2019 international clinical practice guidelines for 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 a high risk of VTE recurrence and bleeding during anticoagulant therapy. The International Initiative on Thrombosis and Cancer is an independent academic working group aimed at establishing a global consensus for the treatment and prophylaxis of VTE in patients with cancer. The International Initiative on Thrombosis and Cancer last updated its evidence-based clinical practice guidelines in 2016 with a free, web-based mobile phone application, which was subsequently endorsed by the International Society on Thrombosis and Haemostasis. The 2019 International Initiative on Thrombosis and Cancer clinical practice guidelines, which are based on a systematic review of the literature published up to December, 2018, are presented along with a Grading of Recommendations Assessment Development and Evaluation scale methods, with the support of the French National Cancer Institute. These guidelines were reviewed by an expanded international advisory committee and endorsed by the International Society on Thrombosis and Haemostasis. Results from head-to-head clinical trials that compared direct oral anticoagulant with low-molecular-weight heparin are also summarised, along with new evidence for the treatment and prophylaxis of VTE in patients with cancer.

Introduction

Cancer-associated thrombosis is the second leading cause of death in cancer patients after disease progression.[1] Patients with cancer are four to seven times more likely to develop venous thromboembolism (VTE) than are patients without cancer. Furthermore, the incidence of cancer-associated thrombosis is increasing worldwide.[2–4] Multiple factors are responsible for this increase in VTE incidence, including cancer type, the use of central venous catheters for chemotherapy, and other associated surgical and medical anticancer treatments (eg, radiotherapy, antiangiogenic agents, immunomodulatory drugs, hormonal therapy, and erythropoiesis-stimulating agents).[5–7]

Treatment of established VTE in patients with cancer is complex. Systemic chemotherapy can lead to drug–drug interactions that could alter the efficacy of anticancer treatments or oral anticoagulants, and could also cause thrombocytopenia, which increases the risk of bleeding. Ascertaining the need for VTE prophylaxis in patients with cancer is another challenge due to widely varying risks of VTE development and bleeding across different cancer types, disease stages, and anticancer treatments. Options for the treatment[8–10] and prevention[11,12] of cancer-associated thrombosis have also expanded with clinical trials that have compared direct oral anticoagulants and low-molecular-weight heparin (LMWH) in patients with cancer. Although direct oral anticoagulants offer advantages over parenteral anticoagulants and show a favourable risk–benefit profile, these agents pose challenges in terms of oral administration, drug–drug interactions, and bleeding risk, which necessitate appropriate patient selection for their use (table 1).[13,14]

The International Initiative on Thrombosis and Cancer (ITAC) developed the first international evidence-based clinical practice guidelines[15,16] in 2013 to provide clinicians with practical and accessible recommendations for the treatment and prevention of cancer-associated thrombosis. The ITAC clinical practice guidelines use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[17] and are available through an internationally accessible, free, web-based mobile application (app). The clinical practice guidelines and the app were updated in 2016[18] and subsequently endorsed by the International Society on Thrombosis and Haemostasis (ISTH). This 2019 update of the ITAC guidelines includes a review of new evidence on anticoagulants for patients with cancer, particularly new data for risk stratification of VTE for decision making on primary prophylaxis strategies, and the use of direct oral anticoagulants for the prevention and treatment of cancer-associated thrombosis.

Guideline development

The guideline development process incorporates measures to ensure impartiality and transparency while establishing the recommendations. All iterations of the ITAC guidelines are an academic initiative by the international branch of the Group Francophone Thrombose et Cancer; a not-for-profit organisation based at St Louis-Hospital, Paris, France. Authors, including the independent external global advisory panel (appendix p 90), were not paid for their contributions to the preparation of the ITAC clinical practice guidelines update, and no manuscript preparation services were used.

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For more on the **ITAC-CME Treatment Guidelines Mobile App and on the International Thrombosis and Cancer Initiative (ITAC)** see www.itaccme.com

See Online for appendix

For more on the **Group Francophone Thrombose et Cancer** see www.thrombose-cancer.com

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	FIIa	FXa	FXa	FXa
Dosing	Therapeutic: 150 mg twice daily; 110 mg twice daily for patients ≥80 years following at least 5 days of parenteral anticoagulant	Therapeutic: 15 mg twice daily for 3 weeks followed by 20 mg once daily	Therapeutic: 10 mg twice daily for 7 days, followed by 5 mg twice daily	Therapeutic: 60 mg once daily 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; inter-individual variability: 30–40%	~50%; interindividual variability: 30%	~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: dose adjustment recommended (GFR 15–29 mL/min); not recommended if GFR <15 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: dose adjustment recommended (GFR 15–29 mL/min); 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 required; hepatic disease with caoagulopathy 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 caoagulopathy and clinically 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, CYP2J2	P-glycoprotein inducers or inhibitors, CYP3A4	P-glycoprotein inducers or inhibitors, CYP3A4
Specific trials in patients with cancer	None	SELECT D;[9] CASSINI[11]	ADAM-VTE;[10] AVERT[12]	HOKUSAI[8]
Specific antidote	Idarucizumab, aripazine	Andexanet alfa, aripazine	Andexanet alfa, aripazine	Andexanet alfa, aripazine

GFR=glomerular filtration rate.

Table 1: **Characteristics of direct oral anticoagulants in patients with cancer**

Guideline development methodology

Similar to the 2013[15,16] and 2016[18] ITAC guideline updates, the present ITAC update was prepared by an independent working group of 14 members, using GRADE methodology (panel 1) and methodological support from the Institut National du Cancer (ie, an updated literature search using MEDLINE and several other databases, such as Embase and the Cochrane Central Register of Controlled Trials). The ITAC working group comprises independent international academic clinicians and methodology experts from various specialties (ie, experts from oncology, haematology, internal medicine, vascular medicine, biology, and epidemiology), including two methodologists (CF and HR) and two guideline development coordinators (DF and JD). Articles identified for inclusion from the literature search and selection process (from Jan 1, 2015, to Dec 31, 2018; see search strategy and selection criteria) underwent a critical appraisal, which included an assessment of the articles' methodological strength and clinical relevance by the two methodologists. The methodologists' decision was then approved by the rest of the working group. All articles identified in the literature search, with the methodological support of the Institut National du Cancer, were analysed according to the selection criteria. Every step of the critical appraisal process has been documented and is available for review in the appendix. Data were independently extracted into tables by both methodologists. Any identified discrepancies were resolved by all members of the working group. Conclusion tables that summarise information from the critical appraisal and data extraction were prepared for

each clinical question and were used to develop recommendations according to GRADE methodology.[17] The ITAC working group convened regularly through teleconferences, the 2017–18 annual meetings of the American Society of Hematology (ASH), and the 2018 ISTH to discuss the available evidence (data extraction tables and conclusion tables are provided in the appendix) and formulate the recommendations. Minutes from these meetings have been documented and stored by the ITAC methodologists and are available for review by Institut National du Cancer, ISTH, or any other relevant organisation. A detailed description of the methodology used for the literature search, the guideline development, and results of the data extraction are provided in the appendix.

Independent external advisory panel

The updated 2019 guidelines were peer reviewed by an international panel of 83 experts encompassing medical and surgical specialties involved in the management of patients with cancer, including one nurse, and two volunteer patient representatives. Panel experts were identified by all the ITAC working group members on the basis of their knowledge, clinical expertise, publication record, and contributions to their field. Panel members were given an evaluation grid (9-point scale, ranging from "don't agree" to "agree" [0–9]) to complete. Feedback was analysed by the working group and revisions were incorporated into this Review. This Review was then submitted to the ISTH Guidance and Guidelines Committee for commenting, which subsequently endorsed the methodology used to create these guidelines.

