major haemorrhage was associated with VKA.

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).[10,89–91]

Patients with cancer undergoing surgery

A systematic review[92] 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-analysis[93] 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-analysis[94] and a meta-analysis in general surgery,[95] 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 study[97] 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 study[98] 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 study[99] 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.

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 with 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).

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.[20] The updated search identified one randomised trial (CERTIFY)[100] 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).[101] 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 reduce the VTE relative risk compared with placebo in hospital-admitted patients with cancer (RR 0·91, 95% CI 0·21–4·0; I^2 68%).

The MAGELLAN trial[102] 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)[103–110] and six randomised clinical trials[111–116] comparing anticoagulant prophylaxis with no intervention or placebo in ambulatory patients receiving systemic anticancer therapy. Overall, a significant 45·0% reduction in VTE occurrence was reported across the six meta-analyses assessing the safety and efficacy of LMWH compared with no intervention or placebo.[103–106,108,109] 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).[103,105] 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[105] reported that patients were 65·0% more likely to experience a bleeding event with LMWH (7875 patients in the total population across the 11 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[106–108] 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[114] 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,

***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 cancers 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[10]

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.[89] Several other retrospective and prospective studies have further validated this risk score, although rates vary between studies.[89,90]

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.[89] Patients with a score of ≥5 have a 35·0% risk of developing VTE within 6 months after diagnosis of cancer.[89] 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[91]

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.[90]

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, 0·187–0·935; p=0·039). The prospective, open-label, randomised, multicentre CONKO-004 trial[112] 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 within the first 3 months of the study (HR 0·12, 95% CI 0·03–0·52), with no difference in major bleeding, overall survival, or progression-free survival between treatment groups.

Three randomised clinical trials (TOPIC-1[113] [353 patients], TOPIC-2[113] [547 patients], and FRAGMATIC[111] [2202 patients]) and one meta-analysis[110] assessed VTE prophylaxis in patients with lung cancer. The TOPIC study included two double-blind trials comparing the LMWH certoparin (3000 IU per day) with placebo in ambulatory patients with metastatic breast cancer (TOPIC-1) or with stage III or IV non-small-cell lung carcinoma (NSCLC; TOPIC-2). VTE occurrence did not differ between treatment groups for TOPIC-1 or TOPIC-2. However, a separate post-hoc analysis showed that certoparin significantly reduced VTE occurrence in patients with stage IV NSCLC compared with placebo (3·5% with cetropatin *vs* 10·2% with placebo, p=0·032; appendix p 39) without increasing bleeds. Mortality was not different between groups. The FRAGMATIC[111] multicentre, open-label, randomised trial assessed LMWH prophylaxis on 1-year survival in newly diagnosed patients with small-cell lung cancer or those with NSCLC of any stage. LMWH did not increase overall survival or metastasis-free survival. However, VTE risk was lower with LMWH than without primary prophylaxis (5·5% *vs* 9·7%; HR 0·57, 95% CI 0·42–0·79). Major bleeding did not differ between groups, but a composite measure of major plus clinically relevant non-major bleeding was higher with the addition of LMWH. In the meta-analysis (2185 patients),[110] 1-year and 2-year survival benefits of anticoagulation (VKA or heparin) were reported in limited-stage, but not advanced-stage, patients with cancer. Anticoagulation significantly improved overall 1-year (RR 1·18, 95% CI 1·06–1·32, p=0·004) and 2-year (RR 1·27, 1·04–1·56, p=0·02) survival in patients with lung cancer. However, subgroup analyses indicated that survival benefits were statistically significant in limited-stage patients with cancer (RR 1·30, 1·03–1·65, p=0·03 for 1-year survival; RR 1·33, 1·05–1·68, p=0.02 for 2-year survival) but not advanced-stage patients with cancer (RR 1·09, 0·87–1·36, p=0·48 for 1-year survival; RR 1·16, 0·77–1·73 for 2-year survival), and in small-cell lung cancer (RR 1·21, 1·07–1·38, p=0·003 for 1-year survival; RR 1·29, 1·01–1·65, p=0·04 for 2-year survival) but not in patients with NSCLC (RR 1·10, 0·87–1·39 for 1-year survival; RR 1·24, 0·86–1·78 for 2-year survival). Compared with control, anticoagulation significantly reduced the VTE risk (RR 0·55, 0·31–0·97).

Since the 2013 CPGs, one new meta-analysis[107] 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)[116] 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[115] of the PROTECHT trial,[117] 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.[115]

Two randomised studies (with 342 patients[118] and 991 patients[119]) and one meta-analysis (6632 patients[120]) 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,[121] 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[122] assessed VTE prophylaxis in paediatric patients with cancer with tunnelled 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[123] 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[124] assessed the risk of intracranial haemorrhage associated with VTE anti-coagulation 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.[125] 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[126] (2208 patients) 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[127] 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[128] 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[129] (24401 patients), the incidence of thrombocytopenia was significantly greater with unfractionated heparin (1·4%) than with LMWH (0·5%). Another retrospective study[130] reported outcomes associated with concomitant VTE and thrombo-cytopenia 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[131] 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.

