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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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, Maria Cecilia Guillermo Exposito, Takayuki Ikezoe, Syed A Abutalib, Luis A Meillon-Garcia, 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, 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.

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, with vitamin K antagonists (after LMWH) providing a secondary treatment option, until direct oral anticoagulants emerged as alternative first-line treatment options in 2016. 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. 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.

The International Initiative on Thrombosis and Cancer (ITAC) first developed evidence-based clinical practice guidelines in 2013, using Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology. The 2016 and 2019 updates 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. 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%). 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, and also received support from the Institut National du Cancer. Guideline development is based on GRADE methodology (panel 1; fully detailed in appendix pp 3–23). The panel, which comprised 19 independent international academic experts from various specialties,
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, thromboembolism, 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,3 three randomised clinical trials4–6 and 12 meta-analyses7–19 assessed the efficacy and safety of LMWHs or direct oral anticoagulants for the treatment of cancer-associated thrombosis.5

**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 LMWH10–12,24–26 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 2019,3 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,27 CASTA-DIVA,28 and CANVAS29) 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.3 A new retrospective database study, which used propensity score matching and competing risk analysis, compared 33740 patients with cancer and concomitant deep vein thrombosis who had inferior vena cava filters with 54845 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 also be 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. 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, 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), rivaroxaban (CASTA-DIVA), or any direct oral anticoagulant (CANVAS). 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, there have been no new randomised controlled trials comparing LMWHs with vitamin K antagonists. Five pivotal randomised controlled trials (CANTHANOX, CLOT, LITE, CATCH, and ONCENOX) 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. Data from the LMWH control group of the HOKUSAI-VTE cancer trial, two prospective single-arm cohorts, and one retrospective study 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.30-31

Direct oral anticoagulants versus LMWHs
Three new randomised controlled trials comparing direct oral anticoagulants with LMWHs (CARAVAGGIO, CASTA-DIVA, and CANVAS; appendix p 110–12), and 11 meta-analyses focusing pooling results from HOKUSAI-VTE Cancer, SELECT-D, ADAM-VTE, and CARAVAGGIO (2894 patients), 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. One meta-analysis, 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) 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, 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 1·52, 95% CI 0·88–2·63). Overall survival was also similar between groups. In the CASTA-DIVA trial, 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 7·9% 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, 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, SELECT D, CARAVAGGIO, CASTA-DIVA, and CANVAS (3690 patients) were presented at the 2021 American Society of Hematology meeting. 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). 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, the risk of recurrent VTE was not different in patients receiving direct oral anticoagulants, compared with those receiving LMWHs (RR 0·54, 95% CI 0·32–0·89), 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, totalling 3352 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.

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, 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. There are no new data for fondaparinux and there is insufficient evidence to support the use of apixaban, despite one small randomised controlled trial. 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). 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 (14273 patients) 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 surgery.
surgery (laparotomy and laparoscopic) is unchanged (grade 1A). A new meta-analysis (18 studies, 7495 patients) 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). 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.

Mechanical methods of prophylaxis

Unchanged since the 2019 ITAC guidelines, 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. In a network meta-analysis...

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

Prophylaxis of VTE in surgically-treated patients with cancer

International Advisory Panel ranking: 8·52 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: 8·38 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: 8·50 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).
of patients with gynaecological cancer undergoing major abdominopelvic surgery, comparing different methods of thromboprophylaxis, intermittent pneumatic compression plus LMWH was best for VTE prevention.\textsuperscript{52}

**Inferior vena cava filters placement**

No additional studies have been available since the 2019 ITAC guidelines.\textsuperscript{7} 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.\textsuperscript{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.\textsuperscript{53} 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.\textsuperscript{51}

Ten new meta-analyses (1415–15678 patients),\textsuperscript{50–59} one subgroup analysis of a randomised controlled trial (273 patients with pancreatic cancer),\textsuperscript{50} and three observational studies\textsuperscript{60–62} 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.\textsuperscript{50} 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).\textsuperscript{52} 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.\textsuperscript{50} Since 2019,\textsuperscript{50} 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).\textsuperscript{52} 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).\textsuperscript{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),\textsuperscript{51} 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 0·35–0·60; p<0·0001) and a significant increase in major bleeding risk (1·43, 1·01–2·04). According to an updated Cochrane meta-analysis,\textsuperscript{58} 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).\textsuperscript{59} Two other meta-analyses reported consistent findings.\textsuperscript{55,56}

