Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19

Dominique Farge, Corinne Frere*, Jean M Connors, Alok A Khorana, Ajay Kakkar, Cihan Ay, Andres Muñoz, Benjamin Brenner, Pedro H Prata, Dialina Brilhante, Darko Antic, Patricia Casais, María Cecilia Guillermo Esposito, Takayuki Ikezoe, Syed A Abutalib, Luis A Meillon-García, Henri Bounameaux, Ingrid Pabinger, James Douketis, the International Initiative on Thrombosis and Cancer (ITAC) advisory panel*

The International Initiative on Thrombosis and Cancer is an independent academic working group of experts aimed at establishing global consensus for the treatment and prophylaxis of cancer-associated thrombosis. The 2013, 2016, and 2019 International Initiative on Thrombosis and Cancer clinical practice guidelines have been made available through a free, web-based mobile phone application. The 2022 clinical practice guidelines, which are based on a literature review up to Jan 1, 2022, include guidance for patients with cancer and with COVID-19. Key recommendations (grade 1A or 1B) include: (1) low-molecular-weight heparins (LMWHs) for the initial (first 10 days) treatment and maintenance treatment of cancer-associated thrombosis; (2) direct oral anticoagulants for the initial treatment and maintenance treatment of cancer-associated thrombosis in patients who are not at high risk of gastrointestinal or genitourinary bleeding, in the absence of strong drug–drug interactions or of gastrointestinal absorption impairment; (3) LMWHs or direct oral anticoagulants for a minimum of 6 months to treat cancer-associated thrombosis; (4) extended prophylaxis (4 weeks) with LMWHs to prevent postoperative venous thromboembolism after major abdominopelvic surgery in patients not at high risk of bleeding; and (5) primary prophylaxis of venous thromboembolism with LMWHs or direct oral anticoagulants (rivaroxaban or apixaban) in ambulatory patients with locally advanced or metastatic pancreatic cancer who are treated with anticancer therapy and have a low risk of bleeding.

Introduction

Cancer-associated venous thromboembolism (VTE), which includes deep vein thrombosis, pulmonary embolism, and central venous catheter-related VTE, is the second leading cause of death in patients with cancer after progression. Patients with cancer-associated thrombosis are at high risk of recurrent VTE and anticoagulant-related bleeding,[1] which are associated with high morbidity and resource use. The prevalence of cancer-associated thrombosis is increasing because of multiple factors, including longer patient survival, anticancer therapies, increased detection of incidental VTE during surveillance imaging, and wider use of central venous catheters.[2]

Monotherapy with low-molecular-weight heparins (LMWHs) for at least 3 up to 6 months was the standard of care for the treatment of cancer-associated thrombosis,[3] with vitamin K antagonists (after LMWH) providing a secondary treatment option, until direct oral anticoagulants emerged as alternative first-line treatment options in 2016.[4,5] Anticoagulant choice for cancer-associated thrombosis is based on evidence from well designed clinical trials, but should also incorporate a personalised medicine approach that considers cancer type, VTE and bleeding risk factors, drug–drug interactions, and patient preferences. Thromboprophylaxis can be used selectively in patients with cancer at high risk of VTE, for example in patients with pancreatic cancer.[3–5] Risk assessment models and computerised tools can identify patients at greatest risk of cancer-associated thrombosis, to allow for an appropriate, personalised approach for thromboprophylaxis.[5]

The International Initiative on Thrombosis and Cancer (ITAC) first developed evidence-based clinical practice guidelines in 2013,[3] using Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology.[6] The 2016 and 2019 updates[4,5] to the ITAC guidelines were made available through a free, companion, web-based mobile application. Since December 2019, the COVID-19 pandemic has been raising specific issues in patients with both cancer and SARS-CoV-2 infection, such as an increased risk of hypercoagulability, which results in both macrovascular and microvascular thrombosis.[7] A meta-analysis of observational, cohort, and cross-sectional studies reported the pooled incidences of VTE in patients with COVID-19 admitted to the ward (7·1%) or to the intensive care unit (27·9%).[8] Because patients with cancer have a baseline increased risk of VTE compared with patients without cancer, the combination of both COVID-19 and cancer—and its effect on VTE risk and treatment—is of concern. The 2022 ITAC guidelines cover new evidence on the treatment and prophylaxis of cancer-associated thrombosis, including in patients with cancer and with COVID-19.

Guideline development

Development of the 2022 ITAC guidelines followed the same process and methods as with previous iterations,[3–5] and also received support from the *Institut National du Cancer*. Guideline development is based on GRADE methodology[6] (panel 1; fully detailed in appendix pp 3–23). The panel, which comprised 19 independent international academic experts from various specialties,

Lancet Oncol 2022; 23: e334–47

*Contributed equally

Unité de Médecine Interne (UF04): CRMR MATHEC, Maladies Auto-immunes et Thérapie Cellulaire (Prof D Farge MD PhD) **and Hematology-Transplantation Department** (P H Prata MD), **Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris, Nord-Université de Paris, Paris, France; Faculté de Médecine, Institut de Recherche St-Louis, EA-3518, Université de Paris, Paris, France** (Prof D Farge); **Department of Medicine, Research Institute of the McGill University Health Centre, McGill University, Montreal, QC, Canada** (Prof D Farge); **INSERM UMRS 1166, GRC 27 GRECO, DMU BioGeM, Assistance Publique Hôpitaux de Paris, Sorbonne University, Paris, France** (C Frere MD PhD); **Hematology Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA** (J M Connors MD PhD); **Taussig Cancer Institute and Case Comprehensive Cancer Center, Cleveland Clinic, Cleveland, OH, USA** (Prof A A Khorana MD); **Thrombosis Research Institute, London, UK** (Prof A Kakkar MBBS PhD); **Faculty of Medical Sciences, University College London, London, UK** (Prof A Kakkar); **Clinical Division of Hematology and Hemostaseology, Department of Medicine, Medical University of Vienna, Vienna, Austria** (Prof C Ay MD PhD, Prof I Pabinger MD PhD); **Medical Oncology Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain** (Prof A Munõz MD); **Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa,**

Israel (Prof B Brenner MD); **Francisco Gentil Portuguese Institute of Oncology, Lisbon Center, Lisbon, Portugal** (D Brilhante MD); **Clinic for Hematology, Clinical Center Serbia, University of Belgrade, Belgrade, Serbia** (D Antic MD); **Instituto de Investigaciones en Salud Pública, Universidad de Buenos, Buenos Aires, Argentina** (P Casais MD); **Departamento Clínico de Medicina, Manuel Quintela Clinic Hospital, Montevideo, Uruguay** (Prof M C Guillermo Esposito MD); **Department of Hematology, Fukushima Medical University, Fukushima, Japan** (Prof T Ikezoe MD); **Cancer Treatment Centers of America, Chicago, IL, USA** (S A Abutalib MD); **The ABC Medical Center, Mexico City, Mexico** (Prof L A Meillon-García MD); **Faculty of Medicine, University of Geneva, Geneva, Switzerland** (Prof H Bounameaux MD); **Department of Medicine, McMaster University, Hamilton, ON, Canada** (Prof J Douketis MD)

Correspondence to: Prof Dominique Farge, Unité de Médecine Interne (UF04): CRMR MATHEC, Maladies Auto-immunes et Thérapie Cellulaire, Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris, Nord-Université de Paris, Paris 75010 , France
itaccme@gmail.com

For more on **ITAC-CME Treatment Guidelines mobile app** see https://www.itaccme.com

See **Online** for appendix

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

used the PICO (Population, Intervention, Comparator, and Outcomes) model to formulate specific clinical questions and to determine outcomes of interest. An updated literature search was done from Jan 1, 1996, to Jan 1, 2022, with MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. The literature search strategy used keywords including all VTE and cancer types, patients treated by all cancer-associated therapies, and all anticoagulant drugs and devices. Antiplatelet therapy was beyond the scope of this Review. Keywords did not include specific items on other patient-related outcomes or quality of life. The main outcomes were the rates of VTE (de-novo or recurrent VTE), major and minor bleeding, thrombocytopenia, and death. The 2022 ITAC guidelines were critically reviewed by an independent, multi-disciplinary advisory panel of 87 members (appendix pp 120–22), and were endorsed by the International Society on Thrombosis and Haemostasis.

Guideline recommendations

Treatment of established VTE

Recommendations for the treatment of incidental or symptomatic cancer-associated thrombosis are shown in panel 2. Since the 2019 ITAC guidelines,[5] three randomised clinical trials[9–11] and 12 meta-analyses[12–23] assessed the efficacy and safety of LMWHs or direct oral anticoagulants for the treatment of cancer-associated thrombosis.[12]

Initial treatment of established VTE (up to 10 days)

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

An increased number of patients with cancer-associated thrombosis receiving LMWHs (n=1840) in six randomised clinical trials comparing direct oral anticoagulants with LMWH[9–11,24–26] resulted in an upgrade from 1B to 1A for LMWHs as an initial treatment in the first 5–10 days. Fondaparinux and unfractionated heparin remain acceptable alternative treatment options without new evidence.