Guideline recommendations

The ITAC guidelines use GRADE methodology to make recommendations for VTE treatment and prophylaxis for patients with cancer. Although the best quality data are from large, phase 3 randomised controlled trials, patients with less frequently seen cancers are normally excluded, either because of cancer type or because of other factors, such as risk of bleeding and thrombocytopenia. Moreover, patients with primary brain tumours, active CNS metastases, and haematological malignancies, especially acute leukaemias, are frequently excluded from these trials. Therefore, data on the treatment and prophylaxis of VTE in these patient subgroups are scarce, and our GRADE level recommendations are based on evidence from studies that often exclude these patients.

Treatment of established VTE

Recommendations for treatment of established VTE in patients with cancer are shown in panel 2. Six randomised clinical trials comparing direct oral anticoagulants to vitamin K antagonists have been done in unselected patients.[19–24] Apixaban, dabigatran, edoxaban, and rivaroxaban were shown to be non-inferior when compared with vitamin K antagonists for the treatment of non-cancer VTE, with similar or lower rates of major bleeding and clinically relevant non-major bleeding. Direct oral anticoagulants are endorsed by several societies, such as American College of Chest Physicians[25] and European Society of Cardiology,[26] as first-line treatment for VTE in the general population.[25,26] Randomised controlled trials that have assessed the efficacy and safety of direct oral anticoagulants for cancer-associated thrombosis are reviewed herein (table 2).

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 could 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 an 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 considered 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

Initial treatment

LMWH, unfractionated heparin, or fondaparinux (followed by a vitamin K antagonist)

The recommendation on initial treatment with parenteral anticoagulation is unchanged since the 2016 guideline update. For the first 5–10 days of anticoagulant treatment, LMWH is recommended, with fondaparinux and unfractionated heparin as alternative treatment options.

Panel 2: Treatment of established venous thromboembolism (VTE)

Initial treatment of established VTE

International Advisory Panel ranking: 8·18 out of 9

1 Low-molecular-weight heparin (LMWH) is recommended for the initial treatment of established VTE in patients with cancer when creatinine clearance is ≥30 mL per min (grade 1B). Values and preferences: LMWH is easier to use than unfractionated heparin. A regimen of LMWH, taken once per day, is recommended, unless a twice-per-day regimen is required because of patient characteristics (eg, fragile patients who are at risk of haemorrhage).
2 For patients who do not have a high risk of gastrointestinal or genitourinary bleeding, a regimen of rivaroxaban (in the first 10 days) or edoxaban (started after at least 5 days of parenteral anticoagulation) can also be used for the initial treatment of established VTE in patients with cancer when creatinine clearance is ≥30 mL/min (grade 1B).
3 Unfractionated heparin can also be used for the initial treatment of established VTE in patients with cancer when LMWH or direct oral anticoagulants are contraindicated, or not available (grade 2C).
4 Fondaparinux can also be used for the initial treatment of established VTE for patients with cancer (grade 2D). Values and preferences: fondaparinux is easier to use than unfractionated heparin.
5 Thrombolysis in patients with cancer with established VTE can only be considered on a case-by-case basis, with specific attention paid to contraindications, especially bleeding risk—eg, 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 appropriate expertise.
6 In the initial treatment of VTE, inferior vena cava filters may be considered when anticoagulant treatment is contraindicated or, in the case of pulmonary embolism, when recurrence occurs 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 (up to 6 months) and long term (beyond 6 months)

International Advisory Panel ranking: 8·09 out of 9

1 LMWHs are preferred over vitamin K antagonists for the treatment of VTE in patients with cancer when creatinine clearance is ≥30 mL/min (grade 1A). Values and preferences: daily subcutaneous injection can represent a burden for patients.
2 Direct oral anticoagulants are recommended for patients with cancer when creatinine clearance is ≥30 mL/min in the absence of strong drug–drug interactions or gastrointestinal absorption impairment (grade 1A). Use caution in patients with gastrointestinal tract malignancies, especially upper gastrointestinal tract malignancies, as the available data show increased risk of gastrointestinal tract bleeding with edoxaban and rivaroxaban. Data for other direct oral anticoagulants are needed as it is not clear whether other direct oral anticoagulants will have the same risk profile.
3 LMWH or direct oral anticoagulants should be used for a minimum of 6 months to treat established VTE in patients with cancer (grade 1A).
4 After 6 months, termination or continuation of anticoagulation (LMWH, direct oral anticoagulants, or vitamin K antagonists) should be based on individual evaluation of the benefit–risk ratio, tolerability, drug availability, patient preference, and cancer activity (guidance in the absence of data).

Treatment of VTE recurrence in patients with cancer under anticoagulation

International Advisory Panel ranking: 8·0 out of 9

In the event of VTE recurrence, three options can be considered: (1) increase LMWH by 20–25% or switch to direct oral anticoagulants; (2) for direct oral anticoagulants, switch to LMWH; and (3) for vitamin K antagonists, switch to LMWH or direct oral anticoagulants (guidance based on evidence of very low quality and an unknown balance between desirable and undesirable effects). Values and preferences: individual decision. Effect of therapy should be monitored by improvement of symptoms.

Treatment of established catheter-related thrombosis

International Advisory Panel ranking: 8·19 out of 9

1 For the treatment of symptomatic catheter-related thrombosis in patients with cancer, anticoagulant treatment is recommended for a minimum of 3 months and as long as the central venous catheter is in place; in this setting, LMWHs are suggested and direct comparisons between LMWHs, direct oral anticoagulants, and vitamin K antagonists have not been made (guidance).
2 In patients with cancer with catheter-related thrombosis, the central venous catheter can be kept in place if it is functional, well positioned, and not infected, with a good resolution of symptoms under close surveillance while anticoagulation therapy is administered. No standard approach in terms of duration of anticoagulation is established (guidance).

Two new studies[27,28] reported results consistent with previous data. One updated meta-analysis[27] of patient subgroups across six studies (which included 446 patients with cancer)[27] showed a greater reduction in mortality with LMWH than with unfractionated heparin (Peto odds ratio [OR] 0·53, 95% CI 0·33–0·85, p=0·009).