Panel 5: VTE treatment in unique situations

International Advisory Panel ranking: 8·46 out of 9·00

1. A brain tumour per se is not a contraindication for anticoagulation for established venous thromboembolism (VTE; grade 2C).
2. For the treatment of established VTE in patients with cancer with a brain tumour, we prefer low-molecular-weight heparin (LMWH; guidance).
3. We recommend the use of LMWH or unfractionated heparin (UFH) started postoperatively for the prevention of VTE in patients with cancer undergoing neurosurgery (grade 1A).
4. Primary prophylaxis of VTE in medically treated patients with cancer and with brain tumour who are not undergoing neurosurgery is not recommended (grade 1B).
5. In the presence of severe renal failure (creatinine clearance <30 mL/min), we suggest using UFH followed by early vitamin K antagonists (possible from day 1) or LMWH adjusted to anti-Xa level for the treatment of established VTE (guidance, in the absence of data and an unknown balance between desirable and undesirable effects).
6. In patients with severe renal failure (creatinine clearance <30 mL/min), an external compression device can be applied, and pharmacological prophylaxis should be considered on a case-by-case basis; in patients with severe renal failure (creatinine clearance <30 mL/min), UFH can be used on a case-by-case basis (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the level of VTE risk).
7. In patients with cancer and thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is >50 g/L and bleeding is not evident; for patients with a platelet count <50 g/L, decisions on treatment and dose should be made on a case-by-case basis with the utmost caution (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk *vs* VTE risk).
8. In patients with cancer with mild thrombocytopenia, a platelet count >80 g/L, pharmacological prophylaxis might be used; if the platelet count is <80 g/L, pharmacological prophylaxis should only be considered on a case-by-case basis and careful monitoring is recommended (guidance, in the absence of data and a balance between desirable and undesirable effects depending on the bleeding risk *vs* VTE risk).
9. In pregnant patients with cancer, standard treatment for established VTE and standard prophylaxis should be implemented (guidance, in the absence of data and based on the contraindication of vitamin K antagonists during pregnancy).

Search strategy and selection criteria

The updated literature search (appendix p 3) for all studies published in French or English between November, 2010, and January, 2016, was done by the Institut National du Cancer using MEDLINE and PubMed Central databases with the following subject headings: "cancer", "VTE", "anticoagulant drugs", and "devices". Additional key articles and other clinical practice guidelines[13,15–17,132] on overlapping clinical questions were consulted and included. The search included meta-analyses, systematic reviews, randomised clinical trials, or non-randomised prospective or retrospective studies (in the absence of randomised clinical trials). Suitable articles were selected using article selection grids for each clinical question.

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 anticancer drug interactions. More than 35 clinical trials are underway to compare DOACs with LMWH.

Contributors

The Institut National du Cancer (INCa) designed the methods used to develop the clinical practice guidelines, and provided logistical support by doing the MEDLINE OVID reference searches. The guidelines were developed by an independent working group of academic clinicians, researchers, and experts (all authors of this Review). DF and HB were the acting coordinators for the working group. They coordinated the preparation of the manuscript, and the contribution of the authors. DF and JD were the methodologists. They assessed the methodological strength and clinical relevance of the articles identified by the literature search (critical appraisal), the article selection, and the extraction of the data into evidence tables. All authors reviewed and approved the INCa literature search, the critical appraisal of articles, the article selection, the data extraction, and the evidence tables. DF wrote the first draft of the literature review. All working group members edited and contributed to the development of the literature review. Guideline consensus was achieved during two meetings, at which the working group collectively drafted and ranked the recommendations. The manuscript was reviewed by a multidisciplinary advisory panel of 56 experts (eg, oncology, haematology, palliative medicine, internal medicine, vascular medicine, biology, and epidemiology). All working group members approved the final recommendations and the manuscript.

Declaration of interests

DF was a subinvestigator in the Apex study with Portola, and reports non-financial support from LEO Pharma, Aspen Pharmacare, and Pfizer, outside the submitted work. HB reports grants and personal fees from the Thrombosis Research Institute (London), and personal fees from Bayer Pharmaceuticals, and Sanofi-Aventis, outside the submitted work. BB reports personal fees from Sanofi, Pfizer, ROVI Laboratories, Daiichi Sankyo, Bayer Pharmaceuticals, and Aspen Pharmacare, outside the submitted work. FC reports personal fees from Bayer Pharmaceuticals, and non-financial support from LEO Pharma and Aspen Pharmacare, outside the submitted work. PD reports personal fees from a pooled funding source (Bayer Pharmaceuticals, Daiichi Sankyo, LEO Pharma, Aspen Pharmacare, and Celgene) and from Aspen Pharmacare and LEO Pharma, outside the submitted work. AAK reports personal fees and non-financial support from Janssen, LEO Pharma, Sanofi, Pfizer, and Angiodynamics, and personal fees from Bayer Pharmaceuticals, Roche, Daiichi Sankyo, and Boehringer Ingelheim, outside the submitted work. IP reports personal fees from Bayer Pharmaceuticals, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer, outside the submitted work. JD reports grants and personal fees from Boehringer Ingelheim, and personal fees from Janssen, Pfizer, Bayer Pharmaceuticals, Bristol-Myers Squibb, Sanofi, and Daiichi Sankyo, outside the submitted work. AK reports grants and personal fees from Bayer Pharmaceuticals, and personal fees from Boehringer Ingelheim, Daiichi Sankyo, Sanofi, and Janssen, outside the submitted work. SS declares no competing interests.

Acknowledgments

The original 2013 international clinical practice guidelines were funded in part by the Institut National du Cancer with the stipulation that the guidelines would be updated every 4 years. The present update was funded by the International Initiative on Thrombosis and Cancer, the international branch of the Groupe Francophone Thrombose et Cancer—a not for profit organisation. Logistical support was provided by CME solutions, ULC (Montreal, Canada).

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