Direct oral anticoagulants

Rivaroxaban or edoxaban were recommended (grade 1B) in 2019,[5] as initial treatment options in patients with cancer-associated thrombosis who are not at high risk of gastrointestinal or genitourinary bleeding. New evidence from four randomised clinical trials (ADAM-VTE,[26] CARAVAGGIO,[9] CASTA-DIVA,[10] and CANVAS[11]) found that direct oral anticoagulants are non-inferior to LMWHs for the outcomes of recurrent VTE and mortality. The recommendation for direct oral anticoagulants, including apixaban, is upgraded from 1B to 1A. Starting doses of apixaban (10 mg twice daily for the first 7 days) and rivaroxaban (15 mg twice daily for the first 21 days) are used. Edoxaban requires 5 days of parenteral anticoagulant, typically LMWHs, before initiating treatment with the standard 60 mg daily dose.

Inferior vena cava filters

The recommendation for inferior vena cava filters is unchanged from the 2019 ITAC guidelines.[5] A new retrospective database study, which used propensity score matching and competing risk analysis, compared 33 740 patients with cancer and concomitant deep vein thrombosis who had inferior vena cava filters with 54 845 patients without inferior vena cava filters, showing improved pulmonary embolism-free survival (hazard ratio [HR] 0·69, 95% CI 0·64–0·75; p<0·001), without increased risk of recurrent deep vein thrombosis.[27] Another propensity-matched retrospective study compared the use of inferior vena cava filters in 247 patients with cancer, in whom anticoagulant therapy was contraindicated, with 247 matched patients with cancer but without inferior vena cava filters, reporting a non-significant lower risk of death (12·2% *vs* 17·0%, p=0·13), and a significantly lower risk of pulmonary embolism-related mortality (0·8% *vs* 4·0%; p=0·04).[28]

Panel 2: **Treatment of incidental or symptomatic established venous thromboembolism (VTE) in patients with cancer**

Initial treatment of established VTE (up to 10 days of anticoagulation)

International Advisory Panel ranking: 8·67 out of 9·00

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/min (grade 1A). 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 patients' characteristics (eg, risk of bleeding or moderate renal failure) or the need for technical intervention (eg, surgery or changing regimen). When a twice-per-day regimen is required, only enoxaparin (1 mg/kg, twice-daily) can be used.
2 For patients who do not have a high risk of gastrointestinal or genitourinary bleeding, rivaroxaban or apixaban (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 1A).
3 Unfractionated heparin can be also used for the initial treatment of established VTE for patients with cancer when LMWH or direct oral anticoagulants are contraindicated, or not available (grade 2C).
4 Fondaparinux can be also 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.
5 Thrombolysis in patients with cancer and 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 might 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 (up to 6 months) and long-term (beyond 6 months) maintenance

International Advisory Panel ranking: 8·61 out of 9·00

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 (edoxaban, rivaroxaban, or apixaban) 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.
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: 8·43 out of 9·00

1 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 antagonist, 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: 8·61 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 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 and with catheter-related thrombosis, the central venous catheter can be kept in place if it is functional, well positioned, and not infected, with good resolution of symptoms under close surveillance while anticoagulation therapy is administered. No standard approach in terms of duration of anticoagulation is established (guidance).

Thrombolysis

Data on the benefits and risks of thrombolytic therapy in patients with cancer-associated thrombosis are scarce. The 2019 ITAC recommendation on thrombolysis is unchanged.[5] A new retrospective database study compared two matched groups of 1297 patients with lower-extremity proximal or vena cava deep vein thrombosis undergoing catheter-directed thrombolysis or anticoagulation alone, finding no significant difference in mortality (2·6% *vs* 1·9%, p=0·23), but an increased risk of intracranial haemorrhage (1·3% *vs* 0·4%, p=0·017) with thrombolytic therapy.[29]

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

Unchanged from the 2019 ITAC guidelines,[5] LMWHs (which are preferred over vitamin K antagonists when creatinine clearance ≥30 mL/min) or direct oral anticoagulants as first-line treatment in patients without contraindications (strong drug–drug interactions, impaired gastrointestinal absorption, or high bleeding risk), are recommended (grade 1A) for early maintenance and long-term treatment of cancer-associated thrombosis. Three new randomised controlled trials showed that direct oral anticoagulants were non-inferior to LMWHs for the outcome of VTE recurrence with apixaban (CARAVAGGIO),[9] rivaroxaban (CASTA-DIVA),[10] or any direct oral anticoagulant (CANVAS).[11] New data since the 2019 guidelines have supported LMWH or direct oral anticoagulants treatment for up to 12 months.[30,31]

LMWHs versus vitamin K antagonists

Since the 2016 ITAC guidelines,[4] there have been no new randomised controlled trials comparing LMWHs with vitamin K antagonists. Five pivotal randomised controlled trials (CANTHANOX,[32] CLOT,[33] LITE,[34] CATCH,[35] and ONCENOX[a]) showed that LMWHs for 6 months are more effective than vitamin K antagonists in patients with cancer-associated thrombosis, without an increase in bleeding risk.[3,4] Data from the LMWH control group of the HOKUSAI-VTE cancer trial,[24] two prospective single-arm cohorts,[37,38] and one retrospective study[30] showed no increase in major bleeding at 6 months and 12 months when a 12-month LMWH regimen was used as treatment.

Direct oral anticoagulants versus vitamin K antagonists

Comparisons between direct oral anticoagulants and vitamin K antagonists are limited to post-hoc analyses of patients with cancer included in randomised controlled trials comparing direct oral anticoagulants with warfarin in patients with and without cancer, which reported no difference in the risks of recurrent VTE, major bleeding, or clinically relevant non-major bleeding between direct oral anticoagulants and vitamin K antagonists.[4,5]

Direct oral anticoagulants versus LMWHs

Three new randomised controlled trials comparing direct oral anticoagulants with LMWHs (CARAVAGGIO,[9] CASTA-DIVA,[10] and CANVAS;[11] appendix p 110–12), and 11 meta-analyses[13–23] pooling results from HOKUSAI-VTE Cancer,[24] SELECT-D,[25] ADAM-VTE,[26] and CARAVAGGIO (2894 patients),[9] showed that direct oral anticoagulants confer a reduced risk of recurrent VTE (relative risk [RR] 0·62, 95% CI 0·43–0·91), without an increase in major bleeding (1·31, 0·83–2·08). Direct oral anticoagulants were associated with a substantial increase in the risk of clinically relevant non-major bleeding in all, but one, meta-analyses.[20] One meta-analysis,[13] focusing on gastrointestinal cancers (483 patients), reported a significantly higher risk of major bleeding in patients receiving direct oral anticoagulants (RR 2·3, 95% CI 1·08–4·88) than in patients receiving LMWHs. The published ADAM-VTE trial (300 patients)[26] reported that apixaban for 6 months was safe, with no major bleeds in 145 patients assigned apixaban, and two (1·4%) events in 142 assigned dalteparin (HR not estimable, p=0·138), with recurrent VTE in one (0·7%) of 145 assigned apixaban and nine (6·3%) of 142 assigned dalteparin (HR 0·099, 95% CI 0·013–0·78; p=0·0281), without any difference in overall survival at 6 months. In the CARAVAGGIO trial,[9] 1170 patients with cancer and with symptomatic or incidental VTE received apixaban (10 mg twice-daily for the first 7 days, followed by 5 mg twice-daily) or dalteparin (200 IU/kg daily for 1 month, followed by 150 IU/kg daily) for 6 months, with stratification by symptomatic or incidental VTE and active cancer or a history of cancer. For the primary outcome of recurrent VTE at 6 months, apixaban was non-inferior to LMWH (5·6% of patients receiving apixaban *vs* 7·9% of patients receiving dalteparin; HR 0·63, 95% CI 0·37–1·07; p<0·001 for non-inferiority). Major bleeding events (3·8% under apixaban *vs* 4·0% under dalteparin) did not differ between groups (HR 0·82, 95% CI 0·40–1·69; p=0·60). Clinically relevant non-major bleeding events were not significantly different between groups (9·0% under apixaban *vs* 6·0% under dalteparin, HR 1·42, 95% CI 0·88–2·30). Overall survival was also similar between groups. In the CASTA-DIVA trial,[10] 158 patients with cancer and with symptomatic or incidental VTE at high risk of recurrence (modified Ottawa score ≥1) received rivaroxaban (15 mg twice-daily for 3 weeks, and then 20 mg daily) or dalteparin (200 IU/kg daily for 1 month, and then 150 IU/kg daily) for 3 months. Rates of recurrent VTE within 3 months did not differ between groups (6·4% under rivaroxaban *vs* 10·1% under dalteparin). The study did not fulfil the predefined criteria for non-inferiority (HR 0·75, 95% CI 0·21–2·66; p=0·13) due to a lower-than-expected VTE rate with dalteparin. Rates of major bleeding (1·4% with rivaroxaban *vs* 3·7% with dalteparin; HR 0·36, 95% CI 0·04–3·43), major or clinically relevant non-major bleeding (12·2% with rivaroxaban *vs* 9·8 % with dalteparin; 1·27, 0·49–3·26) or death from any cause were similar in both