	Treatment of acute cancer-associated thrombosis			VTE prophylaxis	
	HOKUSAI VTE-CANCER[8]	SELECT-D[9]	ADAM-VTE[10]	CASSINI[11]	AVERT[12]
Number of randomised patients	1050	406	300	841	574
Trial design	Non-inferiority	Pilot	Superiority	Superiority	Superiority
Direct oral anticoagulants	Edoxaban (dalteparin for at least 5 days, followed by edoxaban 60 mg once daily, for 6–12 months)	Rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily for 2–6 months)	Apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily for 6 months)	Rivaroxaban (10 mg once daily)	Apixaban (2·5 mg twice daily)
Comparator	Low-molecular-weight heparin (daltaparin 200 IU/kg once daily for the first 30 days, followed by 150 IU/kg daily)	Low-molecular-weight heparin (daltaparin 200 IU/kg once daily for the first 30 days, followed by 150 IU/kg daily)	Low-molecular-weight heparin (daltaparin 200 IU/kg once daily for the first 30 days, followed by 150 IU/kg daily)	Placebo	Placebo
Inclusion criteria	Patients with cancer and symptomatic or incidental acute VTE	Patients with cancer and symptomatic or incidental VTE and deep vein thrombosis	Patients with cancer and symptomatic or incidental acute VTE	Ambulatory patients with cancer at intermediate-to-high risk for VTE (Khorana score ≥2) who were initiating chemotherapy	Ambulatory patients with cancer at intermediate-to-high risk for VTE (Khorana score ≥2) who were initiating chemotherapy
Cancers included	Cancer other than basal-cell or squamous-cell skin cancer	Active solid or haematological cancers, other than basal-cell or squamous-cell skin carcinoma; patients with upper gastrointestinal malignancy were excluded	Active solid or haematological cancers, other than basal-cell or squamous-cell skin carcinoma	Solid tumours or lymphomas with locally advanced or metastatic disease; primary brain tumour, known brain metastases, or haematological malignancies (except lymphoma) were excluded	Cancer other than basal-cell or squamous-cell skin carcinoma, acute leukaemia, or myeloproliferative neoplasms
Primary outcome measures	Composite measure of recurrent VTE or major bleeding within 12 months after randomisation	VTE recurrence in the 6 months after randomisation	Major bleeding including fatal bleeding	Composite measure of deep vein thrombosis, pulmonary embolism, and VTE-related death; major bleeding	Objectively documented VTE (proximal deep vein thrombosis, and pulmonary embolism) over a 6-month follow-up major bleeding
Primary outcome results	Edoxaban 12·8%; dalteparin 13·5%	Rivaroxaban 4%; dalteparin 11%	Apixaban 0%; dalteparin 2·1%	Composite on-treatment: rivaroxaban 2·6%, placebo 6·4%; composite up to 6 months: rivaroxaban 6·0%, placebo 8·8%; major bleeding: rivaroxaban 2·0%, placebo 1·0%	VTE: apixaban 4·2%, placebo 10·2%; major bleeding: apixaban 3·5%, placebo 1·8%
Major secondary outcomes	Recurrent VTE: edoxaban 7·9%, dalteparin 11·3%; major bleeding: edoxaban 6·9%, dalteparin 4·0%	Major bleeding: rivaroxaban 13%, dalteparin 4%; clinically relevant non-major bleeding: rivaroxaban 6%, dalteparin 4%	Recurrent VTE, including deep vein thrombosis, pulmonary embolism, and fatal pulmonary embolism: apixaban 3·4%, dalteparin 14·1%; major, fatal, and clinically relevant non-major bleeding: apixaban 9·0%, dalteparin 9·0%	Clinically relevant non-major bleeding: rivaroxaban 2·7%, placebo 2·0%	Clinically relevant non-major bleeding: apixaban 7·3%, placebo 5·5%

VTE=venous thromboembolism.

Table 2: **Randomised clinical trials assessing the efficacy and safety of direct oral anticoagulants in the treatment and prophylaxis of cancer-associated thrombosis**

Another meta-analysis[28] assessing the first 5–10 days of anticoagulant therapy in patients with cancer analysed mortality at 3 months in five studies (418 patients in total), and recurrent VTE in three studies (422 patients in total). Compared with unfractionated heparin, LMWH was associated with no significant difference in mortality (risk ratio [RR] 0·66, 95% CI 0·40–1·10) and VTE recurrence (RR 0·69, 0·27–1·76). Fondaparinux was not statistically different from LMWH or unfractionated heparin with regard to mortality at 3 months (RR 1·25, 95% CI 0·86–1·81), recurrent VTE (RR 0·93, 0·56–1·54), or major (RR 0·82, 0·40–1·66) or minor (RR 1·53, 0·88–2·66) bleeding.

Direct oral anticoagulants

Rivaroxaban or edoxaban (after at least 5 days of parenteral anticoagulation) are now recommended as initial treatment options in patients with cancer-associated thrombosis who are not at high risk of gastrointestinal or genitourinary bleeding. The determination of bleeding risk associated with gastrointestinal or genitourinary cancer types involves consideration of patient-specific factors that might include the extent of the cancer and its propensity for bleeding.

Differences exist across direct oral anticoagulants in anticoagulant initiation within the first days of treatment. In randomised controlled trials involving patients without

cancer, 5 days of a parenteral agent, typically LMWH, is required before initiating dabigatran[21] or edoxaban[24] at standard dosage. For apixaban[23] and rivaroxaban[19,20] treatment with a parenteral agent is not needed, but a higher dose is given for the first 7 days with apixaban and the first 21 days with rivaroxaban. Edoxaban[8] and rivaroxaban[9] are two direct oral anticoagulants that have been assessed in published randomised controlled trials of patients with cancer-associated thrombosis (Eastern Cooperative Oncology Group performance status of ≤2, bodyweight >40–60 kg, and creatinine clearance >30 mL/min), which used a LMWH (dalteparin) as a comparator. Edoxaban and rivaroxaban were non-inferior to dalteparin with respect to the proportion of patients who had recurrent VTE and survival at 6 months, and who had a higher risk of bleeding. If a patient with cancer needs to be treated with a direct oral anticoagulant, 5 days of a parenteral agent are required before starting edoxaban at standard dose, or at a reduced dose when specific criteria apply (eg, bodyweight ≤60 kg, creatinine clearance ≤50 mL/min, or concomitant use of strong P-glycoprotein inhibitors). Rivaroxaban is given at 15 mg twice daily for the first 21 days of anticoagulation, then switched to 20 mg daily. Preliminary data (presented as an abstract)[10] from a randomised controlled trial of 300 patients using apixaban for cancer-associated thrombosis showed that when compared with LMWH, apixaban is not associated with a higher risk of bleeding.

Inferior vena cava filters

The recommendation on the use of inferior vena cava filters for the initial treatment of VTE is unchanged since the 2016 guideline update. Inferior vena cava filters might be considered if anticoagulant treatment is contraindicated, or if there is recurrent pulmonary embolism despite appropriate anticoagulant therapy. Eight new retrospective studies on the use of inferior vena cava filters in patients with cancer have been published since the 2016 ITAC guidelines,[18,29–36] with similar limitations as previous studies (eg, retrospective design and small sample size). The findings were consistent with the previous ITAC guidelines,[15,18] which showed that inferior vena cava filters in patients with cancer appear to increase the risk of recurrent VTE, with no evidence of improvement in survival. One new propensity-matched retrospective cohort analysis[37] examined patients who developed symptomatic VTE recurrence on anticoagulant therapy, including a subgroup of patients with cancer who received inferior vena cava filters after recurrent VTE in the first 3 months of anticoagulant therapy. For patients with deep vein thrombosis, propensity score-matched groups, with or without filter insertion, showed no significant difference in death (three [17·7%] of 17 patients *vs* six [12·2%] of 49 patients, p=0·56). For patients who had a pulmonary embolism, propensity score-matched groups showed a significant decrease in all-cause death with filter insertion compared with no filter insertion (one [2·1%] of 48 patients *vs* 23 [25·3%] of 91 patients, p=0·02); however, the proportion of patients with pulmonary embolism-related mortality was not significantly different between the groups (one [2·1%] of 48 patients *vs* 16 [17·6%] of 91 patients, p=0·08).

Thrombolysis

Data for thrombolysis in patients with cancer are scarce. Individual patient decision making in consultation with clinicians experienced with parenteral or catheter directed thrombolysis is advised.