**Direct oral anticoagulants**

One new meta-analysis pooling the results from CASSINI\textsuperscript{63} and AVERT\textsuperscript{64} 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.\textsuperscript{58} Three additional meta-analyses reported similar findings.\textsuperscript{55,56}

**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,\textsuperscript{16,17} and subgroup analyses of three other trials.\textsuperscript{18,19,20} Subgroup analysis of the 273 patients with pancreatic cancer included in the CASSINI study\textsuperscript{21} 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 (3003 patients with pancreatic cancer),\textsuperscript{21} 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.\textsuperscript{3} In one new meta-analysis of nine randomised controlled trials (5443 patients),\textsuperscript{22} 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);\textsuperscript{23} 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.\textsuperscript{4} 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).\textsuperscript{24} 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.\textsuperscript{25,26}

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.\textsuperscript{27} In a retrospective study of thromboprophylaxis in 125 patients with acute lymphoblastic leukaemia, LMWH compared with no prophyllaxis 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.\textsuperscript{28}

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.\textsuperscript{4} In a pilot randomised controlled trial\textsuperscript{29} 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 0·34–0·95). One patient (1·9%) on rivaroxaban had major bleeding.\textsuperscript{30} 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).\textsuperscript{31}

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).\textsuperscript{32} 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%).\textsuperscript{33} 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.\textsuperscript{34}

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,\textsuperscript{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).\textsuperscript{35} 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).\textsuperscript{36} 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).\textsuperscript{37} Data from randomised controlled trials...
rates of intracerebral haemorrhage were 5·8% and 15% versus 26% under LMWHs (p=0·03), and the respective 12-month cumulative incidence of any haemorrhage radiographic images for eligible patients 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 were 5·8% and 15% (p=0·09), with no difference in minor bleeding and recurrent VTE. 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, and vitamin K antagonists have not been done (guidance).

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).

In patients with cancer who are obese, consideration for a higher dose of LMWH should be given for cancer surgery (guidance).

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).

In children with acute lymphoblastic leukaemia undergoing induction chemotherapy, we recommend LMWH as thromboprophylaxis (grade 2A).

In children requiring central venous catheters, we suggest the use of implanted ports over peripherally inserted central catheter lines (guidance).

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

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 × 10⁹ per L and there is no evidence of bleeding; for patients with a platelet count <50 × 10⁹ 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 × 10⁹ per L, pharmacological prophylaxis could be used; if the platelet count is <80 × 10⁹ per L, pharmacological prophylaxis can only be considered on a case-by-case basis and careful monitoring is recommended. In the CASSINI⁶₄ and AVERT⁶₅ trials, patients with a platelet count as low as 50 × 10⁹ 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 and 74 patients included in HOKUSAI-VTE Cancer trial. Since the 2019 ITAC guidelines, 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 were 5·8% and 15% (p=0·09), with no difference in minor bleeding and recurrent VTE. 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. Rates of recurrent VTE did not differ between groups. The recommendation for VTE prophylaxis in brain tumours patients has remained unchanged since 2019.
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.

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.65,66 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,65,66 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. 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. 

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, Athersys, Antios, Bristol Myers Squibb, Sanofi, and Takeda, outside the submitted work. AAK reports consulting fees from Amgen, Bayer, Bristol Myers Squibb, Janssen, Pfizer, and Sanofi; and is the President of Thrombosis Canada and the Chair of the European Thrombosis and Haemostasis. DB 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 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 Hirscha Medical, Johnson & Johnson, Rovi, and Sanofi, outside the submitted work. DB reports honoraria for lectures from Roche and Sanofi; and support for attending meetings or travel from LEO Pharma and Sanofi; and participated in the advisory board of Apsalzano (Pfizer), outside the submitted work. DA reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Bayer, 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. MGCE 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 Shinryaku, and Pfizer, outside the submitted work. SAA reports grants or contract from AstraZeneca; support for attending meetings from Curusience; 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 in the foundation board of the Promotion Suisse outside the submitted work. IP reports honoraria for lectures and advisory boards from Bayer, Daiichi Sankyo, 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 (U01 HL 14302-01).

References
1. Weitz JJ, 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 FL, Horváth-Pühi 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.
Chest a randomized trial.

161: versus dalteparin in cancer-associated thromboembolism:

Front Cardiovasc Med 7: 2020; 10: 2020; thrombosis: a meta-analysis of randomized controlled trials.

oral anticoagulants for secondary prevention of cancer associated

2020; 42: 428–40.

oral anticoagulants in patients with active cancer: a systematic

136: 1433–41.

cancer patients with venous thromboembolism: a systematic review

7: 2020; of direct oral anticoagulants analysis.