groups. Preliminary results from the CANVAS trial,[11] with randomised and preference cohorts, were presented at the 2021 American Society of Clinical Oncology meeting. In the randomised cohort, 671 patients with symptomatic or incidentally diagnosed VTE received either a direct oral anticoagulant (type determined by the treating investigator) or LMWHs with or without transition to warfarin for 6 months. The primary outcome of recurrent VTE occurred in 6·1% of patients in the direct oral anticoagulant group versus 8·8% in the LMWH group (difference –2·7, 90% CI –6·1 to 0·7), meeting non-inferiority criteria. The proportion of secondary outcomes of major bleeding (5·2% with direct oral anticoagulants *vs* 5·6% with LMWHs), clinically relevant non-major bleeding (5·8% with direct oral anticoagulants *vs* 2·6% with LMWHs), and all-cause deaths (21·5% with direct oral anticoagulants *vs* 18·4% with LMWHs) were similar for both groups. Results from an updated meta-analysis pooling the results from HOKUSAI-VTE Cancer,[24] SELECT D,[25] ADAM-VTE,[26] CARAVAGGIO,[9] CASTA-DIVA,[10] and CANVAS (3690 patients)[11] were presented at the 2021 American Society of Hematology meeting.[39] After a follow-up of 3 to 6 months, use of direct oral anticoagulants significantly decreased the risk of recurrent VTE compared with LMWHs (RR 0·67, 95% CI 0·52–0·85), with a non-significant increase in the risk of major bleeding (1·17, 0·82–1·67), but a significant increase in the risk of clinically relevant non-major bleeding events (1·66, 1·31–2·09).[39]

The randomised controlled trials comparing direct oral anticoagulants with LMWHs for the treatment of cancer-associated thrombosis (appendix pp 110–12) included a substantial proportion of patients with incidental VTE, with location varying from deep vein thrombosis to pulmonary embolism. In a systematic review and meta-analysis including 774 patients with cancer and with incidental VTE,[20] the risk of recurrent VTE was not different in patients receiving direct oral anticoagulants, compared with those receiving LMWHs (RR 0·54, 95% CI 0·26–1·11), nor was the risk of major bleeding (1·29, 0·74–2·28). These findings further support managing patients with incidental cancer-associated thrombosis in a similar manner as symptomatic cancer-associated thrombosis. Randomised controlled trials comparing direct oral anticoagulants with LMWHs were heterogeneous in terms of sample size, cancer types, study design, primary outcomes, treatment duration, and compliance to long-term treatment (appendix pp 110–112).

Duration of anticoagulation

Five randomised controlled trials,[9,11,24–26] totalling 3532 patients treated for at least 6 months, further support the use of either LMWH or direct oral anticoagulants for at least 6 months with a grade 1A recommendation. No new studies on either treatment of VTE recurrence while on anticoagulation or treatment of established central venous catheter-associated thrombosis have been identified since the 2019 ITAC guidelines, which remain unchanged.[5]

VTE prophylaxis in patients with cancer

Recommendations for VTE prophylaxis are shown in panel 3. Risk factors and stratification scores to identify high-risk patients who could benefit from primary VTE prophylaxis are summarised in the appendix (pp 113–16).

VTE prophylaxis in patients undergoing cancer surgery

Unchanged since the 2019 ITAC guidelines,[5] anticoagulant prophylaxis should be started between 12 h and 2 h preoperatively and continued for at least 7–10 days postoperatively with once-daily low-dose LMWHs or low-dose unfractionated heparin thrice-daily. New data support the grade 1A recommendation for extended-duration LMWHs prophylaxis for 4 weeks after major cancer abdominal or pelvic surgery (laparotomy or laparoscopy) in patients without a high-bleeding risk.[40] There are no new data for fondaparinux and there is insufficient evidence to support the use of apixaban, despite one small randomised controlled trial.[41] Similarly, no evidence currently exists to support the use of other direct oral anticoagulants in this setting.

LMWHs versus unfractionated heparin

A new network meta-analysis of 20 randomised controlled trials in 1693 patients with gynaecological cancer undergoing major abdominopelvic surgery treated with LMWH or unfractionated heparin showed no difference in rates of VTE (RR 1·16, 95% CI 0·85–1·56) or major bleeding (0·62, 0·32–1·23).[42] Daily LMWH is associated with a lower risk of heparin-induced thrombocytopenia and is more convenient than twice-daily or thrice-daily unfractionated heparin. Regarding patients with previous heparin-induced thrombocytopenia (definite or possible), the literature search did not retrieve any specific data in patients with cancer concerning the common practice on the use of fondaparinux.

Preoperative pharmacological thromboprophylaxis

A new meta-analysis of 12 studies (14 273 patients),[43] mostly retrospective studies including patients with cancer, found that preoperative pharmacological prophylaxis reduced the risk of VTE after major gynaecological and gynaecological cancer surgery compared with no preoperative pharmacological prophylaxis (odds ratio [OR] 0·59, 95% CI 0·39–0·89), without increased bleeding (1·26, 0·98–1·62).

Comparison between doses of LMWHs

No new studies were identified comparing different doses of LMWHs.

Extended-duration (4 weeks) thromboprophylaxis

The 2019 ITAC recommendation for extended-duration prophylaxis with LMWH in patients undergoing cancer

Panel 3: Prophylaxis of venous thromboembolism (VTE) in patients with cancer

Prophylaxis of VTE in surgically-treated patients with cancer

International Advisory Panel ranking: 8·62 out of 9·00

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 (grade 2C) or direct oral anticoagulants (grade 2B) as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer. Values and preferences: as per the first recommendation.
3 Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in patients with cancer is recommended (grade 1A).
4 Extended prophylaxis (4 weeks) with LMWH to prevent postoperative VTE after major abdominal or pelvic surgery (either laparotomy or laparoscopy) is recommended in patients with cancer who do not have a high risk of bleeding (grade 1A). Values and preferences: longer duration of injections.
5 Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated (grade 2A). Values and preferences: no injection.
6 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: 8·44 out of 9·00

1 We recommend prophylaxis with LMWH or fondaparinux when creatinine clearance is ≥30 mL/min, or with unfractionated heparin 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, unfractionated heparin, or fondaparinux might affect the choice.
2 Primary pharmacological prophylaxis of VTE with LMWH (grade 1A) or with direct oral anticoagulants (rivaroxaban or apixaban; grade 1B) 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. Values and preferences: subcutaneous injections.
3 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).
4 Primary prophylaxis with direct oral anticoagulant (rivaroxaban or apixaban) is recommended in ambulatory patients who are receiving systemic anticancer therapy and are at intermediate-to-high-risk of VTE, identified by a validated risk assessment model (ie, a Khorana score ≥2), and not actively bleeding or not at a high risk for bleeding (grade 1B).
5 In patients with myeloma treated with immunomodulatory drugs combined with steroids or other systemic anticancer therapies, VTE primary pharmacological prophylaxis is recommended (grade 1A); in this setting, oral anticoagulants (vitamin K antagonists at low or therapeutic doses and apixaban at prophylactic doses), LMWH at prophylactic doses, or low-dose aspirin (100 mg daily) can be used, and have shown similar effects with regard to preventing VTE (grade 2B). Values and preferences: subcutaneous injections.

Prophylaxis of catheter-related thrombosis

International Advisory Panel ranking: 8·52 out of 9·00

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).

surgery (laparotomy and laparoscopic) is unchanged (grade 1A).[5] A new meta-analysis (18 studies, 7495 patients)[40] showed a significantly reduced risk of symptomatic VTE (1·0% *vs* 2·0%; RR 0·48, 95% CI 0·31–0·74), without increased risk of clinically relevant non-major bleeding (4·0% *vs* 4·9%; 1·00, 0·66–1·50). One randomised controlled trial compared apixaban, 2·5 mg twice-daily, with enoxaparin, 40 mg daily, for 28 days for postoperative prophylaxis (400 patients, 19·3% of benign tumours).[41] The proportion of patients in the apixaban and enoxaparin groups with major bleeding (0·5% in both groups; OR 1·04, 95% CI 0·07–16·76), clinically relevant non-major bleeding (5·4% *vs* 9·7%; 1·88, 0·87–4·10), and VTE (1·0% *vs* 1·5%; 1·57, 0·26–9·50) was similar.[41]

Mechanical methods of prophylaxis

Unchanged since the 2019 ITAC guidelines,[5] monotherapy with mechanical methods of prophylaxis is not recommended, except when pharmacological methods are contraindicated. Five small Japanese randomised controlled trials assessed mechanical methods of thromboprophylaxis in surgical patients with cancer, with inconsistent findings.[44–48] In a network meta-analysis

of patients with gynaecological cancer undergoing major abdominopelvic surgery, comparing different methods of thromboprophylaxis, intermittent pneumatic compression plus LMWH was best for VTE prevention.[42]

Inferior vena cava filters placement

No additional studies have been available since the 2019 ITAC guidelines.[5] The recommendation against routine use of inferior vena cava filters as primary VTE prophylaxis is unchanged.