Early maintenance (up to 6 months) and long-term (beyond 6 months) treatment

Unchanged from the 2016 clinical practice guidelines, LMWHs are the preferred treatment over vitamin K antagonists for cancer-associated thrombosis. Edoxaban and rivaroxaban are now also recommended for early maintenance and long-term treatment of VTE in patients with cancer without contraindications, including risk of strong drug–drug interactions or impaired gastrointestinal absorption or excessive bleeding risk, especially patients with gastrointestinal or urogenital malignancies. A list of drugs that can potentially interfere with the action of direct oral anticoagulants is included in the appendix (p 88) and should be considered in clinical decision-making about direct oral anticoagulant use. Patients who were receiving these drugs were excluded from the randomised trials assessing direct oral anticoagulants for the prevention and treatment of cancer-associated thrombosis.

LMWH versus vitamin K antagonists

Since the 2016 ITAC guidelines, no new randomised controlled trials comparing LMWH with vitamin K antagonists have been published. LMWH is preferred over vitamin K antagonists for early maintenance treatment of cancer-associated thrombosis. The 2016 guidelines reviewed five randomised controlled trials in patients with cancer (CANTHANOX, CLOT, LITE, ONCENOX, and CATCH), two randomised controlled trials in unselected patients with cancer patient subgroups, and nine meta-analyses that reported on the benefits and risks of LMWH versus short-term heparin, followed by vitamin K antagonists in the early maintenance and long-term treatment of confirmed venous thromboembolism.[18] One new meta-analysis[38] reported on the risk of intracranial haemorrhage with LMWH compared with vitamin K antagonists in patients with cancer (n=2089). There were no significant differences in risk of major bleeding between the two anticoagulant therapies during the first 6 months of treatment (RR 0·49, 95% CI 0·10–2·3).[38]

Direct oral anticoagulants versus vitamin K antagonists

Several randomised controlled trials have assessed direct oral anticoagulants in the treatment and prevention of VTE in the general population.[19–24] Direct oral anticoagulants have been shown to be non-inferior to vitamin

K antagonists for the treatment and prevention of recurrent VTE and are associated with a similar or lower risk of bleeding. Consistent with results obtained in studies that predominantly included patients without cancer, direct oral anticoagulants were at least non-inferior to vitamin K antagonists for the prevention of VTE recurrence in patients with cancer subgroups (approximately 5% of patients) from these trials (OR 0·63, 95% CI 0·37–1·10), with no difference in major bleeding or clinically relevant non-major bleeding (OR 0·77, 0·41–1·44).[39]

Direct oral anticoagulants versus LMWH

Two randomised controlled trials[8,9] comparing direct oral anticoagulants and LMWH (dalteparin) for cancer-associated thrombosis have been published since the 2016 update. Direct oral anticoagulants were at least as effective as dalteparin at reducing VTE recurrence, but with an increased risk of bleeding (1·74-times higher increased risk of major bleeding and 2·31-times higher risk of a clinically relevant non-major bleeding).[40] In the Hokusai VTE cancer trial,[8] 1050 patients with cancer with symptomatic or incidentally diagnosed VTE were randomly assigned to receive either edoxaban (dalteparin for at least 5 days, followed by edoxaban 60 mg, once daily) or dalteparin (200 IU/kg once daily for 1 month, followed by 150 IU/kg daily), for 6–12 months. The primary outcome was a composite of recurrent VTE or major bleeding within 12 months after randomisation, regardless of treatment duration. Edoxaban was non-inferior to dalteparin: 67 (13%) of 522 patients in the edoxaban group, compared with 71 (14%) of 524 patients in the dalteparin group, developed a primary outcome event (hazard ratio [HR] 0·97, 95% CI 0·70–1·36, p=0·006 for non-inferiority, p=0·87 for superiority). The proportion of patients with VTE recurrence was numerically lower with edoxaban, but this difference did not reach statistical significance (8% in the edoxaban group *vs* 11% in the dalteparin group, p=0·09). The proportion of patients with major bleeding was higher with edoxaban than with dalteparin (7% *vs* 4%, p=0·04). The proportion of patients with clinically relevant non-major bleeding and overall survival were similar between groups. In the SELECT-D trial,[9] 406 patients with cancer with symptomatic or incidental pulmonary embolism, or symptomatic lower-extremity proximal deep vein thrombosis, were randomly assigned to receive either rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg daily for 2–6 months) or dalteparin (200 IU/kg daily during the first month, then 150 IU/kg daily for up to 6 months). The primary outcome was VTE recurrence in the 6 months after randomisation. Notably, the data safety monitoring board decided to exclude patients who had upper gastrointestinal malignancy from participating in the trial. The 6-month cumulative rate of VTE recurrence with rivaroxaban was significantly lower than with dalteparin (4% in the rivaroxaban group *vs* 11% in the dalteparin group, HR 0·43, 95% CI 0·19–0·99). However, the proportion of patients with clinically relevant non-major bleeding was significantly higher with rivaroxaban than with dalteparin (13% in the rivaroxaban group *vs* 4% in the dalteparin group, HR 3·76, 95% CI 1·63–8·69). A non-statistically significant increase in major bleeding was observed with rivaroxaban (6% in the rivaroxaban group *vs* 4% in the dalteparin group). Overall survival was similar between groups.

Preliminary results from the ADAM VTE trial[10] were presented at the 2018 ASH meeting. 300 patients with various types of cancer-associated thromboses, including upper extremity and splanchnic vein thrombosis, were randomly assigned to receive apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily thereafter) versus dalteparin (200 IU/kg daily for 1 month, followed by 150 IU/kg daily thereafter) for 6 months. The proportion of patients with major bleeding, which was the primary outcome, was low, with no significant difference between treatments (none of the 145 patients in the apixaban group *vs* three [2%] of 142 patients in the dalteparin group, p=0·99). The proportions of patients with a secondary safety composite endpoint of major and clinically relevant non-major bleeding were equivalent, at 9% for both groups. Recurrent VTE, a secondary efficacy outcome, occurred in five (3%) patients in the apixaban group compared with 20 (14%) patients in the dalteparin group (HR 0·26, 95% CI 0·09–0·80, p=0·018).

Duration of anticoagulation

A review of the updated evidence supports the use of LMWH or direct oral anticoagulants for at least 6 months for cancer-associated thrombosis and we have extended the Grade 1A recommendation on the duration of anticoagulation use (either LMWH or direct oral anticoagulants) from 3 to 6 months for patients with established VTE. One meta-analysis[41] of 16 randomised controlled trials (5167 patients with cancer) assessed the safety and efficacy of LMWH, vitamin K antagonist, and direct oral anticoagulants for long-term cancer-associated thrombosis treatment, with six randomised controlled trials having a 6–12 months of follow-up. Eight studies compared LMWH with vitamin K antagonists (2327 patients). LMWH was associated with a 42% reduction in VTE recurrence compared with vitamin K antagonists (RR 0·58, 95% CI 0·43–0·77).[41] No difference was found in the proportion of patients with major (RR 1·09, 95% CI 0·55–2·12) or minor bleeding (0·78, 0·47–1·27), 12-month mortality (1·00, 0·88–1·13), or thrombocytopenia (0·94, 0·52–1·69). Five studies compared direct oral anticoagulants with vitamin K antagonists (including a total of 982 patients). The meta-analysis could not exclude a beneficial or harmful effect of direct oral anticoagulants compared with vitamin K antagonists on VTE recurrence (RR 0·66, 95% CI

Panel 3: Prophylaxis for patients with venous thromboembolism (VTE)