55: 430–39.

4: 2020; 382: 204:
thromboembolisms: a systematic review and network meta-

Cochrane Database Syst Rev 2021; 12: CD006649.

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.

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; 12: 1128–36.

Samaranayake CB, Anderson J, McCabe C, Zahir SF, Upham JW, Keir G. Direct oral anticoagulants for cancer associated venous thromboembolism: a systematic review and network meta-

analysis. Intern Med J 2020; 50: 272–81.

Haykal T, Zayed Y, Deliwaia 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.

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.

Elhawawy A, Shnoda M, Mahmoud K, Elgendery 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: 60–65.

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 Oncor Hematol 2020; 154: 103074.

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.

Sahtisto 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 Cardio Onco 2020; 2: 428–48.

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

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.

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.

Young AM, Marshall A, Thrallwall 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: 2077–23.

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.

Balabahdara 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.

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: 1053–44.

Brzozovsky Y, Yeung HM, 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.

Måhe I, Flaisance 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.

Moik F, Colling M, Måhe 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 2020; 20: 619–34.

Meyer G, Marjanovic Z, Valcl 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.

Lee AY, 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.

Hull RD, Pinoe 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.

Lee AY, 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.

Deitche SR, Kessler CM, Merh 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.

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 2012; 13: 1028–35.

Jara-Palomares L, Solier-Lopez A, Elías-Hernández T, et al. Tinzaparin in cancer associated thrombosis beyond 6 months: TICAT study. Thromb Res 2017; 157: 90–96.

Ferre 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.

Knoll W, Ferguson N, Ivanovik 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: 314–22.

Guntupalli SR, Brennecka B, 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.

Insin P, Vitoopinyaparb K, Thadanipon K, et al. Prevention of venous thromboembolism in gynecological cancer patients undergoing major abdominal/pelvic surgery: a systematic review and network meta-analysis. Cancers (Basel) 2021; 161: 304–13.
Results from a pre-specified subgroup analysis of the randomized controlled phase II study. Anticancer Res 2019; 39: 2015–25.

Huta T, Yarski 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.

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

Obstt S, 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: 501–62.

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.

Zwicker JI, Rookkumar J, Pilugandla 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.

Rutjes AW, Pierrere 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.

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.

Barbarwai 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.

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.

Thein KZ, Quick DP, Htut TW, Tjiani I, 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.

Ferre C, Cricht 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.

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.

Schinemann 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.

Rithel C, Lynggaard LS, Als-Nielsen B, et al. Prophylaxis of thromboprophylaxis during therapy with asparaginase in adults with acute lymphoblastic leukaemia. Cochrane Database Syst Rev 2020; 10: CD013399.

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

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.

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

Sibi 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.

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.

Khorrana 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.

Carrièr M, Ahou-Nasser K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. N Engl J Med 2019; 380: 711–19.

Maraveyas A, Waters J, Roy R, et al. Gemcitabine versus gemcitabine plus dalteparin thromboprophylaxis in pancreatic cancer. Eur J Cancer 2012; 48: 1281–92.

Pelzer U, Opitz B, Deutschendorf 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.

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 randomized, placebo-controlled, double-blind study. Lancet Oncol 2009; 10: 943–49.

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.

Zapparollo G, Veronesi N, Granziola S, Gobbi L, Stubbs B, Cohen AT. Primary thromboprophylaxis in prevention of multiple myeloma patients: an exploratory meta-analysis on aspirin use. Semin Hematol 2018; 55: 182–84.

Ikesaka R, Siegel 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: e12537.

Liu Y, Li 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; 2019: 9082924.

Taxbro R, Hammarskjöld F, Thein 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.

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

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 leukaemia: a randomized comparison. Clin Lymphoma Myeloma Leuk 2019; 19: e184–94.

Porfida A, Giordano M, Sturlaile 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.

Wood P, Boyer G, Melhuish E, et al. Intracerebral haemorrhage in patients with brain metastases receiving therapeutic anticoagulation. J Neurooncog Psychiatry 2021; 92: jnpo-2020-324488.

Carney BJ, Uhllmann EL, Pilugandla 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.

Carney BJ, Uhllmann EL, Pilugandla 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-Attacho 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’Brian S14, 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 CV-CVT). Blood Adv 2020; 4: 6632–39.
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 GoVID-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.

Copyright © 2022 Elsevier Ltd. All rights reserved.