VTE prophylaxis in medically-treated patients with cancer who are hospitalised

The 2022 ITAC guidelines for medical prophylaxis in hospitalised patients have remained unchanged from the 2019 publication. A phase 2 trial randomly assigned 50 patients with solid tumours, myeloma, or lymphoma at high risk for VTE based on the Padua risk score to fixed-dose enoxaparin (40 mg daily) or weight-adjusted-dose enoxaparin (1 mg/kg daily) during hospitalisation.[49] No symptomatic VTE or bleeding events were observed in either group within 14 days after randomisation.

VTE prophylaxis in ambulatory patients with cancer receiving systemic anticancer therapy

The risks of VTE and bleeding vary by cancer type, treatment, and patient characteristics, ranging from 3% to 5% in patients with early stage cancer to 30% in patients with metastatic disease.[50] The ITAC guidelines have remained unchanged since 2019 and do not recommend routine primary prophylaxis with LMWHs, vitamin K antagonists, or direct oral anticoagulants for ambulatory patients with cancer.[4,5]

Ten new meta-analyses (1415–15 678 patients),[50–59] one subgroup analysis of a randomised controlled trial (273 patients with pancreatic cancer),[60] and three observational studies[61–63] compared anticoagulant prophylaxis with no intervention or placebo. In one updated meta-analysis of 24 randomised controlled trials with VTE or death as primary outcomes, thromboprophylaxis conferred a 50% reduction in the incidence of VTE, with similar reductions in studies with LMWHs or direct oral anticoagulants.[53] VTE risk reduction was found in patients with pancreatic cancer (OR 0·26, 95% CI 0·14–0·48) and lung cancer (0·42, 0·26–0·67).[53]Another meta-analysis of six randomised controlled trials (4626 patients) showed that primary thromboprophylaxis (with LMWHs or direct oral anticoagulants) compared with placebo or standard care reduced the risk of VTE by 55% (95% CI 0·28–0·67) in patients with a Khorana score of at least 3, and by 42% (0·36–0·83) in patients with a Khorana score of at least 2, without increased risk of major bleeding.[59] Since 2019,[5] the use of LMWHs or direct oral anticoagulants (apixaban and rivaroxaban) for thromboprophylaxis has gained evidence in subgroups of ambulatory patients with cancer receiving chemotherapy at high risk of VTE (Khorana score ≥2) and low risk of bleeding, with optimal net clinical benefit for LMWHs (grade 1A) or direct oral anticoagulants (grade 1B).

LMWH

A meta-analysis from 14 randomised controlled trials (8278 patients) comparing parenteral thromboprophylaxis with placebo or standard care in ambulatory patients with cancer receiving chemotherapy found no difference in mortality at 1 year (RR 0·99, 95% CI 0·93–1·06).[57] LMWH reduced the risk of symptomatic deep vein thrombosis and pulmonary embolism (RR 0·58, 95% CI 0·47–0·71), with the most certain benefit in patients with lung cancer (0·59, 0·42–0·81) dominating the overall reduction, with no increase in major bleeding (1·27, 0·92–1·74), and a significant increase in minor bleeding (1·34, 1·19–1·59).[57] In a second meta-analysis that included 14 randomised controlled trials with VTE as primary outcome in ambulatory patients with cancer receiving chemotherapy (8226 patients),[53] anticoagulant prophylaxis was compared with placebo (eight studies), no treatment (five studies), or aspirin treatment (one study), and it was associated with a reduced risk of VTE (OR 0·45, 95% CI 0·36–0·56; p<0·0001) and a significant increase in major bleeding risk (1·43, 1·01–2·04). According to an updated Cochrane meta-analysis,[50] with 11 randomised controlled trials (3931 patients) comparing LMWH with no prophylaxis, LMWHs reduced the rate of symptomatic VTE (RR 0·62, 95% CI 0·46–0·83), with a significant increase in major bleeding (1·63, 1·12–2·35). In patients with multiple myeloma, LMWHs were associated with a significantly decreased rate of symptomatic VTE compared with vitamin K antagonists (RR 0·33, 95% CI 0·14–0·83; 439 patients), whereas the difference between LMWH and aspirin was not significant (0·51, 0·22–1·17; 781 patients).[50] Two other meta-analyses reported consistent findings.[52,56]

Direct oral anticoagulants

One new meta-analysis pooling the results from CASSINI[64] and AVERT[65] found that direct oral anticoagulants significantly reduced the rate of overall VTE (RR 0·56, 95% CI 0·35–0·89) but not the rate of symptomatic VTE (0·58, 0·29–1·13) compared with no prophylaxis, with no differences in major bleeding (1·96, 0·8–4·82) or clinically relevant non-major bleeding (1·28, 0·74–2·2) observed between treatment groups.[51] Three additional meta-analyses reported similar findings.[50,52,56]

Anticoagulant thromboprophylaxis in selected patients according to tumour type

Patients with pancreatic cancer

The 2022 ITAC recommendation for VTE primary prophylaxis with LMWHs (grade 1A) or direct oral anticoagulants (grade 1B) in ambulatory patients with locally advanced or metastatic pancreatic cancer receiving chemotherapy and with a low bleeding risk is supported

by two randomised controlled trials,[66,67] and subgroup analyses of three other trials.[60,68,69] Subgroup analysis of the 273 patients with pancreatic cancer included in the CASSINI study[60] showed a significant decrease in a composite endpoint of symptomatic deep vein thrombosis, asymptomatic proximal deep vein thrombosis, any pulmonary embolism, and VTE-related death (HR 0·35, 95% CI 0·13–0·97), without an increase in major bleeding or clinically relevant non-major bleeding during treatment with rivaroxaban compared with placebo. In one meta-analysis of five randomised controlled trials (1003 patients with pancreatic cancer),[55] thromboprophylaxis compared with placebo decreased the VTE rate by 69% (RR 0·31, 95% CI 0·19–0·51; p<0·0001), with similar reductions of VTE in studies with LMWHs (0·30, 0·17–0·53) or direct oral anticoagulants (0·37, 0·14–0·99), without excess in bleeding.

Patients with lung cancer

The 2019 ITAC guidelines for patients with lung cancer is unchanged, because the benefit from thromboprophylaxis is offset by the risk of bleeding.[5] In one new meta-analysis of nine randomised controlled trials (5443 patients),[54] LMWH prophylaxis reduced the risk for VTE (RR 0·54, 95% CI 0·43–0·69), without an increase in overall survival (1·02, 0·83–1·26);[54] this meta-analysis did not assess risk for bleeding.

Patients with multiple myeloma treated with immunomodulatory drugs

The 2022 ITAC guidelines have remained unchanged from the 2019 publication.[5] A meta-analysis of ten studies (1964 patients) comparing thromboprophylaxis with aspirin or LMWH with no intervention found that aspirin reduced the risk of VTE compared with no intervention (OR 0·20, 95% CI 0·07–0·61), but increased the VTE risk compared with LMWH (2·60, 1·08–6·25).[70] Intervention with either aspirin or LMWH did not increase the risk of bleeding. Two prospective, small, single-arm studies reported that apixaban, 2·5 mg twice-daily, was safe and well tolerated.[61,63]

Patients with acute lymphoblastic leukaemia

One Cochrane systematic review in patients with acute lymphoblastic leukaemia receiving asparaginase-based therapy identified 23 non-randomised studies of anticoagulant thromboprophylaxis, but methodological limitations precluded treatment effect estimates.[58] In a retrospective study of thromboprophylaxis in 125 patients with acute lymphoblastic leukaemia, LMWH compared with no prophylaxis in 99 historical controls was associated with a reduced incidence of VTE (OR 0·42, 95% CI 0·21–0·83) without an increase in major bleeding risk.[62]

Prophylaxis of central venous catheter-related VTE

The 2022 ITAC guidelines against routine primary prophylaxis of central venous catheter-related VTE have remained unchanged from the 2016 publication.[4] In a pilot randomised controlled trial[71] of 105 patients with cancer and with new central venous catheters receiving rivaroxaban 10 mg daily, or no intervention, VTE occurred in 5·8% of patients in the rivaroxaban group and 9·4% patients in the control group (HR 0·58; 95% CI 0·14–2·5). One patient (1·9%) on rivaroxaban had major bleeding.[71] One meta-analysis of 22 studies (4131 cases, 5272 controls) in patients with breast cancer showed that arm ports were associated with a higher VTE risk than chest ports (RR 2·23, 95% CI 1·04–4·79; p=0·041).[72] In one randomised controlled trial (399 patients), peripherally inserted central catheters were associated with a higher risk of VTE and adverse events than implanted port catheters (HR 10·2, 95% CI 2·3–44·6, p=0·0002).[73] Another prospective, non-randomised study of 423 patients treated with chemotherapy via a peripherally inserted central catheter reported substantially lower rates of upper extremity VTE when patients received prophylaxis with rivaroxaban (10 mg daily; 3·76%) or enoxaparin (40 mg daily; 3·03%), compared with no prophylaxis (12·4%).[74] Conversely, peripherally inserted central catheter–central venous catheter were associated with a lower risk of catheter-related deep vein thrombosis compared with centrally inserted central venous catheter (RR 0·34, 95% CI 0·12–0·98, p=0·03) in another randomised controlled trial of 93 untreated patients receiving induction therapy for acute myeloid leukaemia.[75]

Prevention and treatment of VTE in special cancer situations

Recommendations on prevention and treatment of VTE in special clinical situations are shown in panel 4.