Prophylaxis of VTE in patients with cancer who have undergone surgery

International Advisory Panel ranking: 8·63 out of 9

1 Use of low-molecular-weight heparin (LMWH) once per day (when creatinine clearance is ≥30 mL/min) or low-dose unfractionated heparin three times per day is recommended to prevent postoperative VTE in patients with cancer; pharmacological prophylaxis should be started 2–12 h preoperatively and continued for at least 7–10 days; there are no data allowing conclusions regarding the superiority of one type of LMWH over another (grade 1A). Values and preferences: LMWH once per day is more convenient.
2 There is insufficient evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer (grade 2C). Values and preferences: as per the first recommendation above.
3 Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in patients with cancer is recommended (grade 1A). Values and preferences: as per the first recommendation above.
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 1A). 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 patients with medical cancer

International Advisory Panel ranking: 8·00 out of 9

1 We recommend prophylaxis with LMWH or fondaparinux when creatinine clearance is ≥30 mL/min, or with unfractionated heparin in hospitalised patients with cancer and reduced mobility (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, unfractionated heparin, or fondaparinux might influence the choice.
2 Primary prophylaxis with LMWH, vitamin K antagonists, or direct oral anticoagulants in ambulatory 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 ambulatory patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and who have a low risk of bleeding (grade 1B). Values and preferences: subcutaneous injections.
4 Primary pharmacological prophylaxis of VTE with LMWH is not recommended outside of a clinical trial for patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy, including patients who have a low risk of bleeding (guidance).
5 Primary prophylaxis with direct oral anticoagulant (rivaroxaban or apixaban) is recommended in patients who are ambulatory who are receiving systemic anticancer therapy at intermediate-to-high risk of VTE, identified by cancer type (ie, pancreatic) or by a validated risk assessment model (ie, a Khorana score ≥2), and not actively bleeding or not at a high risk of bleeding (grade 1B).
6 In patients treated with immunomodulatory drugs combined with steroids or other systemic anticancer therapies, 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: 8·51 out of 9

1 Use of anticoagulation for routine prophylaxis of catheter-related thrombosis 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).
3 In patients requiring central venous catheters, we suggest the use of implanted ports over peripherally inserted central catheter lines (guidance).

0·33–1·31), major (0·77, 0·38–1·57) and minor (0·84, 0·58–1·22) bleeding, or mortality (0·93, 0·71–1·21).

No new studies have investigated VTE recurrence under anticoagulant treatment since the 2016 ITAC guidelines. In addition, no new studies on established central venous catheters associated thrombosis were found. Therefore, the 2016 ITAC guideline recommendation is unchanged.

VTE prophylaxis in patients with cancer

Recommendations for VTE prophylaxis in patients with cancer are presented in panel 3. The literature search did not identify any specific data for the perioperative management of anticoagulation in patients with cancer with established VTE who are already receiving anticoagulant treatment. In the absence of specific data, perioperative management of anticoagulation in these patients was not addressed in this Review. Risk factors and assessment models to identify high-risk patients that could benefit from primary thromboprophylaxis are summarised in panel 4. The most widely used model was developed by Khorana and colleagues[48] for ambulatory patients receiving chemotherapy.

VTE prophylaxis in patients undergoing cancer surgery

LMWH versus unfractionated heparin

A previous expanded meta-analysis[59] (12 890 patients with cancer), which was consistent with its earlier version,[60] and a meta-analysis in general surgery,[61] indicated that perioperative prophylaxis with daily LMWH was similar to unfractionated heparin three times daily (RR 0·78, 95% CI 0·53–1·15), and superior to unfractionated heparin twice daily (RR 0·66, 0·44–0·99). A new meta-analysis[62] of 12 studies (ten randomised controlled trials, two retrospective studies) confirmed that LMWH was associated with a decreased risk for deep vein thrombosis compared with unfractionated heparin (175 events in 5002 patients with cancer *vs* 164 events in 2717 patients with cancer; RR 0·81, 95% CI 0·66–1·00), with no significant differences in rates of bleeding (RR 0·73, 0·49–1·08). Daily LMWH is more convenient than twice-daily or three-times-daily unfractionated heparin and could be more cost-neutral or even cost-saving when compared with treatment with unfractionated heparin. Since the 2016 ITAC guidelines, no new evidence supports the use of fondaparinux as an alternative to LMWH thromboprophylaxis.

Comparison between doses of LMWH

Our updated literature search found no new studies comparing different doses of LMWH for patients with cancer who had undergone surgery. As recommended in the 2016 ITAC guidelines, the highest prophylactic dose of LMWH studied should be used in clinical practice.

Extended-duration (4 weeks) thromboprophylaxis

The 2016 ITAC guidelines for extended prophylaxis with LMWH for patients with cancer undergoing laparotomy and laparoscopic surgery remains unchanged, with four new supporting meta-analyses changing the grade of the recommendation from grade 1B to 1A. In the first meta-analysis,[63] extended-duration prophylaxis (2–6 weeks) significantly reduced the risk of any VTE (2·6% *vs* 5·6%, RR 0·44, 95% CI 0·28–0·70) and proximal deep vein thrombosis (1·4% *vs* 2·8%, RR 0·46, 0·23–0·91), but not symptomatic pulmonary embolism (0·8% *vs* 1·3%, RR 0·56, 0·23–1·40). There was no significant increase in major bleeding (1·8% *vs* 1·0%, RR 1·19, 0·47–2·97). In the second meta-analysis,[62] extended-duration thromboprophylaxis was associated with a significant decrease in the incidence of deep vein thrombosis (RR 0·57, 95% CI

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

Patients with cancer are at increased risk of VTE, which is determined by the clinical setting and the presence of various risk factors.[42] A time-dependent association between VTE and cancer has also been observed, with most VTE events occurring within the first 6 months after cancer diagnosis.

Risk factors

- Risk factors associated with the tumour characteristics: primary site, histological grade, tumour node metastasis staging
- Risk factors associated with the cancer treatments: surgery or hospitalisation; central venous catheters; systemic anticancer therapy, including radiotherapy, chemotherapy (eg, cisplatin), anti-angiogenesis agents, immunomodulatory drugs, hormonal therapy, erythropoiesis-stimulating agents, or red blood cell or platelet transfusions
- General individual VTE risk factors: history of previous venous thromboembolism, advanced age, obesity, immobility, prothrombotic variants (eg, factor V Leiden), and comorbidities

Emerging biomarkers[43-47]

- Blood-count parameters: platelets and leucocytes
- Markers of activation of blood coagulation and platelets: D-dimers, high endogenous thrombin generation potential, soluble P-selectin
- Markers of neutrophil extracellular trap formation (ie, citrullinated histone H3)
- Microvesicle-associated tissue factor activity
- High podoplanin expression and isocitrate dehydrogenase 1 mutation (in brain tumours only)

Risk assessment models

The Khorana Risk Scoring Model[48] was developed for VTE risk assessment in patients receiving chemotherapy. This risk score was externally validated in the Vienna CATS study[42] and other studies,[49,50] although subsequent publications questioned its reproducibility in some patient populations.[51–53] Several variations of the Khorana risk score have been done to improve risk assessment, including the extended Vienna CATS Score,[54] the PROTECHT,[49] and the CONKO score (appendix p 88).[50]

The COMPASS-CAT risk assessment model[55] was developed for use in only breast, colorectal, lung, and ovarian cancer and includes the following variables: anthracycline or anti-hormonal therapy, time since cancer diagnosis, central venous catheter, stage of cancer, presence of cardiovascular risk factors, recent hospitalisation for acute medical illness, personal history of venous thromboembolism, and platelet count.