Patients with brain tumours

The 2022 ITAC guidelines recommend the use of LMWHs or direct oral anticoagulants for the treatment of established VTE in patients with a brain tumour (grade 2A). Since the 2019 ITAC guidelines,[5] one meta-analysis of seven retrospective studies (1291 patients) showed that patients with glioma receiving full-dose anticoagulants (LMWH, unfractionated heparin, or vitamin K antagonist) for cancer-associated thrombosis have an increased risk of intracerebral haemorrhage compared with patients without anticoagulants (OR 3·66, 95% CI 1·84–7·29).[76] Similarly, a matched retrospective study of 291 patients with brain metastasis reported that anticoagulation conferred a non-significant increased risk of intracerebral haemorrhage (HR 1·31, 95% CI 0·96–1·79; p=0·09).[77] In a retrospective cohort of 79 patients with metastatic brain tumours who developed intracerebral haemorrhage on anticoagulation for VTE, the cumulative incidence of recurrent VTE was significantly lower in patients restarting anticoagulation compared with patients who did not (8·1% *vs* 35·3%; p=0·003).[78] Data from randomised controlled trials

Panel 4: **Treatment of venous thromboembolism (VTE) in unique situations**

International Advisory Panel ranking: 8·32 out of 9·00

1 For the treatment of established VTE in patients with a brain tumour, low-molecular-weight heparin (LMWH) or direct oral anticoagulants can be used (grade 2A).
2 We recommend the use of LMWH or unfractionated heparin commenced postoperatively for the prevention of VTE in patients with cancer undergoing neurosurgery (grade 1A).
3 Primary pharmacological prophylaxis of VTE in medically-treated 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 concentration for the treatment of established VTE (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 VTE risk).
6 In patients with cancer and with thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is >50 × 10^9 per L and there is no evidence of bleeding; for patients with a platelet count <50 × 10^9 per 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).
7 In patients with cancer and with mild thrombocytopenia, platelet count >80 × 10^9 per L, pharmacological prophylaxis could be used; if the platelet count is <80 × 10^9 per L, pharmacological prophylaxis can only be considered on a case-by-case basis and careful monitoring is recommended. In the CASSINI[64] and AVERT[65] trials, patients with a platelet count as low as 50 × 10^9 per L were allowed to receive thromboprophylaxis (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 who are pregnant, we suggest the use of LMWH for treatment of established VTE and for VTE 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 antagonist 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).
10 For the treatment of symptomatic catheter-related thrombosis in children 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, direct comparisons between unfractionated heparin, LMWHs, direct oral anticoagulants, and vitamin K antagonists have not been done (guidance).
11 In children with acute lymphoblastic leukaemia undergoing induction chemotherapy, we recommend LMWH as thromboprophylaxis (grade 2A).
12 In children requiring central venous catheters, we suggest the use of implanted ports over peripherally inserted central catheter lines (guidance).

comparing the efficacy and safety of direct oral anticoagulants versus LMWHs in patients with brain tumours were limited to three patients included in the SELECT-D trial[25] and 74 patients included in HOKUSAI-VTE Cancer trial.[24] Since the 2019 ITAC guidelines,[5] three retrospective studies assessed the safety of direct oral anticoagulants versus LMWHs in patients with primary or metastatic brain tumours treated for VTE. In the first retrospective study, after reviewing all intracerebral haemorrhage radiographic images for eligible patients (n=172), the 12-month cumulative incidence of any intracerebral haemorrhage with direct oral anticoagulants was 0%, compared with 36·8% with LMWHs (95% CI 22·3–51·3; p=0·007) in patients with primary brain tumours, and 27·8% (5·5–56·7) versus 52·9% (37·4–66·2; p=0·38) in patients with brain metastases.[79] In the second chart review study (n=125), the rate of major bleeding was 9·6% under direct oral anticoagulants versus 26% under LMWHs (p=0·03), and the respective rates of intracerebral haemorrhage were 5·8% and 15% (p=0·09), with no difference in minor bleeding and recurrent VTE.[80] In the third study (n=111), the 6-month cumulative incidence of intracerebral haemorrhage was 4·3% (95% CI 0·74–13·2) with direct oral anticoagulants versus 5·9% (1·5–14·9) with LMWHs, and the 6-month cumulative incidence of bleeding was 14·3% (6·2–25·8) versus 27·8% (15·5–41·6), respectively.[81] Rates of recurrent VTE did not differ between groups.[81] The recommendation for VTE prophylaxis in brain tumours patients has remained unchanged since 2019.[5]

Patients with thrombocytopenia

The 2022 ITAC guidelines for patients with cancer and with thrombocytopenia have remained unchanged from the 2019 publication.[5] In a prospective non-randomised study of patients with VTE and thrombocytopenia (platelets <100×10^9 per L, n=121), the 60-day incidence of major bleeding was 12·8% (95% CI 4·9–20·8) with full-dose anticoagulation, and 6·6% (95% CI 2·4–14·7) with a lower dose anticoagulation (HR 2·18, 95% CI

Panel 5: **Treatment and prophylaxis of venous thromboembolism (VTE) for patients with cancer and with COVID-19**

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

1 Recommendations for the treatment of established VTE for patients with cancer are similar, independent of whether or not they have COVID-19 (guidance).
2 Recommendations for the prophylaxis of VTE in patients with cancer are similar in those with and without COVID-19 (guidance).

- Patients with cancer and with COVID-19, whether they are hospitalised, post-discharge, or ambulatory, should be assessed for risk of VTE as any other patient with COVID-19 (guidance)
  - Pharmacological prophylaxis during hospitalisation should be given, with the same dose and anticoagulant type as in patients with cancer who do not have COVID-19, based on current institutional practice (guidance).
  - Post-discharge VTE prophylaxis is not advised in patients with cancer and with COVID-19; as with any patient with cancer, individual assessment of benefit–risk ratio should be done (guidance).
  - Primary pharmacological prophylaxis of VTE in ambulatory patients with cancer who have COVID-19 is not recommended routinely (guidance).

Search strategy and selection criteria

The updated literature search was done by the *Institut National du Cancer* using MEDLINE, Embase, and Cochrane Central Register of Controlled Trials with the following subject headings: "exp cancer" AND "exp venous thromboembolism" AND "anticoagulant drugs and devices" AND "COVID-19". The literature search was restricted to articles in English published from Dec 15, 2018, to Jan 1, 2022. 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 for potential inclusion based on article critical appraisal grids designed by the Institut National du Cancer for each clinical question. For inclusion in the analysis, studies had to focus on the treatment of established venous thromboembolism (VTE) in patients with cancer, prophylaxis of VTE in patients with cancer (surgical and medical settings), and treatment and prophylaxis of central venous catheter related VTE in patients with cancer. When data from studies specific to patients with cancer were not available, studies done in the general population (non-cancer specific data) were included if they fulfilled the inclusion criteria. Members of the working group had the opportunity to add any additional references for the individual questions that might have been missed in the literature search. Studies in patients with VTE 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 also excluded. The main study outcomes were rates of VTE (first event or recurrence), major bleeding, clinically relevant non-major bleeding, and death.