The ONKOTEV[56] score is based on a Khorana score of >2, then adds metastatic disease, previous venous thromboembolism, and vascular or lymphatic compression.
A combination of genetic and clinical factors was used to develop the TiC-Onco score,[57] which performed better than the Khorana risk score in identifying patients with cancer who are at risk of venous thromboembolism.

Pabinger and colleagues[58] followed a prespecified process to develop and externally validate in a single prospective cohort (MICA) of 832 patients with cancer a simple clinical prediction model that only includes the tumour site category (very high and high versus intermediate or low) and D-dimer levels as a continuous variable, and a nomogram and online risk calculator is provided for estimating an individual patient´s risk of venous thromboembolism.

For more on the **online risk calculator** see http://catscore.meduniwien.ac.at

0·39–0·83), without a significant increase in bleeding (RR 1·48, 0·78–2·8). Three observational studies (two prospective and one retrospective) provided evidence for extended-duration prophylaxis after radical cystectomy[64,65] and liver resection.[66] There is strong evidence to support extending the duration of prophylaxis for 4 weeks after cancer surgery provided that patients are not at high risk of bleeding. A third meta-analysis[67] reported that extended-duration prophylaxis significantly reduced the risk for all VTE (OR 0·38, 95% CI 0·26–0·54), all reported cases of deep vein thrombosis (0·39, 0·27–0·55), and proximal deep vein thrombosis (0·22, 0·10–0·47), with a non-significant reduction in symptomatic VTE (0·30, 0·08–1·11) and a non-significant increase in major bleeding (1·10, 0·67–1·81). A fourth meta-analysis provided corroborating findings from the third meta-analysis.[68]

Mechanical methods of prophylaxis

Since the 2016 ITAC guidelines, one randomised controlled trial[69] assessed the clinical effectiveness of mechanical methods of thromboprophylaxis in 682 patients with cancer. Patients with intermittent pneumatic compression alone had a higher risk of VTE compared with patients with intermittent pneumatic compression who were also receiving LMWH (3·6% in the intermittent pneumatic compression alone group *vs* 0·6% in the intermittent pneumatic compression plus LMWH group, p=0·008), although bleeding risk was higher in the LMWH group (1·2% *vs* 9·1%, p<0·001). Two small randomised studies involving 30 patients[70] and 90 patients[71] found no benefit of adding LMWH to mechanical methods of prophylaxis. Unchanged from the 2016 ITAC guidelines, the use of mechanical methods of prophylaxis as monotherapy is not recommended, except when pharmacological methods are contraindicated.

Inferior vena cava filter placement

No additional studies were available since the 2016 ITAC guidelines. The recommendation against the routine use of inferior vena cava filters as primary VTE prophylaxis is unchanged.

VTE prophylaxis in medically treated patients with cancer who are hospitalised

No new studies have been published that have addressed prophylaxis in patients with cancer who are hospitalised with an acute medical illness.

VTE prophylaxis in ambulatory patients with cancer who are receiving systemic anticancer therapy

The risk for symptomatic VTE is approximately 5–10% in ambulatory patients receiving chemotherapy, with the risk of VTE and of bleeding varying by cancer type, cancer treatment, and by patient characteristics.[72] Unchanged from the 2016 ITAC guidelines, primary prophylaxis is not recommended routinely in all ambulatory patients with cancer receiving systemic anticancer therapy. The recommendation relating to primary prophylaxis in patients with cancer should take into account that only small numbers of patients with some common cancer types were included in the trials (ie, cancer of the breast, colorectum, and prostate) and that results might only pertain to specific direct oral anticoagulants (ie, apixaban and rivaroxaban).

The updated search identified five randomised controlled trials and seven meta-analyses (with the number of patients included in these meta-analyses ranging from 738 to 12 352 patients) that compared anticoagulant prophylaxis to no intervention or placebo in ambulatory patients receiving systemic anticancer therapy. The duration of thromboprophylaxis in medical patients with cancer is uncertain and has not been evaluated for more than a 6-month duration, and should be re-evaluated periodically on the basis of individual patient risk–benefit assessment.

LMWH

A randomised trial[73] assessed 12 weeks of prophylaxis with LMWH (dalteparin 5000 IU daily) versus no prophylaxis in 117 patients with cancer with a Khorana score of 3 or higher. A non-significant reduction in a composite measure of symptomatic and asymptomatic VTE (detected by weekly lower limb ultrasound) was observed with LMWH compared with placebo (12% *vs* 21%, HR 0·69, 95% CI 0·23–1·89), with no difference in major bleeding between the groups (one event recorded in each group). A second open-label trial[74] assessed an increased dose of LMWH (enoxaparin 1 mg/kg daily) in 390 patients with small-cell lung cancer. The trial was designed to assess the effect of LMWH on mortality. No benefit was shown for overall and progression-free survival, but there was a significant reduction in VTE events (HR 0·31, 95% CI 0·11–0·84). A third randomised controlled trial[75] investigated the effect of LMWH on survival for patients with resected non-small-cell lung cancer. The trial reported no significant difference in 5-year overall survival (HR 1·24, 95% CI; 0·92–1·68) or occurrence of symptomatic VTE (subdistribution HR 0·94, 95% CI 0·68–1·30) between patients with resected non-small-cell lung cancer receiving tinzaparin versus no treatment. An updated meta-analysis[72] assessed 26 randomised controlled trials comparing any oral or parenteral anticoagulant or mechanical intervention to no thromboprophylaxis or placebo (12 352 patients). LMWH reduced the risk of symptomatic VTE (RR 0·54, 95% CI 0·38–0·75) compared with no prophylaxis, with a non-significant increase in major bleeding (RR 1·44, 0·98–2·11). In a subgroup of patients with multiple myeloma, LMWH was associated with a significant reduction in the risk of symptomatic VTE compared with vitamin K antagonists (RR 0·33, 95% CI 0·14–0·83), although the difference between LMWH and aspirin was not statistically

significant (RR 0·51, 0·22–1·17). A second meta-analysis[76] involving 18 randomised controlled trials (total of 9575 patients) reported that prophylaxis with a parenteral anticoagulant (unfractionated heparin, LMWH, or fondaparinux) in all ambulatory patients with cancer receiving chemotherapy was associated with a reduced risk of symptomatic VTE (RR 0·56, 95% CI 0·47–0·68) and a statistically significant increase in minor bleeding risk (RR 1·70, 1·13–2·55). Major bleeding was not increased (RR 1·30, 95% CI 0·94–1·79).

Direct oral anticoagulants

Since the 2016 ITAC guidelines, two randomised controlled trials[11,12] have assessed direct oral anticoagulants for the primary prevention of VTE in selected ambulatory patients with cancer at intermediate-to-high risk for VTE occurrence, defined by a Khorana score of 2 or higher. Patients receiving chemotherapy have an 8–12% risk of developing VTE, depending on the cancer site.[77] The CASSINI trial[11] compared up to 6 months of thromboprophylaxis with rivaroxaban (10 mg daily) to placebo in 841 patients with cancer who were initiating chemotherapy, after excluding 49 (4·5%) of 1080 eligible patients found to have lower extremity VTE at the time of enrolment. Patients with primary or metastatic brain cancer were also excluded. The primary endpoint was a composite measure of symptomatic or asymptomatic deep vein thrombosis or pulmonary embolism, and VTE-related death. Patients receiving rivaroxaban had fewer primary endpoint events than did those on placebo while receiving treatment (HR 0·40, 95% CI 0·20–0·80), whereas the difference between the groups was non-significant over the entire 6-month observation period (HR 0·66, 95% CI 0·40–1·09, p=0·10). When combining the composite primary endpoint with all-cause mortality, using a prespecified intention-to-treat analysis, patients on rivaroxaban had fewer events than did those on placebo (23·1% *vs* 29·5%, HR 0·75, 95% CI 0·57–0·97). There was no difference in major bleeding (HR 1·96, 95% CI 0·59–6·49). The AVERT trial[12] compared apixaban (2·5 mg twice daily) with placebo for 6 months in 573 patients with cancer who were initiating chemotherapy. Based on the modified intention-to-treat analysis, there was a lower risk of the primary outcome of symptomatic and incidental VTE with apixaban (4·2% *vs* 10·2%, HR 0·14, 95% CI 0·26–0·65, p<0·001), but an increased risk of major bleeding (3·5% *vs* 1·8%, HR 2·00, 1·01–3·95, p=0·046). Both studies excluded patients considered at increased risk of bleeding and also had a high proportion of patients who discontinued medication (36–50%) for both the active drug and for placebo. The CASSINI[11] and AVERT[12] trials indicate a net clinical benefit of initiating anticoagulant prophylaxis with a direct oral anticoagulant (rivaroxaban 10 mg daily or apixaban 2·5 mg twice daily) in selected patients with cancer initiating chemotherapy, prompting a new ITAC-recommendation (panel 3).

Anticoagulant thromboprophylaxis in selected patients according to tumour type

Patients with lung cancer

Two new meta-analyses[78,79] consistently showed that in patients with lung cancer, LMWH confers a relative VTE risk reduction, with an increase in bleeding. Another meta-analysis[80] of six randomised controlled trials in ambulatory patients with lung cancer receiving chemotherapy (4315 patients) reported a 4·0% incidence of VTE with LMWH compared with 7·9% in groups without prophylaxis or placebo (RR 0·51, 95% CI 0·40–0·65), with no significant difference in major bleeding (RR 1·47, 0·79–2·75) and a significant increase in clinically relevant non-major bleeding (RR 3·2, 2·09–5·06). Overall survival was not increased with LMWH (pooled RR 1·02, 95% CI 0·94–1·11).

Patients with pancreatic cancer

One meta-analysis[81] since the 2016 guidelines reported a significant reduction in VTE in patients with pancreatic cancer (RR 0·18, 95% CI 0·08–0·40), without a significant increase in bleeding events. The best net clinical benefit of thromboprophylaxis with LMWH is observed in patients with pancreatic cancer who are receiving chemotherapy, whereas in other patient groups, including patients with lung cancer, this benefit is reported to be offset by an increased risk of bleeding. The use of VTE prophylaxis with LMWH for ambulatory patients with pancreatic cancer receiving chemotherapy is supported by two randomised controlled trials[82,83] and is recommended at a grade 1B level.

Unselected cancer types

One new meta-analysis[84] of seven randomised controlled trials assessed the effects of oral anticoagulants (vitamin K antagonists or apixaban) versus placebo or no intervention of primary VTE prophylaxis in patients with cancer (1486 patients). In the six randomised controlled trials that compared a vitamin K antagonist with no prophylaxis, no survival advantage with vitamin K antagonist therapy was found, but a significant increase in major (RR 2·93, 95% CI 1·86–4·62) and minor (RR 3·14, 1·85–5·32) bleeding was observed.

Myeloma patients treated with immunomodulatory drugs

No new studies have assessed LMWH or direct oral anticoagulant thromboprophylaxis in these patients with myeloma treated with immunomodulatory drugs since the 2013 ITAC clinical practice guidelines. Therefore, our previous recommendation is unchanged.

Prophylaxis of central venous catheter-related VTE

The recommendation against routine primary prophylaxis of central venous catheter-related VTE is unchanged. One new meta-analysis[85] of 13 studies (3420 patients) in patients with a central venous catheter did not confirm or exclude a beneficial or detrimental

Panel 5: Special situations

International Advisory Panel ranking: 8·12 out of 9

1 For the treatment of established venous thromboembolism in patients with a brain tumour, low-molecular-weight heparin (LMWH) or direct oral anticoagulants can be used (grade 2B).
2 We recommend the use of LMWH or unfractionated heparin commenced postoperatively for the prevention of venous thromboembolism in patients with cancer who are undergoing neurosurgery (grade 1A).
3 Primary pharmacological prophylaxis of venous thromboembolism in patients with a brain tumour who are not undergoing neurosurgery is not recommended (grade 1B).
4 In the presence of severe renal failure (creatinine clearance <30 mL/min), we suggest using unfractionated heparin followed by early vitamin K antagonists (possible from day 1) or LMWH adjusted to anti-Xa level for the treatment of established venous thromboembolism (guidance, in the absence of data and an unknown balance between desirable and undesirable effects).
5 In patients with severe renal failure (creatinine clearance <30 mL/min), an external compression device can be applied, and pharmacological prophylaxis could be considered on a case-by-case basis; in patients with severe renal failure (creatinine clearance <30 mL/min), unfractionated heparin 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 risk of venous thromboembolism).
6 In patients with cancer with thrombocytopenia, full doses of anticoagulant can be used for the treatment of established venous thromboembolism if the platelet count is >50 G/L and there is no evidence of bleeding; for patients with a platelet count below 50 G/L, decisions on treatment and dosage 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* venous thromboembolism risk).
7 In patients with cancer with mild thrombocytopenia with a platelet count >80 G/L, pharmacological prophylaxis can be used; if the platelet count is below 80 G/L, pharmacological prophylaxis can 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 venous thromboembolism risk).
8 In patients with cancer who are pregnant, we suggest the use of LMWH for treatment of established venous thromboembolism and for venous thromboembolism prophylaxis and avoidance of vitamin K antagonists and direct oral anticoagulants (guidance, in the absence of data and based on the contraindication of vitamin K antagonists and direct oral anticoagulants during pregnancy).
9 In patients with cancer who are obese, consideration for a higher dose of LMWH should be given for cancer surgery (guidance).

effect of low-dose vitamin K antagonist compared with no vitamin K antagonists on mortality, symptomatic catheter-related VTE, major bleeding, minor bleeding, or premature catheter removal, but found moderate certainty evidence that LMWH reduced central venous catheter-related thrombosis compared with no LMWH (RR 0·43, 95% CI 0·22–0·81) without increase in major or minor bleeding. One combined systematic review and meta-analysis[86] showed that centrally inserted central venous catheters were associated with a decrease in central venous catheter-related VTE compared with peripherally inserted central venous catheters (OR 0·45, 95% CI 0·32–0·62).[86]

VTE treatment in special cancer situations

Recommendations on VTE prevention and treatment for patients in special clinical situations are presented in panel 5.