1·21–3·93).[82] The incidence of recurrent VTE was 5·6% (95% CI 0·2–11%) with full-dose anticoagulation and 0% with modified-dose anticoagulation.[82] One retrospective study of 15 337 patients with cancer reported that patients with severe thrombocytopenia (platelets $<50\times10^9$ per L, n=166) compared with patients who had a normal platelet count had a similar risk for major bleeding at 10 days (OR 0·84, 95% CI 0·20–3·49) and 30 days (0·90, 0·32–2·49), regardless of the LMWH dose used.[83]

Children with cancer

Since the 2019 ITAC guidelines,[5] a new randomised study (n=949) compared low-dose unfractionated heparin, prophylactic LMWH, and antithrombin supplementation in children with acute lymphoblastic leukaemia during induction therapy.[84] Low-dose unfractionated heparin was associated with a higher VTE rate (8·0%) compared with prophylactic LMWH (3·5%; p=0·011) or antithrombin (1·9%; p<0·001),[84] with no difference in major bleeding.[84] One network meta-analysis of primary pharmacological thromboprophylaxis in children with acute lymphoblastic leukaemia (n=1318) reported that LMWH was the only agent associated with a significantly decreased risk of VTE compared with standard of care (OR 0·23, 95% CI 0·06–0·81).[85] In children with acute lymphoblastic leukaemia undergoing induction chemotherapy, we recommend LMWHs as thromboprophylaxis (grade 2A). In a multicentre, prospective cohort study (including 41% of patients with cancer), children with peripherally inserted central catheters had a significantly higher incidence of catheter-related VTE than children with centrally inserted central catheters (HR 8·5, 95% CI 3·1–23·0; p<0·001).[86] The predefined EINSTEIN-Jr randomised controlled trial analysis comparing rivaroxaban versus standard of care in children with central venous catheter-VTE showed no recurrent VTE or major bleeding in both groups.[87] Together, the data on central venous catheter-VTE prompted two new ITAC guidelines for the treatment and prophylaxis of VTE in children requiring a central venous catheter.

Since the 2019 ITAC guidelines,[5] no new studies have addressed the treatment and prevention of VTE in patients with cancer and with renal failure, or in obese patients.

VTE treatment and prophylaxis in patients with cancer and with COVID-19

Studies reporting the incidence of venous and arterial thrombosis in patients with cancer who have COVID-19 are scarce.[88–90] No large differences in the rates of VTE between patients with COVID-19 with and without cancer were found. In two studies that assessed risks factors for VTE,[89,90] cancer-specific factors, such as cancer type or chemotherapy, did not correlate with increased risk, rather obesity, renal failure, and severity of COVID-19 were associated. A large cancer and COVID-19

registry of 2804 patients found similar VTE rates in patients who had been hospitalised with cancer compared with reported rates in patients without cancer.[91] There are no specific data regarding the benefit and risk of different anticoagulants for the treatment or prevention of VTE in patients with cancer and with COVID-19. Available data in the general population are summarised in the appendix (pp 81–83).

Recommendations for the treatment and prophylaxis of VTE in patients with cancer and with COVID-19 are shown in panel 5. Patients with cancer and with COVID-19 should be assessed for risk of VTE like any patient with COVID-19. Pharmacological prophylaxis during hospitalisation should be given, with the same dose and type of anticoagulant as in patients with cancer who do not have COVID-19. Post-discharge VTE prophylaxis is also not advised; however, as with any patient with cancer, individual assessment of benefit-risk ratio is warranted, as one randomised controlled trial found that rivaroxaban 10 mg daily for 35 days improved clinical outcomes in patients with COVID-19 at high risk of VTE.[92]

Conclusion

Cancer-associated VTE remains an important clinical problem, associated with increased morbidity and mortality. The 2022 updated ITAC guidelines incorporate emerging data within established approaches for the prevention and treatment of cancer-associated thrombosis. The ITAC guidelines' companion free web-based mobile application will assist the practising clinician with decision making at various levels to provide optimal care of patients with cancer to treat and prevent 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 (lead methodologist) and PHP assessed the methodological strength and clinical relevance of the articles identified by the literature search (critical appraisal), selected the articles, and did 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 (equal contribution), JMC, 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 achieved during four meetings, at which the working group collectively drafted and ranked the recommendations. The manuscript was reviewed by a multidisciplinary advisory panel of 87 experts. All working group members approved the final recommendations and the manuscript.

Declaration of interests

DF is the founding cochair of the International Initiative on Thrombosis and Cancer. CF reports honoraria for lectures from Bayer, Bristol Myers Squibb, and LEO Pharma; and support for attending meetings from LEO Pharma and Pfizer, outside the submitted work. JMC reports research funding to her institution from CSL Behring; consulting fees from Abbott; honoraria for lectures from Bristol Myers Squibb, Roche, and Sanofi; and participated in the advisory board of Abbott, Alnylam, Anthos, Bristol Myers Squibb, Sanofi, and Takeda, outside the submitted work. AAK reports consulting fees from Anthos, Bayer, Bristol Myers Squibb, Janssen, Pfizer, and Sanofi; honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Anthos, Bayer, Bristol Myers Squibb, Janssen, Pfizer, and Sanofi; payment for expert testimony to his institution; and support for attending meetings or travel from Bayer, Janssen, Pfizer, and Sanofi, outside the submitted work. AK reports consulting fees from Verseon; and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from CCL Pharma, outside the submitted work. CA reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bayer, Bristol Myers Squibb, Daiichi-Sankyo, Pfizer, and Sanofi, outside the submitted work. AM reports royalties or licenses for risk assessment model in venous thromboembolism in patients with cancer; consulting fees from AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Incyte, Lilly, LEO Pharma, MSD, Pfizer, Roche, Sanofi, and Servier; honoraria for lectures from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Lilly, LEO Pharma, Menarini, Pfizer, Rovi, Sanofi, and Stada; and support for attending meetings or travel from Amgen, AstraZeneca, Celgene, Merck Serono, and Roche, outside the submitted work. BB reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Horiba Medical, Johnson & Johnson, Rovi, and Sanofi, outside the submitted work. DB reports honoraria for lectures from Bayer and Sanofi; support for attending meetings or travel from LEO Pharma and Sanofi; and participated in the advisory board of Apixabano (Pfizer), outside the submitted work. DA reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Roche, Janssen, Takeda, and Pfizer; participated in the advisory board of AstraZeneca, Bayer, Janssen, Pfizer, Roche, and Takeda, outside the submitted work; and is the president of the Serbian Lymphoma Group. PC reports support for attending meetings from Sanofi–Aventis, outside the submitted work, and is a member of the guidelines and guidance Committee of the International Society on Thrombosis and Haemostasis. MCGE reports support for attending meetings from Nolver Uruguay, outside the submitted work. TI reports honoraria for lectures from Asahi Kasei Pharma, Bristol Myers Squibb, Daiichi Sankyo, Nippon Shinyaku, and Pfizer, outside the submitted work. SAA reports grants or contract from AstraZeneca; support for attending meetings from Curoscience; and a leadership or fiduciary role in AstraZeneca, ASTCT, and ASSCO POS, outside the submitted work. LAM-G reports receiving consulting fees from Novartis; and honoraria for lectures from Novartis, Amgen, Astellas, AstraZeneca, Janssen, Roche, and Teva, outside the submitted work. HB participated in the data safety monitoring board of the COVID-HEP and the Dawn-Antico COVID-19 studies; is a member of the steering committee of the GARFIELD VTE Study; is the President of the Swiss Academy of Medical Science, the President of the Société Académique de Genève, and participated to the foundation board of the Promotion Santé Suisse outside the submitted work. IP reports honoraria for lectures and advisory boards from Bayer, Daiichi Sanchyo, Pfizer, and Sanofi, outside the submitted work; and is the Chair of the European Thrombosis and Haemostasis Association. JD reports consulting fees from Sanofi; honoraria for lectures from LEO Pharma, Pfizer, and Servier, outside the submitted work; and is the President of Thrombosis Canada and the cochair of the International Initiative on Thrombosis and Cancer. PHP declares no competing interests.

Acknowledgments

AK is the recipient of an US National Institutes of Health grant (UO1 HL 144302-01).

References

1 Weitz JI, Haas S, Ageno W, et al. Cancer associated thrombosis in everyday practice: perspectives from GARFIELD-VTE. *J Thromb Thrombolysis* 2020; **50:** 267–77.

2 Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood* 2021; **137:** 1959–69.

3 Farge D, Debourdeau P, Beckers M, et al. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *J Thromb Haemost* 2013; **11:** 56–70.

4 Farge D, Bounameaux H, Brenner B, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol* 2016; **17:** e452–66.

5 Farge D, Frere C, Connors JM, et al. 2019 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol* 2019; **20:** e566–81.

6 Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; **336:** 924–26.

7 Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020; **135:** 2033–40.

8 Jiménez D, García-Sanchez A, Rali P, et al. Incidence of VTE and bleeding among hospitalized patients with coronavirus disease 2019: a systematic review and meta-analysis. *Chest* 2021; **159:** 1182–96.

9 Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med* 2020; **382:** 1599–607.

10 Planquette B, Bertoletti L, Charles-Nelson A, et al. Rivaroxaban versus dalteparin in cancer-associated thromboembolism: a randomized trial. *Chest* 2022; **161:** 781–90.

11 Schrag D, Uno H, Rosovsky RPG, et al. The comparative effectiveness of direct oral anti-coagulants and low molecular weight heparins for prevention of recurrent venous thromboembolism in cancer: the CANVAS pragmatic randomized trial. *Proc Am Soc Clin Oncol* 2021; **39** (suppl 15)**:** 12020 (abstr).