Patients with brain tumours

Since the 2016 ITAC clinical practice guidelines, one retrospective study[87] found that the risk of recurrent VTE did not significantly differ between patients with cancer with or without primary or metastatic brain tumours (364 patients, 11 patients [95% CI 6·7–17·9] per 100 patient-years *vs* 13·5 [9·3–19·7] per 100 patient-years), but that risks of intracranial bleeding were higher for patients with metastatic brain tumours (4·4% *vs* 0%, p=0·004). One new meta-analysis,[88] based on nine retrospective studies, reported that the risk of intracranial haemorrhage in patients with brain tumours on anticoagulation was two times higher than in patients without anticoagulation (OR 2·13, 95% CI 1·00–4·56), and more than three times higher in patients with glioma (OR 3·75, 95% CI 1·42–9·95). For patients with brain metastases, therapeutic anticoagulation was not associated with an increased risk of intracranial haemorrhage (OR 1·07, 95% CI 0·61–1·88). A second new meta-analysis[89] of ten randomised controlled trials assessed the benefit-to-risk ratio of several methods of VTE prophylaxis in 1263 patients with brain tumours who were undergoing craniotomy. Prophylactic measures conferred a significant reduction in VTE risk, with no increase in major bleeding. Patients who received unfractionated heparin alone showed a stronger reduction in VTE risk than did those who received placebo (RR 0·27, 95% CI 0·10–0·73), and LMWH combined with mechanical prophylaxis showed a lower VTE risk than did mechanical prophylaxis alone (RR 0·61, 0·46–0·82).

Patients with thrombocytopenia

The recommendation for anticoagulant treatment of established VTE in patients with cancer who have thrombocytopenia is unchanged. Since the 2016 clinical practice guidelines, one retrospective study[90] reported VTE recurrence in ten (21·2%) of 47 patients with haematological malignancy and thrombocytopenia (platelets $<50\times10^9$/L) and VTE recurrence in 18 (22·2%) of 81 patients with haematological malignancy without thrombocytopenia. One systematic review[91] of 121 patients with cancer-associated thrombosis and thrombocytopenia reported a high risk of recurrent VTE (32 [27%] of 119 patients) and bleeding (18 [15%] of 119 patients), but available data do not support one management strategy over another to treat cancer-associated thrombosis in patients with thrombocytopenia.

Patients with renal failure

The recommendation for anticoagulant treatment of established VTE in patients with cancer who have renal failure is unchanged. Since the 2016 guidelines, a

Search strategy and selection criteria

The updated literature search for all studies published between Jan 1, 2015, and Dec 31, 2018, was done by the Institut National du Cancer using MEDLINE and several other databases (eg, Embase and Cochrane Central Register of Controlled Trials), with the following subject headings: "cancer", "venous thromboembolism", and "anticoagulant drugs and devices". The literature search was limited to publications in English or French. Members of the working group had the opportunity to add additional references that the bibliographic search did not identify. Meta-analyses, systematic reviews, randomised clinical trials, or non-randomised prospective or retrospective studies in the absence of randomised clinical trials were included. Articles were selected on the basis of article selection grids designed for each clinical question. For inclusion in the analysis, studies had to focus on the therapeutic management of confirmed venous thromboembolism (VTE) in patients with cancer, prophylaxis of VTE in patients with cancer in the surgical and medical settings, or on the treatment and prophylaxis of thrombosis related to central venous catheter placement in patients with cancer. Studies in patients with thrombosis related to tumour material, or a history of cancer in remission for more than 5 years, were excluded from the analysis. Studies that did not report VTE or side-effects of anticoagulation as outcomes were excluded. The main study outcomes were rates of VTE (first event or recurrence), major and minor bleeding, thrombocytopenia, and death.

post-hoc analysis of data from the CLOT study[92] compared dalteparin with vitamin K antagonist for the prevention of recurrent VTE in a patient subgroup with renal failure (creatinine clearance <60 mL/min, 162 [24%] of 676 patients). Compared with vitamin K antagonists, dalteparin conferred a significantly reduced risk of recurrent VTE (HR 0·15, 95% CI 0·03–0·65, p=0·01), with a similar safety profile. Second, a post-hoc analysis of patients with renal failure (Glomerular Filtration Rate-Modification of Diet in Renal Disease <60 mL/min per 1·73 m^2 in 131 [18%] of 733 patients) in the CATCH study[93] reported a statistically significant increase (131 of 733 patients) in risk of recurrent VTE (RR 1·74, 95% CI 1·06–23·85) and major bleeding (RR 2·98, 1·29–6·90) compared with patients without renal failure, with no significant difference in clinically relevant bleeding or mortality observed between patients treated with LMWH or vitamin K antagonists.

Patients who are obese

Consideration for a higher dose of LMWH should be given in obese patients undergoing cancer surgery. In patients undergoing surgery who do not have cancer, empirically derived higher LMWH dosing regimens have been used for thromboprophylaxis, although the evidence to support this practice is scarce.[94]

Conclusion

Cancer-associated thrombosis is a concerning problem for patients with cancer, increasing both morbidity and mortality. Direct oral anticoagulants have changed the approach to care for patients with atrial fibrillation and VTE, and new data now show a role for direct oral anticoagulants in cancer-associated thrombosis treatment and prophylaxis. The 2019 updated ITAC guidelines place these data in the framework of established approaches to all aspects of treatment and prophylaxis of cancer-associated thrombosis. The guidelines accompany a free ITAC-continuing medical education web-based mobile app that will assist practicing clinicians with decision making at a variety of levels to provide optimal care for patients with cancer to prevent and to treat VTE.

Contributors

The Institut National du Cancer 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 JD were the acting coordinators for the working group. They coordinated the preparation of the manuscript, and the contribution of the authors. CF and HR 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 Institut National du Cancer literature search, the critical appraisal of articles, the article selection, the data extraction, and the evidence tables. DF, CF, JMC, CA, and JD 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 done during two meetings, at which the working group collectively drafted and ranked the recommendations. The manuscript was reviewed by a multidisciplinary advisory panel of 83 experts from several specialties (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 reports non-financial support from Leo Pharma, Aspen Pharmacare, and Pfizer, outside of the submitted work. JD reports participation in advisory boards or educational activities for AstraZeneca, Bayer, Biotie, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Pfizer, Portola, Sanofi, and The Medicines Company; consulting for Actelion, AGEN Biomedical, Boehringer-Ingelheim, Janssen Research and Development, Ortho-Janssen Pharmaceuticals, and Sanofi; serving as chair of the MARINER trial clinical endpoint committee; being employed on The Merck Manual and Up-to-Date publications; grants from Boehringer-Ingelheim; receiving continuing medical education credit for peer review of manuscripts submitted to the *Journal of Thrombosis and Haemostasis*, outside of the submitted work. CA reports personal fees from Bayer and Daiichi-Sankyo, outside of the submitted work. HB reports grants and personal fees from Thrombosis Research Institute (London), and personal fees from Bayer AG, outside of the submitted work. BB was a member of an advisory board or similar committee for Aspen Pharmacare, Bayer, Daiichi-Sankyo, Pfizer, ROVI Laboratories, and Sanofi, outside of the submitted work. JMC reports personal fees from Bristol-Myers Squibb and Portola. CF reports personal fees and non-financial support from Leo Pharma, personal fees and non-financial support from Bayer, Aspen Pharma Care, and Pfizer, outside of the submitted work. AAK reports personal fees and non-financial support from Janssen, Bayer, Halozyme, AngioDynamics, Pfizer, Sanofi, Parexel, Seattle Genetics, Leo Pharma, and Medscape; personal fees from TriSalus, Incyte, Pharmacyclics, and Pharmacyte; grants from Merck, Bristol-Myers Squibb, and Leap, outside of the submitted work. AK reports grants and personal fees from Bayer AG, and personal fees from Boehringer-Ingelheim Pharma, Daiichi Sankyo,

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