12 Kahale LA, Matar CF, Hakoum MB, et al. Anticoagulation for the initial treatment of venous thromboembolism in people with cancer. *Cochrane Database Syst Rev* 2021; **12:** CD006649.

13 Moik F, Posch F, Zielinski C, Pabinger I, Ay C. Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: updated systematic review and meta-analysis of randomized controlled trials. *Res Pract Thromb Haemost* 2020; **4:** 550–61.

14 Giustozzi M, Agnelli G, Del Toro-Cervera J, et al. Direct oral anticoagulants for the treatment of acute venous thromboembolism associated with cancer: a systematic review and meta-analysis. *Thromb Haemost* 2020; **120:** 1128–36.

15 Samaranayake CB, Anderson J, McCabe C, Zahir SF, Upham JW, Keir G. Direct oral anticoagulants for cancer associated venous thromboembolisms: a systematic review and network meta-analysis. *Intern Med J* 2020; **53:** 272–81.

16 Haykal T, Zayed Y, Deliwala S, et al. Direct oral anticoagulant versus low-molecular-weight heparin for treatment of venous thromboembolism in cancer patients: an updated meta-analysis of randomized controlled trials. *Thromb Res* 2020; **194:** 57–65.

17 Dong S, Zhang Y, Li Y, et al. Direct oral anticoagulant for the treatment of vte in cancer patients: a systematic review and meta-analysis. *Ann Pharmacother* 2021; **55:** 430–39.

18 Elbadawi A, Shnoda M, Mahmoud K, Elgendy IY. Efficacy and safety of direct oral anticoagulants *vs*. low molecular weight heparin for cancer-related venous thromboembolism: a meta-analysis of randomized trials. *Eur Heart J Cardiovasc Pharmacother* 2021; **7:** 380–88.

19 Camilli M, Lombardi M, Vescovo GM, et al. Efficacy and safety of novel oral anticoagulants versus low molecular weight heparin in cancer patients with venous thromboembolism: a systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2020; **154:** 103074.

20 Mulder FI, Bosch FTM, Young AM, et al. Direct oral anticoagulants for cancer-associated venous thromboembolism: a systematic review and meta-analysis. *Blood* 2020; **136:** 1433–41.

21 Sabatino J, De Rosa S, Polimeni A, Sorrentino S, Indolfi C. Direct oral anticoagulants in patients with active cancer: a systematic review and meta-analysis. *JACC CardioOncol* 2020; **2:** 428–40.

22 Desai R, Koipallil GK, Thomas N, et al. Efficacy and safety of direct oral anticoagulants for secondary prevention of cancer associated thrombosis: a meta-analysis of randomized controlled trials. *Sci Rep* 2020; **10:** 18945.

23 Yan Y-D, Ding Z, Pan M-M, et al. Net clinical benefit of direct oral anticoagulants in patients with cancer and venous thromboembolism: a systematic review and trade-off analysis. *Front Cardiovasc Med* 2020; **7:** 586020.

24 Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med* 2018; **378:** 615–24.

25 Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol* 2018; **36:** 2017–23.

26 McBane RD 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. *J Thromb Haemost* 2020; **18:** 411–21.

27 Balabhadra S, Kuban JD, Lee S, et al. Association of inferior vena cava filter placement with rates of pulmonary embolism in patients with cancer and acute lower extremity deep venous thrombosis. *JAMA Netw Open* 2020; **3:** e2011079.

28 Quezada A, Jiménez D, Bikdeli B, et al. Outcomes after vena cava filter use in patients with cancer-associated venous thromboembolism and contraindications to anticoagulation. *Thromb Haemost* 2020; **120:** 1035–44.

29 Brailovsky Y, Yeung H-M, Lakhter V, Zack CJ, Zhao H, Bashir R. In-hospital outcomes of catheter-directed thrombolysis versus anticoagulation in cancer patients with proximal deep venous thrombosis. *J Vasc Surg Venous Lymphat Disord* 2020; **8:** 538–544.e3.

30 Mahé I, Plaisance L, Chapelle C, et al. Long-term treatment of cancer-associated thrombosis (CAT) beyond 6 months in the medical practice: USCAT, a 432-patient retrospective non-interventional study. *Cancers (Basel)* 2020; **12:** e2256.

31 Moik F, Colling M, Mahé I, Jara-Palomares L, Pabinger I, Ay C. Extended anticoagulation treatment for cancer-associated thrombosis - rates of recurrence and bleeding beyond 6 months: a systematic review. *J Thromb Haemost* 2021; **20:** 619–34.

32 Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med* 2002; **162:** 1729–35.

33 Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; **349:** 146–53.

34 Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med* 2006; **119:** 1062–72.

35 Lee AYY, Kamphuisen PW, Meyer G, et al. Tinzaparin *vs* warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. *JAMA* 2015; **314:** 677–86.

36 Deitcher SR, Kessler CM, Merli G, et al. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. *Clin Appl Thromb Hemost* 2006; **12:** 389–96.

37 Francis CW, Kessler CM, Goldhaber SZ, et al. Treatment of venous thromboembolism in cancer patients with dalteparin for up to 12 months: the DALTECAN Study. *J Thromb Haemost* 2015; **13:** 1028–35.

38 Jara-Palomares L, Solier-Lopez A, Elias-Hernandez T, et al. Tinzaparin in cancer associated thrombosis beyond 6 months: TiCAT study. *Thromb Res* 2017; **157:** 90–96.

39 Frere C, Farge D, Schrag D, Prata PH, Connors JM. Direct oral anticoagulant versus low molecular weight heparin for the treatment of cancer-associated thromboembolism: 2021 updated meta-analysis of randomized controlled trials. *Blood* 2021; **138** (suppl 1)**:** 668.

40 Knoll W, Fergusson N, Ivankovic V, et al. Extended thromboprophylaxis following major abdominal/pelvic cancer-related surgery: a systematic review and meta-analysis of the literature. *Thromb Res* 2021; **204:** 114–22.

41 Guntupalli SR, Brennecke A, Behbakht K, et al. Safety and efficacy of apixaban *vs* enoxaparin for preventing postoperative venous thromboembolism in women undergoing surgery for gynecologic malignant neoplasm: a randomized clinical trial. *JAMA Netw Open* 2020; **3:** e207410.

42 Insin P, Vitoopinyoparb K, Thadanipon K, et al. Prevention of venous thromboembolism in gynecological cancer patients undergoing major abdominopelvic surgery: a systematic review and network meta-analysis. *Gynecol Oncol* 2021; **161:** 304–13.

43 Bisch S, Findley R, Ince C, Nardell M, Nelson G. Efficacy of pre-operative pharmacologic thromboprophylaxis on incidence of venous thromboembolism following major gynecologic and gynecologic oncology surgery: a systematic review and meta-analysis. *Int J Gynecol Cancer* 2021; **31:** 257–64.

44 Tanaka Y, Yamada A, Hirata S, et al. Efficacy and safety of enoxaparin for prophylaxis of postoperative venous thromboembolism after esophagectomy: a single-center prospective randomized controlled phase II study. *Anticancer Res* 2019; **39:** 2615–25.

45 Hata T, Yasui M, Ikeda M, et al. Efficacy and safety of anticoagulant prophylaxis for prevention of postoperative venous thromboembolism in Japanese patients undergoing laparoscopic colorectal cancer surgery. *Ann Gastroenterol Surg* 2019; **3:** 568–75.

46 Nakagawa K, Watanabe J, Ota M, et al. Efficacy and safety of enoxaparin for preventing venous thromboembolic events after laparoscopic colorectal cancer surgery: a randomized-controlled trial (YCOG 1404). *Surg Today* 2020; **50:** 68–75.

47 Obitsu T, Tanaka N, Oyama A, et al. Efficacy and safety of low-molecular-weight heparin on prevention of venous thromboembolism after laparoscopic operation for gastrointestinal malignancy in japanese patients: a multicenter, open-label, prospective, randomized controlled trial. *J Am Coll Surg* 2020; **231:** 501–509.e2.

48 Patel HD, Faisal FA, Trock BJ, et al. Effect of pharmacologic prophylaxis on venous thromboembolism after radical prostatectomy: the PREVENTER randomized clinical trial. *Eur Urol* 2020; **78:** 360–68.

49 Zwicker JI, Roopkumar J, Puligandla M, et al. Dose-adjusted enoxaparin thromboprophylaxis in hospitalized cancer patients: a randomized, double-blinded multicenter phase 2 trial. *Blood Adv* 2020; **4:** 2254–60.

50 Rutjes AW, Porreca E, Candeloro M, Valeriani E, Di Nisio M. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients receiving chemotherapy. *Cochrane Database Syst Rev* 2020; **12:** CD008500.

51 Li A, Kuderer NM, Garcia DA, et al. Direct oral anticoagulant for the prevention of thrombosis in ambulatory patients with cancer: a systematic review and meta-analysis. *J Thromb Haemost* 2019; **17:** 2141–51.

52 Barbarawi M, Zayed Y, Kheiri B, et al. The role of anticoagulation in venous thromboembolism primary prophylaxis in patients with malignancy: a systematic review and meta-analysis of randomized controlled trials. *Thromb Res* 2019; **181:** 36–45.

53 Becattini C, Verso M, Muñoz A, Agnelli G. Updated meta-analysis on prevention of venous thromboembolism in ambulatory cancer patients. *Haematologica* 2020; **105:** 838–48.

54 Thein KZ, Quick DP, Htut TW, Tijani L, Oo TH. Impact of primary ambulatory thromboprophylaxis (PATP) with low-molecular weight heparins (LMWHs) on survival in patients with lung cancer receiving chemotherapy. *Lung* 2020; **198:** 575–79.

55 Frere C, Crichi B, Bournet B, et al. Primary thromboprophylaxis in ambulatory pancreatic cancer patients receiving chemotherapy: a systematic review and meta-analysis of randomized controlled trials. *Cancers (Basel)* 2020; **12:** e2028.

56 Xin Z, Liu F, Du Y, et al. Primary prophylaxis for venous thromboembolism in ambulatory cancer patients: a systematic review and network meta-analysis. *Ann Palliat Med* 2020; **9:** 2970–81.

57 Schünemann HJ, Ventresca M, Crowther M, et al. Evaluating prophylactic heparin in ambulatory patients with solid tumours: a systematic review and individual participant data meta-analysis. *Lancet Haematol* 2020; **7:** e746–55.

58 Rank CU, Lynggaard LS, Als-Nielsen B, et al. Prophylaxis of thromboembolism during therapy with asparaginase in adults with acute lymphoblastic leukaemia. *Cochrane Database Syst Rev* 2020; **10:** CD013399.

59 Bosch FTM, Mulder FI, Kamphuisen PW, et al. Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis. *Blood Adv* 2020; **4:** 5215–25.

60 Vadhan-Raj S, McNamara MG, Venerito M, et al. Rivaroxaban thromboprophylaxis in ambulatory patients with pancreatic cancer: Results from a pre-specified subgroup analysis of the randomized CASSINI study. *Cancer Med* 2020; **9:** 6196–204.

61 Pegourie B, Karlin L, Benboubker L, et al. Apixaban for the prevention of thromboembolism in immunomodulatory-treated myeloma patients: myelaxat, a phase 2 pilot study. *Am J Hematol* 2019; **94:** 635–40.

62 Sibai H, Chen R, Liu X, et al. Anticoagulation prophylaxis reduces venous thromboembolism rate in adult acute lymphoblastic leukaemia treated with asparaginase-based therapy. *Br J Haematol* 2020; **191:** 748–54.

63 Cornell RF, Goldhaber SZ, Engelhardt BG, et al. Primary prevention of venous thromboembolism with apixaban for multiple myeloma patients receiving immunomodulatory agents. *Br J Haematol* 2020; **190:** 555–61.

64 Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med* 2019; **380:** 720–28.

65 Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med* 2019; **380:** 711–19.

66 Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. *Eur J Cancer* 2012; **48:** 1283–92.

67 Pelzer U, Opitz B, Deutschinoff G, et al. Efficacy of prophylactic low-molecular weight heparin for ambulatory patients with advanced pancreatic cancer: outcomes from the CONKO-004 trial. *J Clin Oncol* 2015; **33:** 2028–34.

68 Agnelli G, Gussoni G, Bianchini C, et al. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. *Lancet Oncol* 2009; **10:** 943–49.

69 Agnelli G, George DJ, Kakkar AK, et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *N Engl J Med* 2012; **366:** 601–09.

70 Zoppellaro G, Veronese N, Granziera S, Gobbi L, Stubbs B, Cohen AT. Primary thromboembolic prevention in multiple myeloma patients: an exploratory meta-analysis on aspirin use. *Semin Hematol* 2018; **55:** 182–84.

71 Ikesaka R, Siegal D, Mallick R, et al. Thromboprophylaxis with rivaroxaban in patients with malignancy and central venous lines (TRIM-Line): a two-center open-label pilot randomized controlled trial. *Res Pract Thromb Haemost* 2021; **5:** e12517.

72 Liu Y, Li L-L, Xu L, et al. Comparison between arm port and chest port for optimal vascular access port in patients with breast cancer: a systematic review and meta-analysis. *BioMed Res Int* 2020; **2020:** 9082924.

73 Taxbro K, Hammarskjöld F, Thelin B, et al. Clinical impact of peripherally inserted central catheters *vs* implanted port catheters in patients with cancer: an open-label, randomised, two-centre trial. *Br J Anaesth* 2019; **122:** 734–41.

74 Lv S, Liu Y, Wei G, Shi X, Chen S, Zhang X. The anticoagulants rivaroxaban and low molecular weight heparin prevent PICC-related upper extremity venous thrombosis in cancer patients. *Medicine* 2019; **98:** e17894.

75 Picardi M, Della Pepa R, Cerchione C, et al. A frontline approach with peripherally inserted versus centrally inserted central venous catheters for remission induction chemotherapy phase of acute myeloid leukemia: a randomized comparison. *Clin Lymphoma Myeloma Leuk* 2019; **19:** e184–94.

76 Porfidia A, Giordano M, Sturiale CL, et al. Risk of intracranial bleeding in patients with primary brain cancer receiving therapeutic anticoagulation for venous thromboembolism: a meta-analysis. *Brain Behav* 2020; **10:** e01638.

77 Wood P, Boyer G, Mehanna E, et al. Intracerebral haemorrhage in patients with brain metastases receiving therapeutic anticoagulation. *J Neurol Neurosurg Psychiatry* 2021; **92:** jnnp-2020-324488.

78 Carney BJ, Uhlmann EJ, Puligandla M, et al. Anticoagulation after intracranial hemorrhage in brain tumors: risk of recurrent hemorrhage and venous thromboembolism. *Res Pract Thromb Haemost* 2020; **4:** 860–65.

79 Carney BJ, Uhlmann EJ, Puligandla M, et al. Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors. *J Thromb Haemost* 2019; **17:** 72–76.

80 Swartz AW, Drappatz J. Safety of direct oral anticoagulants in central nervous system malignancies. *Oncologist* 2021; **26:** 427–32.

81 Lee A, Oley F Jr, Lo M, et al. Direct oral anticoagulants or low-molecular-weight heparins for venous thromboembolism in patients with brain tumors. *Thromb Res* 2021; **208:** 148–55.

82 Carney BJ, Wang T-F, Ren S, et al. Anticoagulation in cancer-associated thromboembolism with thrombocytopenia: a prospective, multicenter cohort study. *Blood Adv* 2021; **5:** 5546–53.

83 Lecumberri R, Ruiz-Artacho P, Trujillo-Santos J, et al. Management and outcomes of cancer patients with venous thromboembolism presenting with thrombocytopenia. *Thromb Res* 2020; **195:** 139–45.

84 Greiner J, Schrappe M, Claviez A, et al. THROMBOTECT—a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents. *Haematologica* 2019; **104:** 756–65.

85 Pelland-Marcotte M-C, Tole S, Pechlivanoglou P, Brandão LR. Effectiveness and safety of primary thromboprophylaxis in children with cancer: a systematic review of the literature and network meta-analysis. *Thromb Haemost* 2019; **119:** 2034–42.

86 Jaffray J, Witmer C, O'Brien SH, et al. Peripherally inserted central catheters lead to a high risk of venous thromboembolism in children. *Blood* 2020; **135:** 220–26.

87 Thom K, Lensing AWA, Nurmeev I, et al. Safety and efficacy of anticoagulant therapy in pediatric catheter-related venous thrombosis (EINSTEIN-Jr CVC-VTE). *Blood Adv* 2020; **4:** 4632–39.

88 Patell R, Bogue T, Bindal P, et al. Incidence of thrombosis and hemorrhage in hospitalized cancer patients with COVID-19. *J Thromb Haemost* 2020; **18:** 2349–57.

89 Zavras PD, Mehta V, Goel S, Pradhan K, Billett HH. Increased incidence of thrombosis in a cohort of cancer patients with COVID-19. *Acta Haematol* 2022; **145:** 152–59.

90 Obispo B, Rogado J, Muñoz-Rivas N, et al. Prevalence of thrombosis in patients with cancer and SARS-CoV-2 infection. *Med Clin (Barc)* 2021; published online Sept 25. https://doi.org/10.1016/j.medcli.2021.08.002.

91 Li A, Kuderer NM, Hsu C-Y, et al. The CoVID-TE risk assessment model for venous thromboembolism in hospitalized patients with cancer and COVID-19. *J Thromb Haemost* 2021; **19:** 2522–32.

92 Ramacciotti E, Barile Agati L, Calderaro D, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. *Lancet* 2022; **399:** 50–59.